INSIDE STANFORD MEDICINE

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Researchers hope that two drugs, when used together, will block the growth of pancreatic tumor cells in humans.

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Molecule disarms deadly *C. difficile* without destroying healthful gut flora

By Bruce Goldman

School of Medicine scientists successfully defeated a dangerous intestinal pathogen, *Clostridium difficile,* with a drug targeting its toxins rather than its life.

By not aiming to kill the pathogen with antibiotics, scientists were able to avoid wiping out sizeable numbers of beneficial gut microbes. And while their study was performed in mice, the drug used has already been tested in clinical trials to treat other, unrelated conditions. So the researchers believe it could be moved rapidly into human trials for the treatment of *C. difficile*, as well.

The findings, which were published online Sept. 23 in *Science Translational Medicine*, constitute the first-ever demonstration of a small molecule's ability to disarm *C. difficile* without incurring the collateral damage caused by antibiotics.

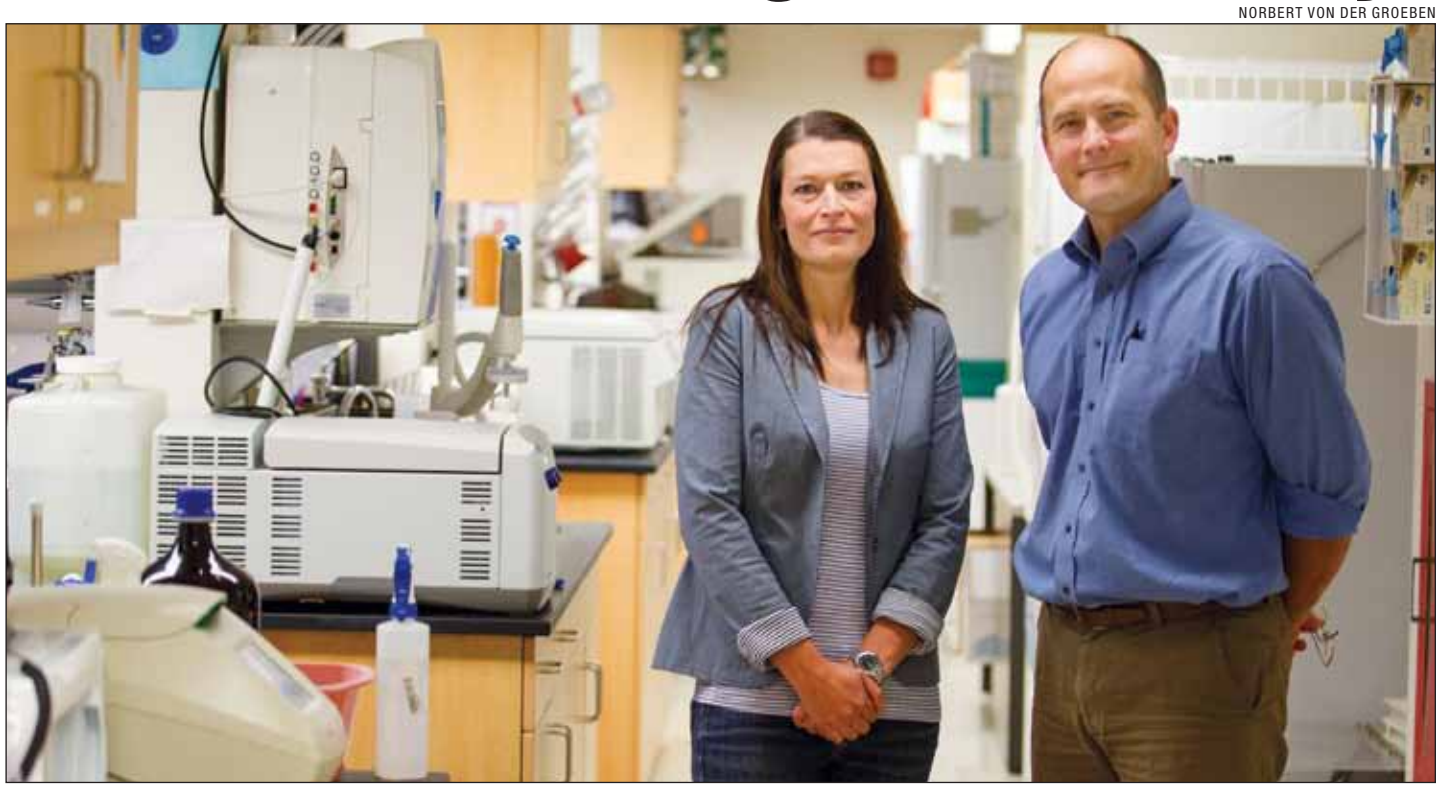
C. difficile is responsible for more than 250,000 hospitalizations and 15,000 deaths per year in the United States, costing the country more than $4 billion in health-care expenses, said the study's senior author, See C. DIFFICILE, page 7

KATERYNA KON / SHUTTERSTOCK

C. difficile **is responsible for more than 250,000 hospitalizations and 15,000 deaths per year in the United States, the study's senior author said.**

Drug prevents Type 1 diabetes in mice, according to new study

NORBERT VON DER GROEBEN



Nadine Nagy and Paul Bollyky and their colleagues hope that a drug called 4-methylumbelliferone could help prevent the onset of Type 1 diabetes in humans.

By Bruce Goldman

The buildup of a substance in the pancreas during the pre-symptomatic stage of Type 1 diabetes is essential to the development of the disease, School of Medicine researchers have shown.

The investigators used a drug to block production of this substance in mouse models, staving off damage to insulin-producing cells and preventing the onset of the autoimmune disorder. The drug, which is currently used in Europe and Asia for treating gallstone-related spasms, has an excellent safety record, the researchers said.

The findings, described in a study published online Sept. 14 in the *Journal of Clinical Investigation*, suggest that it may be possible to prevent the onset of Type 1 diabetes in humans if a similar treatment is initiated before the insulin-producing cells, or beta cells, are attacked by misguided immune cells. Type 1 diabetes, formerly called juvenile diabetes, afflicts one in 300 people in the United States.

The study is the first to link the progression of Type 1 diabetes to changes in the architecture of the extracellular matrix, the carbohydrate- and protein-rich lattice in which the cells composing our tissues are embedded, said Paul Bollyky, MD, PhD, assistant professor of infectious diseases. Bollyky is the study's senior author. The lead author is postdoctoral scholar Nadine Nagy, PhD.

Most pancreatic cells are engaged in manufacturing and secreting digestive enzymes. But the pancreas is also studded with tiny, hormone-producing cell clusters called islets. A human pancreas contains thousands of islets, scattered throughout the organ like raisins in a loaf of cinnamon bread.

Inflamed islets

A pancreatic islet is composed of several cell types, each making a different hormone. Beta See DIABETES, page 7

Filtered sunlight a safe, low-tech treatment for newborn jaundice, researchers find

By Erin Digitale

Newborn jaundice can be treated with filtered sunlight, providing a safe, inexpensive, low-tech solution to a health problem that now causes permanent brain damage or death in more than 150,000 babies in developing countries each year.

That's the finding of a new study by researchers at the School of Medicine and their colleagues that was published Sept.17 in *The New England Journal of Medicine.* In the study, conducted in Nigeria, some mothers and babies sat under outdoor canopies that filtered out harmful wavelengths from sunlight, but still allowed jaundice-treating blue wavelengths to reach the babies' skin. The filtered-sunlight treatment was as safe and effective as the blue-light lamps traditionally used to treat infant jaundice, the study found.

COURTESY OF HENDRIK VREMAN

Nigerian mothers and their infants sit beneath an early prototype of a sunlight-filtering canopy.

"This research has the potential for global impact," said the study's senior author, David Stevenson, MD, the Harold K. Faber Professor in Pediatrics and senior associate dean for maternal and child health at Stanford. "All babies can get jaundice. In settings with no access to modern devices, we've shown we can use something that's available all around the planet — sunlight — to treat this dangerous condition." Stevenson also directs the Johnson Center for Preg- See JAUNDICE, page 6

Large-scale treatment of parasitic-worm diseases cost-effective, study says

By Ruthann Richter

Nathan Lo

School of Medicine researchers and their colleagues are calling for an urgent re-evaluation of global guidelines for the treatment of parasitic-worm diseases in light of a new study showing that large-scale treatment programs are highly cost-effective.

Parasitic-worm diseases afflict some 1.5 billion people in the developing world, causing gastrointestinal problems, anemia, wasting, and cognitive and growth deficits in children, and in some cases, liver, bladder and intestinal problems that can be fatal. About 150,000 people die of complications from these parasitic infections every year.

World Health Organization guidelines on treatment of the diseases focus only See WORMS, page 6

Study: For teens with bulimia, family-based therapy works best

By Erin Digitale

The best therapy for teenagers with bulimia is different than the one for adults, according to the first large study to provide a head-to-head comparison of two well-regarded treatments for adolescents with the eating disorder.

Conducted by researchers at the Stanford School of Medicine and the University of Chicago, the study also shows that teens' families can play a big role in helping them recover from bulimia.

The findings were published online Sept. 17 in the *Journal of the American Academy of Child and Adolescent Psychiatry*.

"We have very little information about how best to address bulimia in adolescents, and have been depending on what we know about the efficacy of treatment in adults," said co-lead author James Lock, MD, PhD, professor of psychiatry and behavioral sciences at Stanford. But teens with bulimia have different needs and less-entrenched illness than adults, he added.

At the end of six months of treatment, adolescents who received family-based therapy were more likely to have stopped their abnormal eating behaviors than those who received the standard treatment for adults, the study found. The difference between therapies persisted six months after treatment ended.

Binging and purging

Bulimia nervosa is characterized by repeated cycles of secretive binging on large amounts of food, followed by purging the body of calories via vomiting, laxative use or excessive exercise. It is linked with both physical and psychological harm, including feelings of poor self-image, shame and guilt, and medical problems such as dehydration, tooth and gum disease, and irregular heartbeat or heart failure.

The study included 130 participants, ages 12-18, who met clinical definitions of full or partial bulimia nervosa. They were randomly assigned to receive six months of therapy with one of three treatments: Family-based therapy, in which the parents and patient worked together to interrupt abnormal eating behaviors; cognitive behavioral therapy, which focused on changing abnormal thoughts about food, eating and body image, with a lesser emphasis on behavioral change; and supportive psychotherapy, which was included to help generate hypotheses for future studies but was not used by researchers in the main analysis of the results. Family-based therapy has been shown to be the most effective treatment for teenagers with anorexia nervosa, while cognitive behavioral therapy is considered the most effective treatment for adults with bulimia.

James Lock

At the end of treatment, 39 percent of participants treated with family-based therapy had abstained from both binging and purging for at least four weeks, compared with 20 percent of participants receiving cognitive behavioral therapy. Six months after treatment ended, both groups continued to improve, but the gap between treatments remained: 44 percent of family-based therapy patients and 25 percent of cognitive behavioral therapy patients were abstaining from binging and purging. A year after treatment ended, the gap had narrowed and was no longer statistically significant, although the researchers are not sure if this is because the two treatments are similarly effective at that time or because some patients did not return for evaluation at the one-year point.

Treatment strategy may depend on child

Although the research did not test why family-based therapy worked better for teens, the finding is not surprising, said Lock, who directs the Comprehensive Eating Disorders Program at Lucile Packard Children's Hospital Stanford. "The strategy for cognitive behavioral therapy requires a fair amount of abstract reasoning, motivation and persistence that often has not reached full capacity in teens," he said, adding that doctors may need to decide on a case-by-case basis whether a teen would benefit from one treatment versus the other. "The cognitive and developmental context is very different for teens than for adult patients," he said.

And it's normal for teenagers to need their parents' assistance in navigating difficult situations, he added. "The big take-home message is that families can really help their kids with bulimia nervosa."

Lock shared lead authorship of the study with Daniel LeGrange, MD, who was at the University of Chicago when the research was conducted and is now professor of psychiatry at the University of California-San Francisco.

Other Stanford-affiliated authors are Stewart Agras, MD, professor emeritus of psychiatry; Susan Bryson, senior scientific programmer; and Booil Jo, PhD, associate professor of psychiatry.

The research was supported by the National Institute of Mental Health.

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

Agras and Lock receive royalties from Oxford University Press for contributions to a textbook about eating disorders. Lock also receives royalties from Guildford Press for books he has written about family-based treatment for anorexia nervosa and bulimia nervosa, and payments from the Training Institute for Child and Adolescent Eating Disorders, where he is a faculty member who trains other clinicians in evidence-based treatment methods for eating disorders. **ISM**

Delivering missing protein heals damaged hearts in animals

By Tracie White

Scientists at the School of Medicine and their colleagues have enabled damaged heart tissue in animals to regenerate by delivering a protein to it via a bioengineered collagen patch.

Pilar Ruiz-Lozano

"This finding opens the door to a completely revolutionary treatment," said Pilar Ruiz-Lozano, PhD, associate professor of pediatrics at Stanford. "There is currently no effective treatment to reverse the scarring in the heart after heart attacks."

The work is described in a paper published online Sept. 16 in *Nature*. Ruiz-Lozano is the senior author. Vahid Serpooshan, PhD, a postdoctoral scholar in cardiology at Stanford, and Ke Wei, PhD, a postdoctoral scholar at UC-San Diego, share lead authorship.

In a heart attack, cardiac muscle cells, called cardiomyocytes, die from a lack of blood flow. Replacing those dead cells is vital for the organ to fully recover. Unfortunately, the adult mammalian heart does not regenerate effectively, causing scar tissue to form.

Heart attacks cause millions of deaths annually worldwide and are predicted to skyrocket in the next few decades — tripling by 2030. About 735,000 Americans suffer a heart attack each year. Many victims now survive the initial injury, thanks to advances in early treatment, but the resulting loss of cardiomyocytes can lead to heart failure and possibly death. "Consequently, most survivors face a long and progressive course of heart failure, with poor quality of life and very high medical costs," Ruiz-Lozano said. Various methods of transplanting healthy muscle cells into a damaged heart have been tried, but have yet to yield consistent success in promoting healing.

Regenerating heart muscle

Previous heart regeneration studies in zebrafish have shown that the epicardium is one of the driving factors for healing a damaged heart, Ruiz-Lozano said. "We wanted to know what in the epicardium stimulates the myocardium, the muscle of the heart, to regenerate." Since adult mammalian hearts do not regenerate effectively, the researchers also wanted to know whether epicardial substances might stimulate regeneration in mammalian hearts and restore function after a heart attack.

She and her colleagues pinpointed Fstl1, a protein secreted by the epicardium, as a growth factor for cardiomyocytes. Not only did this protein kick-start the proliferation of cardiomyocytes in petri dishes, but the researchers were surprised to find that it was missing from damaged epicardial tissue following heart attacks in humans.

> "This finding opens the door to a completely revolutionary treatment."

Reintroducing lost protein

The researchers set out to reintroduce the protein back into the damaged epicardial tissue of mice and pigs that had suffered a heart attack. They did this by suturing a bioengineered patch, loaded with Fstl1, to the damaged tissue. The patches were made of natural material known as collagen that was structurally modified to mimic certain mechanical properties of the epicardium.

Because the patches are made of acellular collagen, meaning they contain no cells, recipients do not need immunosuppressive drugs to avoid rejection. With time, the collagen material gets absorbed into the organ. The researchers believe that the elasticity of the material, which resembles that of the fetal heart, is key to providing a hospitable environment for muscle regrowth.

Within two to four weeks of receiving the patch, heart muscle cells began to proliferate and the animals progressively recovered heart function. "Many were so sick prior to getting the patch that they would have been candidates for heart transplantation," Serpooshan said. The hope is that a similar procedure could eventually be used in human heart-attack patients who suffer severe heart damage.

The work integrated the efforts of multiple labs around the world, including labs at the Sanford Burnham Prebys Medical Discovery Institute in San Diego, UC-San Diego, Boston University School of Medicine, Imperial College London and Shanghai Institutes for Biological Sciences.

Stanford has a patent on the patch, and Ruiz-Lozano is chief scientific officer at Epikabio Inc., which has an exclusive option to license this technology.

Other Stanford-affiliated authors of the study are Marta Diez-Cunado, PhD, postdoctoral scholar; surgeon Mingming Zhao, MD; Giovanni Fajardo, MD, research associate; Andrew Wang, PhD, postdoctoral scholar; Yuka Matsuura, research associate; Morteza Mahmoudi, visiting scholar; Manish Butte, MD, PhD, assistant professor of pediatrics; Phillip Yang, MD, associate professor of cardiovascular medicine; and Daniel Bernstein, MD, professor of pediatric cardiology.

This study was funded by National Institutes of Health, the California Institute for Regenerative Medicine and Stanford Bio-X.

Stanford's Department of Pediatrics also supported the work. **ISM**

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STANFORD MEDICINE

Early-career awards fast track scientist's studies on poverty, health

By Kris Newby

Rita Hamad of Austin, Texas, had just finished her third year as an undergraduate studying economics at Harvard University when she had a change of heart.

"I wanted less emphasis on corporate moneymaking and more on the economics of poverty alleviation," said Hamad.

So she switched her major to chemistry and spent the next fall working in the HIV/AIDS department of the World Health Organization in Geneva. The internship propelled her career into a new direction.

"I saw how people with debilitating illnesses suffer in health-care systems globally, and I decided that I'd like to research ways to help these vulnerable populations," said Hamad, who went on to earn a medical degree and master's degree in public health from the UC Berkeley-UC San Francisco Joint Medical Program. Now, she's working to build a research career that studies poverty as if it were a disease. Applying cutting-edge analytical techniques, she's trying to better understand how the social, psychological, political, cultural and economic circumstances of those living in poverty influence their chances for a healthy life.

As she juggles her duties as a clinician and an instructor in family medicine at Stanford, she is closer than ever to her goal of a research career, with the help of an early-career program — the KL2 mentored career development award — and two pilot grants. Both the program and pilot grants are administered by Spectrum, the Stanford Center for Clinical and Translational Research and Education, which is funded by the National Center for Advancing Translational Sciences at the National Institutes of Health.

> Hamad is working to build a research career that studies poverty as if it were a disease.

Springboards to NIH career grants

Hamad, 33, has chosen to enter research at a time when it is extremely difficult for young investigators to win career-sustaining grants from the NIH, the largest funder of biomedical research in the United States. More researchers than ever are competing for "10 years of essentially flat budgets eroded by the effects of inflation," according to Sally Rockey, deputy director for extramural research at the NIH. What's more, prestigious R01 grants tend to be given to older researchers with proven track records over young investigators with riskier, but more promising, ideas.

"The average age of first-time, R01-funded investigators who have PhDs remains 42, even after seven years of policies at NIH to increase the numbers of new and early-stage investigators," said Robin Barr, director of the NIH's Division of Extramural Activities, in a recent editorial on the NIH website.

The KL2 program offers young physician-scientists like Hamad a competitive edge. First, it provides 75-percent salary support for a minimum of two years, enabling physicians to reduce their hours in the clinic and spend more time on their own research projects. KL2 awardees attend weekly sessions with clinical and methodological research mentors. In these sessions, they also receive advice on study design, grant-proposal writing, data collection and analytics, and on navigating the Stanford research environment. Second, the program offers participants full tuition support for advanced training in disciplines such as biostatistics, epidemiology, study design, genetics, bioinformatics and bioethics.

"I love the tuition support in the KL2 program," said Hamad, who is using it to complete a PhD in epidemiology and learn advanced statistical techniques. These skills will help her in the extraction and interpretation of the many variables in large health, economic and insurance data sets, enabling her to better identify the cause-and-effect relationships between poverty and health.

"Being able to support the careers and see the growth in young investigators like Rita is one of the great pleasures of leading a program like this," said Steven Goodman, MD, MHS, PhD, professor of medicine and of health research and policy, chief of the Division of Epidemiology and director of the Spectrum KL2 program. "And this year, trainees will start to see many more epidemiology course offerings and a much larger pool of research mentors."

To help young investigators like Hamad, Spectrum also offers grants of up to $50,000 to interdisciplinary teams with novel ideas for improving human health. These one-year studies often generate proof-of-hypothesis data that may later be used in applications for larger NIH grants.

NORBERT VON DER GROEBEN

As a young physician-researcher, Rita Hamad is advancing her career with the help of a program and grants administered by Spectrum.

This year, Hamad is the lead investigator on two of these study grants. One is on the long-term effects of neighborhood environments on health outcomes using Denmark's nationwide electronic health database. The other is exploring the impacts of education policy on population health in the United States.

Evidence for policymakers

Hamad's research career is also receiving a boost from the expansion of the Stanford Center for Population Health Sciences. The center, supported in part by Spectrum, is serving as a collaborative hub for population-based research such as hers, bringing together researchers from across the university.

The center soon will provide centralized access to a variety of U.S. and international health databases, as well as to several large insurance-claims data sets from public and private insurers. The center's leadership plans to make these data sets available at a low cost to Stanford trainees and investigators. And center staff will provide technical support to help users get access to the data needed to answer their research questions.

Hamad collaborated with Mark Cullen, MD, the center's director, on a study that examined the impacts of job insecurity on health-care utilization by a large cohort of employees of a manufacturing firm during the recession of 2007-09. Their findings will be published in *Health Services Research* this fall.

"Understanding the nuanced relationships between life experiences and health requires a new focus for research and a new breed of researcher who, like Dr. Hamad, brings skills from health and the social sciences," Cullen said. "Answering these real-life questions lies at the very heart of the agenda for our population health sciences center."

Another study of Hamad's will be published this fall in the *American Journal of Epidemiology.* In this collaboration with David Rehkopf, ScD, MPH, assistant professor of medicine, she explored the impact of the earned-income tax credit on child health in the United States. Such research is critical for informing policy on safety-net programs, especially during a time of strained state and federal budgets. For example, the California legislature decided this year to begin its own earned-income tax credit program because of research like Hamad's.

With the help of these support programs, Hamad, in just two years, has produced actionable data that can be used by policymakers and by health-care providers to improve the overall health of populations.

"It has been so wonderful to be supported by Spectrum's generous resources as I launch my career as a physician-researcher here at Stanford," Hamad said.

For more information on the KL2 and Spectrum pilot grant programs, go to http://spectrum.stanford.edu.

Pilot grant proposals are due Sept. 30. Applications for KL2 career awards will become available in November and are due March 1. ISM

Stanford Health Care president, CEO to step down at year's end

Stanford Health Care announced Sept. 24 that Amir Dan Rubin, president and chief executive officer, will leave at the end of this year to join UnitedHealth Group and its Optum organization as executive vice president.

Rubin became the president and CEO of Stanford Health Care in January 2011. During his tenure, the organization has achieved many important milestones. This year, *U.S. News & World Report* ranked Stanford Health Care the No. 1 hospital in California and in its Best Hospitals Honor Roll Top 15 in the nation. National Research Corporation also ranks Stanford Health Care as the most preferred hospital in its region, and it has achieved the best patient-experience rankings in the Bay Area, according to Medicare.

"Since my arrival, Amir Rubin has been a partner with me and Chris Dawes [president and CEO of Stanford Children's Health] in building Stanford Medicine's excellence in clinical care," said Lloyd Minor, MD, dean of the School of Medicine. "Amir's leadership has had a fundamental impact and helped build the widespread recognition that Stanford Medicine provides life-changing outcomes for our patients. I want to personally thank Amir for the substantial and transformational role he has played in making Stanford Medicine a world-class academic medical center, and for advancing our vision of leading the biomedical revolution in precision health."

Amir Dan Rubin

The new, state-of-the-art Stanford Hospital is under construction and scheduled to be completed in 2018. Additionally, Stanford Health Care has expanded its reach into the surrounding communities by affiliating with ValleyCare hospitals in the East Bay, opening the new Stanford Cancer Center South Bay in San Jose, and continuing to grow its outpatient network of care throughout the Bay Area.

> "I wish to share my heartfelt appreciation for the honor of having served Stanford Health Care as president and CEO."

Stanford Health Care continues to innovate in the provision of virtual care, including providing video visits and an innovative patient portal. Moreover, it has developed employer on-site clinics and new accountable care and health benefits offerings to support the provision of high-value care.

Through the support of generous donors, Stanford Health Care has expanded access to its level-1 trauma center and emergency department, supported its affiliated research and teaching programs, and advanced construction of the new Stanford Hospital.

In announcing his decision, Rubin said, "I wish to share my heartfelt appreciation for the honor of having served Stanford Health Care as president and CEO. It has been the privilege of a lifetime to work with such spectacular people dedicated to healing humanity, through science and compassion, one patient at a time. Words cannot express how incredible it has been to engage with colleagues and supporters who these past years have received Nobel Prizes, achieved nursing Magnet status and won numerous accolades."

"Stanford Health Care, with the contributions of the Stanford School of Medicine, has raised the bar for innovative, patient-centered care not only in California, but the nation," said John Levin, chair of Stanford Health Care's board of directors. "We are greatly appreciative of Amir's five years of energetic and passionate commitment to Stanford Medicine."

Rubin will be joining the nation's leading benefits and health services organization, UnitedHealth Group and its Optum organization, as executive vice president. "In my new role, I look forward to helping improve health and make the broader health-care system work better for everyone in this nation and around the world," said Rubin.

The board of directors announced that it has appointed a transition committee to begin the search for a new leader and to work with the management team at Stanford Health Care to support a seamless transition. ISM

Combination drug therapy shrinks pancreatic tumors in mice

By Krista Conger

A combination of two drugs, one already approved by the Food and Drug Administration, appears to be effective at shrinking pancreatic cancers in laboratory mice, according to a new study by researchers at the School of Medicine.

The drugs, which affect the structure and function of the cancer cell's DNA rather than the activity of its proteins, also slowed the growth of human lung cancer cells in mice. The study clarifies the potential of these types of drugs for treating diseases. The researchers hope to soon test the drug combination in humans with pancreatic cancer.

"Pancreatic cancer is one of the most deadly of all human cancers, and its incidence is increasing," said Julien Sage, PhD, associate professor of pediatrics and of genetics. "Nearly always the cause of the disease seems to be a mutation in a gene called KRAS, which makes a protein that is essential for many cellular functions. Although this protein, and others that work with it in the Ras pathway, would appear to be a perfect target for therapy, drugs that block their effect often have severe side effects that limit their effectiveness. So we decided to investigate drugs that affect the DNA rather than the proteins."

Sage shares senior authorship of the study, which was published online Sept. 21 in *Nature Medicine*, with Jens Siveke, MD, professor of medicine at the Technical University of Munich. Stanford postdoctoral scholar Pawel Mazur, PhD, shares lead authorship with postdoctoral scholar Alexander Herner, MD, of TUM.

Usually, most DNA in a cell is tightly wound around special packaging proteins called histones, like thread on a spool. In this state, the genes on the DNA are inaccessible to a cell's protein-making machinery. But chemical tags called acetyl groups induce histones to relax their grip and allow access to the DNA; to permit gene expression, the cell carefully coordinates the addition and removal of these tags to histones. This expression is facilitated by special proteins that can read a histone's acetyl status. This kind of modification of DNA-associated proteins, as well as of other tags on the DNA itself, helps a cell produce the right proteins at the right times in development and allows it to respond nimbly to its environment. These dynamic modifications are called epigenetics, and they've been shown to be increasingly important in many disease processes.

Tinkering with cells' epigenetics

Mazur and Herner wondered whether tinkering with a cell's epigenetics could control the growth and proliferation of pancreatic cancer cells without causing many of the deleterious side effects seen by drugs that inhibit protein members of the Ras pathway, a cellular signaling cascade that controls cell growth, development and survival.

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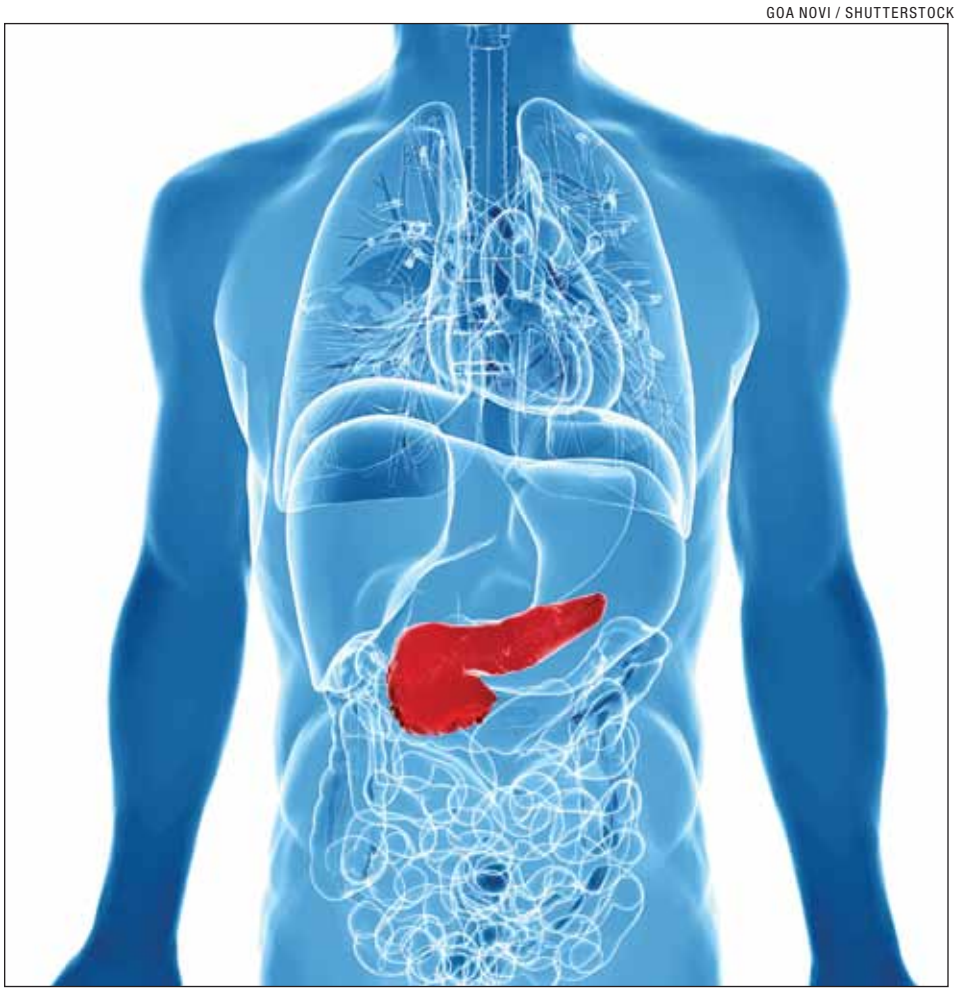

When administered together, two drugs have been found to effectively block the growth of pancreatic tumor cells in mice. Researchers hope the drugs can soon be tested in humans with pancreatic cancer.

They started by investigating the effect of a small molecule they called JQ1 on the growth of human pancreatic tumor cells in a laboratory dish. JQ1 inhibits a family of proteins responsible for sensing acetyl groups on histones. The researchers found that the cells treated with JQ1 grew more slowly and displayed fewer cancerous traits. The molecule was also able to significantly shrink established pancreatic tumors in mice with the disease. However, it did not significantly affect the animals' overall likelihood of survival.

> **"We decided to investigate drugs that affect the DNA rather than the proteins."**

When the researchers investigated the effect of JQ1 treatment more thoroughly, they found that it inhibited the expression of a gene called Myc, which is known to be associated with many types of cancers, including pancreatic cancer. It also decreased the levels of inflammatory molecules known to be involved in the development of pancreatic cancer.

"The effect of JQ1 treatment was OK, but not amazing," said Sage, who is also a member of the Stanford Cancer Institute. "So Pawel had the idea to look for drug combinations that might have a synergistic effect."

Mazur tried eight drugs in combination with JQ1, each targeting either a known cancer-associated pathway or a step involved in epigenetics.

'Strong synergistic effect'

"It happened that the drug that worked best was another epigenetic drug called vorinostat," said Sage. "On its own, vorinostat didn't work very well, but when combined with JQ1 it showed a very strong synergistic effect in both the laboratory mice with pancreatic cancer and in pancreatic cancer cells from people with the disease."

Vorinostat works by inhibiting a family of proteins that remove the acetyl groups from histones. It has been approved by the FDA for use in people with recurrent or difficult-to-treat cutaneous T cell lymphoma. When human pancreatic cancer cells were treated simultaneously with JQ1 and vorinostat, the cells grew more slowly and were more likely to die.

Mice with established pancreatic cancers treated with both of the drugs showed a marked reduction in tumor size and a significant increase in overall survival time. Their tumors showed no signs of developing a resistance to the treatment, and the mice did not develop any noticeable side effects.

Finally, Mazur tested the effect of the combination treatment on a type of lung cancer that, like pancreatic cancer, is driven by mutations in KRAS. He found that together JQ1 and vorinostat also significantly increased the survival of mice with this cancer, called lung adenocarcinoma.

The researchers are now working to learn more about how JQ1 and vorinostat synergize on a molecular level. Mazur found that the combination treatment led to a significant increase in the production of a protein called p57 in the cancer cells. P57, also known as Kip2, blocks cells from dividing. Mutations in p57 have been implicated in cancer development in humans.

He then used a unique genome-editing technique called CRISPR to eliminate the expression of p57 in the pancreas of an adult mouse and showed that, in its absence, treatment with JQ1 and vorinostat was much less successful at inducing cell death.

Mazur and Sage said they hope this newly identified combination treatment can be tested in the clinic within the next five years. The fact that vorinostat is already approved for use in humans may speed the process, they believe. They're also interested in learning whether the treatment may be effective in other types of conditions.

"We don't know yet whether this synergistic effect is specific to cancers driven by mutations in KRAS or if it could also work on other types of cancers," Sage said.

Other Stanford-affiliated authors of the study are postdoctoral scholar Stephano Mello, PhD; medical student Timo Kuschma; research associate Shane Lofgren; laboratory manager Leanne Sayles; assistant professor of medicine Purvesh Khatri, PhD; associate professor of pediatrics Alejandro Sweet-Cordero, PhD; and professor of radiation oncology Laura Attardi, PhD.

The research was supported by the German Research Foundation, the European Union's Seventh Framework Program, the German Cancer Consortium, the Tobacco-Related Disease Research Program, a Stanford Dean's Fellowship, the Stanford Child Health Research Institute and the Lucile Packard Foundation for Children's Health.

Stanford's departments of Pediatrics and of Genetics also supported the work.

ISM

Stanford Medicine community invited to Oct. 12 town hall meeting on precision health

The Stanford Medicine community is invited to a colloquium titled "Precision Health in Action" from 11 a.m. to noon Oct. 12 in Berg Hall at the Li Ka Shing Center for Learning and Knowledge. Light snacks will be served after.

The event will be hosted by Lloyd Minor, MD, dean of the School of Medicine; Amir Dan Rubin, president and CEO of Stanford Health Care; and Christopher Dawes, president and CEO of Lucile Packard Children's Hospital Stanford.

Precision health places primary emphasis on prediction and prevention, rather than on simply treating diseases once they appear. A group of faculty members will discuss the significance of this approach and how their work is helping to advance it during a panel discussion moderated by Minor. The panelists are:

MARK CULLEN, MD, professor of medicine, chief of the Division of General Medical Disciplines and director of the Stanford Center for Population Health Sciences.

VJ PERIYAKOIL, MD, clinical associate professor of geriatrics and director of the Stanford Palliative Care Education and Training Program and the Stanford Letter Project.

MICHAEL SNYDER, MD, professor and chair of genetics and director of the Stanford Center for Genomics and Personalized Medicine.

Community members who plan to attend the town hall should RSVP by today at https://stanfordmedicine.qualtrics.com/SE/?SID=SV_bJTED5OLndI0zid. They may also pose questions for the Stanford Medicine leadership through the Web page.

For more information about precision health, visit https://med.stanford.edu/precision-health.html. **ISM**

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5 QUESTIONS

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

Euan Ashley on diagnosing the undiagnosable

The National Institutes of Health's Undiagnosed Diseases Network launched Sept. 16, and Euan Ashley, MRCP, DPhil, associate professor of cardiovascular medicine and of genetics at the School of Medicine, is co-chair of the UDN steering committee.

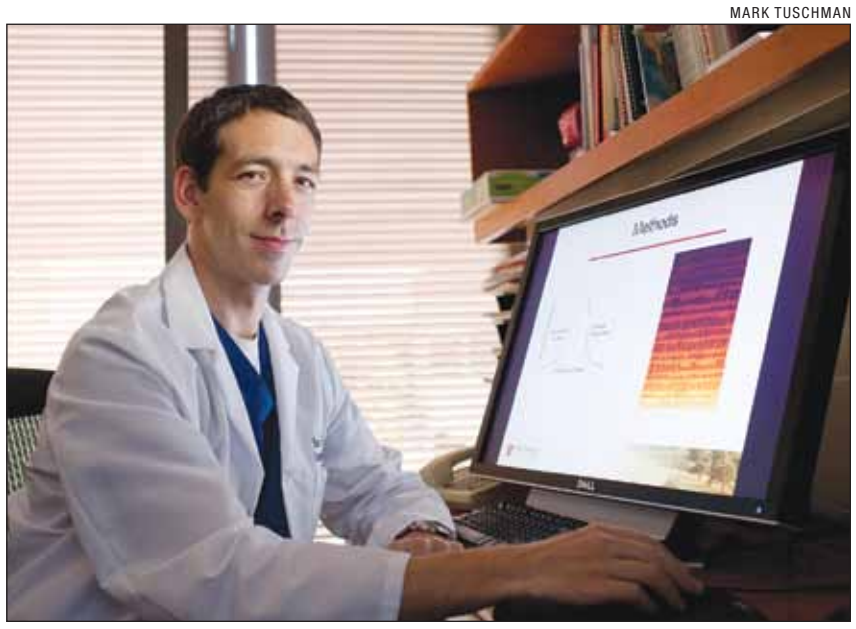
The network, which seeks to provide answers for patients with mysterious conditions and to advance medical knowledge of both rare and common diseases, is an outgrowth of a smaller NIH program begun in 2008 called the Undiagnosed Disease Program. The new, expanded network inaugurates an online application gateway for patients, called the UDN Gateway, that will harness the expertise of physicians at seven medical centers across the United States, while integrating patient access, patient consent forms and patient genome and other data through a single Internet portal. Within two years, the UDN expects to handle 250 patients per year. Information about the network is available at http://www.genome.gov/27562472.

Ashley, who co-directs Stanford's clinical genomics service and the Center for Inherited Cardiovascular Disease, is interested in precision health — the new approach to health that more precisely defines diseases to better understand them, predicts which individuals or populations are at risk and seeks to prevent disease.

After joining the School of Medicine faculty in 2006, Ashley developed a way to estimate a healthy patient's risk of disease based not only on traditional metrics, such as age, gender and family history, but by digging into the patient's genome. In 2013, Ashley was recognized by the White House Office of Science and Technology Policy for his contributions to personalized medicine. He is co-founder of Personalis Inc., a genetic diagnostics company.

In a recent interview with writer Jennie Dusheck, Ashley discussed the network's importance.

MARK TUSCHMAN



Euan Ashley has been named co-chair of the Undiagnosed Diseases Network steering committee. The UDN seeks to provide answers for patients with mysterious conditions and to advance medical knowledge of both rare and common diseases.

1 You've written that the Undiagnosed Disease Network offers hope of ending the "diagnostic odyssey" of patients and their families. What is that odyssey like?

ASHLEY: We are used to devastating illness in medicine, but there's a particular torment that comes from having an undiagnosed illness. Of course, you have the symptoms and signs that any illness has, but just not knowing what it is — not having a name for it, not knowing what the course of it is likely to be, not knowing if you share this with any other people — is a severe form of torment.

And I think in many situations, these individuals and families — because such diseases often afflict children — visit doctor after doctor and are increasingly frustrated. They are spending more and more of their personal time. It's a financial strain and an emotional strain, and they're telling the story again and again and again. If they have the resources, they'll go to one of the major academic centers. But in many cases, there are no answers — sometimes for years. And meanwhile, they are accumulating an expensive electronic trail of test results.

2 How are patients selected to participate in the UDN?

ASHLEY: Generally, we'll focus on the families who are most likely to be helped. If there's clear evidence of a genetic condition, we have a greater chance of diagnosing that. If multiple systems of the body are involved in a very unusual way, or if test results are far out of the range of normal values, those are clues we can use.

For example, if someone's hormone level is four times normal, that gives us a clue. The challenge with genetic data — and we'll have a full genome sequence on every single one of these patients, which is remarkable in itself — is not so much finding the needle in the haystack as finding the right needle in a whole pile of needles. We all have genetic variations. The question is, which of them are important? But if we have blood tests or other results that point us clearly in one direction, that can help us decide which genes to look at.

One criterion we *don't* use is the ability to pay. Anyone may apply regardless of where they live or what their income is or whether they have insurance, and they can be accepted into the network. Rare disease touches all sectors of society and certainly no one of us is immune.

3 What are the main advantages of the new, networked UDN over the original, smaller NIH program? Where is this taking us?

ASHLEY: The original NIH program was designed to test this hypothesis: Is it possible to take the most concentrated group of experts and the full availability of diagnostic tests and apply that to these very difficult cases? Will the best that medical science has to offer do better than these often-futile diagnostic odysseys? The answer to that was a resounding yes.

Bringing together the experts and the latest technology doesn't take us to 100 percent. Only 25 to 35 percent of cases get some kind of solution, but that's far better than without the program.

The new, seven-site network will increase capacity, so more patients can be evaluated. Secondly, not everyone can easily get to NIH, in Bethesda, Maryland. Adding six sites around the United States makes it easier for families to get to a clinic for expert evaluation. And we will also form a global network of such sites.

Another major effort has been to interconnect all the centers administratively, so they all operate as one. There's a single gateway where patients apply, and all the patients are distributed to the sites according to geography and site expertise.

If you have a common disease, you don't need to look very far for similar patients or doctors who know the disease. But with rare diseases, just adding one more patient can double the information you have. When you find the second case of a rare disease, you really are in a new world in terms of understanding it. And with a network, the chances a patient will have access to an expert who has already seen the disease is much greater.

4 What are the benefits of UDN — to patients, clinicians and researchers?

ASHLEY: The network does more than diagnose patients. Of course, just having an answer is a huge psychological benefit to families. But we're not going to stop there. The whole point is to find a way to treat it. And the way to treat it is first of all to understand the disease pathway.

The network also helps patients connect with one another and act as their own advocates. Patients and families can use the network and the Internet to find others with similar conditions. The medical literature is terrible for making such connections because it doesn't reflect the thousands of patients who are never diagnosed. But Google and social networks work beautifully to help patient families find one another.

5 What proportion of patients with no diagnosis have a genetic disease versus some other kind of problem?

ASHLEY: Well, we don't know … ask me next year! Sometimes it's clear that the disease is genetic because four different family members all have the same disease. But if you have a kid with a new syndrome and the rest of the family is fine, it's much harder to tell if it's genetic or not.

In situations where there aren't clear family clues, we definitely look toward the non-genetic explanations. In fact, when Stanford applied to participate in the UDN, we featured our expertise in immunology and infectious disease. Those are two of the major areas where we will work. Autoimmunity is a big frontier whose importance is only now becoming clear. And our ability to study the immune system is increasing dramatically.

We think of genomics as the tip of the spear for these new technologies and measurements. But just right behind that tip are high-throughput protein measurements and measures of immune system function, such as T cells and B cells. Our ability to use genomics to study infectious organisms is an exciting approach we hope to exploit at Stanford.

Looking at patients' environment is also going to be an important source of answers. Patients will fill out a comprehensive survey of standardized questions about their environment, but eventually we could make actual measurements of their environment. ISM

Child Health Research Institute names six faculty scholars

The Stanford Child Health Research Institute has awarded a total of $2.6 million to six faculty members through its its Faculty Scholars Program.

The endowed awards support junior and mid-level faculty who have university-tenure or medical-center line appointments, and whose research aims to improve the health of expectant mothers, embryos, fetuses, infants, children and adolescents.

Following are the names of the Tashia and John Morgridge Faculty Scholars in Pediatric Translational Medicine (2015-20) and their project titles:

CRISTINA ALVIRA, MD, assistant professor of pediatrics: "Essential physiologic roles for nuclear factor kappa B during lung development."

CATHERINE BLISH, MD, PhD, assistant professor of medicine: "Inflammatory pathways of pregnancy, viral infection and preterm birth."

DAVID CAMARILLO, PhD, assistant professor of bioengineering: "Investigating fiber tract strain rate as a cause of concussion."

Following are the names of the Arline and Pete Harman Faculty Scholars (2015-18) and their project titles:

GERALD GRANT, MD, associate professor of neurosurgery: "Molecular characterization of the pediatric blood-tumor barrier."

VIRGINIA WINN, MD, PhD, associate professor of obstetrics and gynecology: "Endothelial dysfunction in preeclampsia: Implications for immediate and long-term health outcomes for mothers and children."

Following is the name of the Bechtel Endowed Faculty Scholar in Pediatric Translational Medicine (2015-20) and her project title:

ANGELLE DESIREE LABEAUD, MD, MS, associate professor of pediatrics: "Integrated vector management as a strategy for reduced disease risk in a newly discovered region of dengue fever in Africa."

For more information about the institute's Faculty Scholars Program, visit http://chri.stanford.edu/research/funding_opportunities. ISM

Worms

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on school-aged children, as they are heavily affected by these diseases and can be easily treated in a school setting. The current guidelines call for annual or biennial treatment of children in high-prevalence areas.

But the latest study, a modeling analysis of four different communities in the Ivory Coast, suggests that more frequent, community-wide treatment programs are far more beneficial, both for children and adults, and are cost-effective.

"Most of the money spent on treating these diseases is focused on helping kids. But there are a lot of symptoms of disability in adults as well, and our results support the expansion of treatment to this adult population," said Nathan Lo, a third-year Stanford medical student and research associate. Moreover, treating adults benefits children by reducing the chances they will become re-infected, he said.

"If you only treat children, it might help them, but they often come home to neighbors, parents and teachers who may be infected, and the children can once again become infected," Lo said. "It's more effective for children if you treat them and the people around them."

Lo is lead author of the study, which was published online Sept. 15 in *The Lancet Global Health*.

Diseases prevalent in developing world

Jason Andrews, MD, the senior author of the study, said current global guidelines for mass drug administration for these infections have been based on expert opinion.

"Our approach was to look at this in a framework that considered the benefits of averting transmission along with morbidity, and to apply a rigorous cost-effectiveness model," said Andrews, an assistant professor of medicine at Stanford. "We found that when you do so, the results strongly support a much broader treatment scope than has been historically recommended."

Parasitic worm diseases are among the most prevalent ailments in the developing world. They include helminth infections, such as roundworm, whipworm and hookworm, which are primarily found in soil. These parasites can slither around in the colon and small intestine, where they produce eggs that are passed in human feces and then spread through soil or water supplies. They are typically contracted by people who walk barefoot in an affected area or drink contaminated food and water.

Schistosoma is the other major category of parasitic worms, which tend to accumulate in the blood vessels around the bladder and intestines. These worms reproduce in waterborne snails and can be contracted by swimming in freshwater lakes or rivers or walking through contaminated, muddy fields.

The parasites can be readily treated with drugs that are cheap and widely available. Albendazole, which costs about 3 cents a pill, can reduce the number of worm eggs from the soil-transmitted helminths by as much as 95 percent, Lo said. Praziquantel, which costs about 21 cents a pill to administer, can reduce egg production by 98 percent in cases of schistosomiasis, which is a disease caused by the *Schistosoma* worms, he said.

In the study, the researchers looked at the value of these drug therapies in different settings, using data from four communities in the Ivory Coast between March 1997 and September 2010. They simulated different treatment scenarios in the four 5,000-person communities, which had varying levels of risk for infection with soil-transmitted helminths and *Schistosoma* in the school-aged and adult populations.

DAVID WILLIAMS / ILLINOIS STATE UNIVERSITY

***Schistosoma* worms and other parasites can be treated with drugs that are cheap and widely available. Above, an adult male *Schistosoma* worm.**

Under current WHO treatment guidelines, three of the four communities would not have been eligible for annual treatment with both drugs because their risks were considered too low, the scientists noted.

The researchers looked at the impact when treatment was expanded to include preschool children and adults, and compared this to a scenario in which no treatment was offered. They also looked at variable timing of treatment — at intervals of three months, four months, six months, one year, two years, three years and four years.

They assumed a total treatment cost of 74 cents per person for school-based delivery and $1.74 per person for community-based delivery, with most of the expense involving drug delivery, staff and planning. Most drugs now are supplied in the developing world free of charge by pharmaceutical companies as part of their corporate global responsibility programs, though for purposes of the study, the researchers assumed the drugs were not donated, Lo said.

To calculate the impact of the various treatment scenarios, the researchers used a measurement known as the disability-adjusted life-year, a standard WHO measure to gauge the impact of disease.

Broader treatment would be cost-effective

They found that expanded, community-wide treatment programs were well worth the investment, with an incremental cost-effectiveness ratio of $167, meaning that it would cost $167 to save one year of a person's life. By the standard health economics yardstick applied in the developing world, a treatment is considered highly cost-effective if it has an incremental cost-effectiveness ratio of less than $1,000, Lo said. By contrast, in the United States, that same cost-effectiveness threshold is $50,000, he said.

Even if treatment costs were much more than estimated in the study — as much as 10 times greater — the researchers found the treatment programs were still highly cost-effective. They also showed that even when treatment programs didn't eliminate disease, they still had sufficient impact on health and disability to make them a worthwhile approach, Lo said.

"People may say, 'Look, we've done mass drug administration, and the disease is still there,'" Lo said. "What we are showing is that even if the prevalence hasn't changed, it's likely you are averting symptoms and improving quality of life and curing people for some period of time. And it's still highly cost-effective."

The scientists also reported that treating people more frequently — at six-month intervals — was a more valuable approach to controlling the diseases. For instance, current WHO guidelines recommend annual treatment among school-aged children when at least 50 percent of them have schistosomiasis. Even in areas where prevalence is lower, more frequent treatment would be cost-effective and beneficial, the study found.

The scientists also found that treating the diseases together, rather than through separate programs, is a more efficient way to control these infections. "Most of the expense involved is in delivery, going out into communities and treating people," Lo said. "So when these diseases are overlapping, as is often the case, it makes sense to give these pills together."

Given the results, the researchers strongly urge WHO to reconsider its treatment guidelines to better manage these scourges.

"Revised guidance is urgently needed to inform the scale-up of treatment programmes worldwide to avert the substantial disability created from soil-transmitted helminthiasis, schistosomiasis and other neglected tropical diseases," the study said.

The other Stanford-affiliated author on the study was Brian Blackburn, MD, clinical associate professor of medicine.

The study was funded by the Stanford School of Medicine's Medical Scholars Research Program and by the Mount Sinai Hospital-University Health Network AMO Innovation Fund.

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

Jaundice

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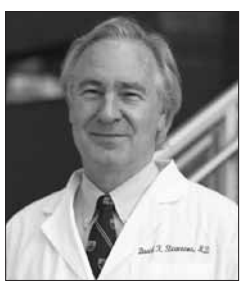
nancy and Newborn Services at Lucile Packard Children's Hospital Stanford.

Jaundice is extremely common in newborns, whose bodies need a few days after birth to develop the enzymes that enable excretion of bilirubin, a compound released during the normal breakdown of red blood cells. If too much bilirubin builds up in the blood, the skin and eyes acquire the hallmark yellow tinge of jaundice. Worse, high bilirubin levels can cause lasting brain damage or infant death.



David Stevenson

Filtering out ultraviolet, infrared rays

Phototherapy with lamps that emit blue wavelengths has been the most prevalent newborn jaundice treatment since the 1960s. But hospitals and health clinics in developing countries often lack the funds, expertise and reliable electricity needed to use the equipment.

The research team built and tested outdoor canopies that used commercially available plastic films to filter out sunburn-causing ultraviolet rays and infrared rays that could make infants overheat. Jaundice-treating blue wavelengths could pass through the filters. The team used different canopies for sunny and overcast days.

"Even with an overcast sky, we still get good light transmission and phototherapy," said study author Hendrik Vreman, PhD, a senior research scientist in pediatrics at Stanford, who developed, built and tested the canopies.

For a clinical trial, the scientists enrolled 447 infants with jaundice at a large, inner-city hospital in Lagos, Nigeria, of whom 224 were randomly assigned to treatment with filtered sunlight and 223 to conventional phototherapy. Infants received at least five hours per day of their assigned treatment, and were evaluated hourly during treatment for signs of hypothermia, overheating, dehydration and sunburn. Infants treated with filtered sunlight were held in their mothers' laps under the canopies and could breastfeed while receiving treatment.

New, conventional methods similarly effective

The two therapies worked similarly well: Filtered sunlight was effective on 93 percent of treatment days, and conventional phototherapy on 90 percent of treatment days. The treatments were also similarly safe.

The team is now studying greenhouse-like structures that incorporate the filters. Such structures will allow for filtered-sunlight therapy in locations that are windy, rainy or have colder climates than Nigeria's.

"We're excited that we can use our understanding of the biology of jaundice and adapt treatment to the local context of a developing country, and the resources that exist there," said Stevenson, who is a member of the Stanford Child Health Research Institute.

The study's lead author is Tina Slusher, MD, associate professor of pediatrics at the University of Minnesota. Another Stanford-affiliated author of the study is Ronald Wong, PhD, senior research scientist in pediatrics.

Researchers at the University of Minnesota, Massey Street Children's Hospital in Lagos and the University of California-San Diego also contributed to the study.

The study was funded by the Thrasher Research Fund and by the National Center for Advancing Translational Sciences of the National Institutes of Health.

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

COURTESY OF HENDRIK VREMAN

A next-generation sunlight-filtering structure on the grounds of Bowen University Teaching Hospital, Ogbomoso, Nigeria.

Diabetes

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cells, for example, produce insulin.

"In Type 1 diabetes, only the beta cells get destroyed," said Bollyky. Why this happens is poorly understood. But it's known that during the disorder's early, pre-symptomatic stage, pancreatic islets become inflamed — that is, they get infiltrated by immune cells. At first quiescent, these warrior cells at some point begin attacking beta cells, eventually destroying enough of them to effectively erase insulin output. By the time a person begins to manifest the disease's hallmark symptom, chronic hyperglycemia, some 90 percent of pancreatic beta cells have been killed off. Neither the cause of immune cells' initial infiltration of pancreatic islets nor the trigger for their transition from mere passive presence to active aggression is yet understood.

But the new study provides important clues.

In a 2014 study, Bollyky's team measured the levels of dozens of substances in the extracellular matrix of postmortem pancreatic tissue. One substance, called hyaluronan, was overly abundant near the pancreatic beta cells of people with Type 1 diabetes. But this was seen only in pancreatic tissue from patients who had been somewhat recently diagnosed, not patients who'd lived with the disease for decades.

Hyaluronan is usually present at trace concentrations in the extracellular matrix that pervades all tissues. But hyaluronan levels spike markedly at the site of an injury. "If you twist your ankle or stub your toe, that swelling you see afterwards is due to hyaluronan," Bollyky said. This substance is prone to soaking up water, causing fluid buildup in the injured region, a cardinal feature of inflammation.

Bollyky said the absence of increased hyaluronan in long-term patients' pancreatic islets didn't mean much, as these people's beta cells had long since bit the dust. But finding excessive deposits of hyaluronan near pancreatic beta cells in recent-onset cases was intriguing.

Curious, Bollyky and his colleagues sought to determine whether this association was incidental or whether hyaluronan's increased presence actually played any causal role. So, they employed a bioengineered strain of laboratory mouse whose immune system is guaranteed to attack its pancreatic beta cells. Essentially 100 percent of these mice eventually develop Type 1 diabetes, and always over about the same period of time, making it easy to study the effects of an experimental manipulation of the disease's progression.

The scientists also looked at another mouse strain often afflicted with a version of Type 1 diabetes that more closely parallels the human form of the disease. (These mice are tougher to study because only about half of them contract the disease, and they do so at variable rates.)

In both strains, Bollyky said, hyaluronan accumulated in pancreatic islets, but not in all of them — just in those where inflammatory immune cells had parked themselves. No excessive hyaluronan deposition was seen in the mice's heart, lung or liver tissue, consistent with the idea that the phenomenon occurs only in inflamed tissues. The islet-associated hyaluronan buildup eventually crescendoed and began tapering off, analogous to the investigators' observations in recent-onset versus long-established Type 1 diabetes cases in their earlier study of human tissue.

Preventing hyaluronan buildup

"We wondered what would happen if we prevented that buildup," Bollyky said. "And we knew a drug that does that." The drug was hymecromone, or 4-methylumbelliferone (4-MU for short). Prescribed in many European and Asian countries for painful, gallstone-associated spasms and sold by about 60 companies worldwide for research purposes, 4-MU inhibits hyaluronan synthesis. It is inexpensive, can be given orally and, over four decades of use, has what Bollyky described as an "extremely boring safety profile": a very low rate of associated adverse events. "It's even approved in Europe for kids," he said. (The Food and Drug Administration has not licensed 4-MU for any indication in the United States.)

In the mice used in the study, as in people, there's a window of time during which immune cells have infiltrated pancreatic islets but most beta cells are still intact. When the researchers initiated 4-MU treatment before the majority of the mice's beta cells had been wiped out, none of the mice developed hyperglycemia. Mice that didn't get 4-MU did. If mice stayed on a 4-MU regimen, they remained diabetes-free for at least a year. But if the regimen was stopped, they quickly became diabetic.

Tissue analysis revealed the continued presence of immune cells situated close to beta cells even in mice getting 4-MU, but the beta cells themselves seemed normal; the immune cells had evidently refrained from attacking them. The scientists also found reduced hyaluronan levels in 4-MU-treated mice's pancreatic islets, indicating that the drug was performing as expected.

Further experiments in the mice showed that hyaluronan prevents the induction of a class of regulatory immune cells, known as Tregs, whose job is to rein in their aggressive fellow immune cells and keep them from damaging healthy tissue. Bollyky likened Tregs' function to that of military police. In the absence of appropriate supervision, immune cells can get trigger-happy, he said. But by impeding hyaluronan synthesis, 4-MU re-establishes the induction of enough Tregs to prevent beta-cell destruction.

No drug has previously been shown to do this in humans, Bollyky said. His group has received preliminary funding from SPARK, a Stanford-based program devoted to fostering drug-development entrepreneurship, and is working with the FDA in preparation for a clinical trial of 4-MU for preventing Type 1 diabetes. The Stanford Office of Technology Licensing has applied for a use patent on associated intellectual property.

The study was performed in collaboration with scientists at the Benaroya Research Institute under the direction of matrix biologist Thomas Wight, PhD, whose group Bollyky was associated with when the work began. Funding for the study came from the Juvenile Diabetes Research Foundation and the National Institutes of Health.

Other Stanford-affiliated co-authors are postdoctoral scholar Vivekananda Sunkari, PhD, and basic life science research associates Gernot Kaber, PhD, and Hedwich Kuipers, PhD.

Stanford's Department of Medicine also supported the work. **ISM**

C. difficile

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Matthew Bogyo, PhD, professor of pathology and of microbiology and immunology. Lead authorship of the study is shared by Kristina Bender, PhD, a former postdoctoral scholar in Bogyo's lab, and Megan Garland, a student in the Medical Scientist Training Program.

"Unlike antibiotics — which are both the front-line treatment for *C. difficile* infection and, paradoxically, possibly its chief cause — the drug didn't kill the bacteria," Bogyo said. Instead, it disabled a toxin *C. difficile* produces, preventing intestinal damage and inflammation and allowing the gut to be repopulated by healthy bacteria that had been decimated by earlier rounds of antibiotic treatment, as well as by *C. difficile*-induced intestinal changes.

Infection often recurs

About one in 20 people, and possibly many more, harbor *C. difficile* in their gut, said study co-author Justin Sonnenburg, PhD, professor of microbiology and immunology, who has conducted pioneering research on the trillions of microbes constituting our intestinal ecosystems. Usually, the pathogen causes no harm, he said. But in those with immune systems weakened by age, chemotherapy or antibiotics that wipe out their "lawn" of beneficial intestinal microbes, *C. difficile* can get a foothold and cause changes that damage the gut. Plus, the pathogen can dehydrate and condense into shrunken, long-lived spores, making it difficult to get rid of. Most *C. difficile* infections originate in settings such as hospitals, clinics and assisted-living facilities.

Making matters worse, in a quarter of patients who get it, the infection recurs despite antibiotic treatment. When it does, antibiotics succeed in eliminating it only 25 percent of the time. About 7 percent of infected people die within 30 days of diagnosis.

Treatments for *C. difficile* infection include fecal transplants, which are often effective. But this treatment's long-term safety is difficult to ascertain, as a stool sample from any given donor contains its own mix of intestinal microbes, and some could have adverse effects on a recipient's health. "We don't have the tools to be able to screen for everything in a donor's stool," said Sonnenburg, noting that gut bacteria have been implicated in obesity, as well as in neurological changes.

Bogyo's group has extensive expertise in studying the activity of proteases, proteins capable of slicing up other proteins. A few years ago, co-author Aimee Shen, PhD, a postdoctoral scholar in Bogyo's lab who is now an assistant professor at the University of Vermont, found that *C. difficile*'s main toxins — secreted proteins known as Toxin A and Toxin B — contain nearly identical sections with protease activity. Moreover, she found, once the toxins are taken up by cells lining the mammalian gut, these sections become activated, setting in motion a chain of intracellular events that causes intestinal inflammation and tissue damage. This is a positive development for *C. difficile*, which thrives in the new environment it has created. But it's another story for myriad other bacterial species residing in the intestine — and disastrous for the infected individual's health, with symptoms ranging from severe diarrhea to intestinal lesions to death.

Matthew Bogyo

Bogyo's team has developed ways of conducting high-throughput screens of small molecules to speedily test their ability to inhibit or enhance the activity of proteases. They put this technique to work in search of small molecules that specifically blocked the *C. difficile* toxins' protease activity.

Helping the good guys

"We figured that a molecule that interfered with the pathogen's virulence could prevent inflammation and the disruption of colon tissue without making the intestinal environment inhospitable to normal, beneficial bacteria the way antibiotics do," said Bogyo. That would lay the groundwork for the "good guys" to make a comeback.

In the first of a series of experiments, the investigators separately incubated each of 120,000 different small molecules with the protease-containing piece of *C. difficile*'s primary toxin, Toxin B. Then, they added a toxin-activating factor and, using a test they'd devised in which protease activity is signaled by fluorescence, looked for drugs that shut down that activity. They identified hundreds of such substances, including a number of compounds with known biological activity.

Bogyo and his associates focused on a compound called ebselen because, in addition to having a strong inhibitory effect, ebselen also has been tested in clinical trials for chemotherapy-related hearing loss and for stroke. Preclinical testing provided evidence that ebselen is safe and tolerable, and it has shown no significant adverse effects in ensuing clinical trials.

Bogyo's team conducted another test to see how ebselen affected human cells. The team incubated the complete Toxin B molecule with the cells in the presence or absence of ebselen. When Toxin B was activated inside a cell, it induced internal damage that caused the cells to assume a rounded shape and die. Ebselen prevented that from happening.

Realizing they might have a potentially effective drug on their hands, Bogyo and his colleagues brought in Sonnenburg, whose lab is adept at using mouse models of *C. difficile* infection. The researchers incubated Toxin B in a solution either containing or lacking ebselen and injected it into mice, then monitored the animals for three days. All of the mice injected with ebselen-pretreated toxin survived, while all of the mice that received the untreated toxin were dead within 48 hours.

In a final set of studies, Bogyo and colleagues tested ebselen in a mouse model that more accurately mimics a clinical scenario in which high-risk individuals are treated prophylactically or at the first symptoms of recurrence. After rounds of multiple antibiotics, the researchers introduced a virulent, multidrug-resistant *C. difficile* strain and then began oral dosing with ebselen. They observed a nearly complete block of inflammation and damage to colon tissue as the result of ebselen treatment.

The upshot of this and other experiments conducted by Bogyo's team is that using ebselen to disable a toxin in *C. difficile* was enough to significantly reduce the clinical symptoms of the infection and block the persistent gut damage in mice.

Bogyo said he hopes to move the drug rapidly into clinical trials for treating *C. difficile* infection.

The study was funded by the National Institutes of Health; SPARK, a program whose goal is to help Stanford researchers with early-stage discoveries transition them to commercial application; and Stanford's Office of Technology Licensing, which has applied for a patent on the intellectual property associated with the use of ebselen for treating *C. difficile*.

Other Stanford-affiliated co-authors of the study are postdoctoral scholars Andrew Hryckowian, PhD, Matthew Child, PhD, and Ehud Segal, PhD; PhD students Jessica Ferreyra and Aaron Puri; life science research professional Steven Higginbottom; David Solow-Cordero, PhD, director of the High Throughput Bioscience Center in the Department of Chemical and Systems Biology; and Niaz Banaei, MD, associate professor of pathology and of infectious diseases.

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

Playwright, actress Anna Deavere Smith to give Jonathan J. King Lecture on Oct. 6

Playwright and actress Anna Deavere Smith will deliver the 25th annual Jonathan J. King Lecture at 5:30 p.m. Oct. 6 at the Li Ka Shing Center for Learning and Knowledge.

Smith's lecture, titled "Health Care: The Human Story," is free and open to the public.

A recipient of the prestigious MacArthur Foundation Fellowship and the National Humanities Medal, Smith is credited with creating a new form of theater: solo documentaries in which she portrays multiple characters to illuminate complex social issues. These plays include *Twilight: Los Angeles,* about the 1992 riots following the Rodney King verdict; *House Arrest,* about the relationship between the press and the presidency; and *Let Me Down Easy,* about health care and the human body. Smith is perhaps best known to the American public for her television roles as Nancy McNally on *The West Wing* and Gloria Akalitus on *Nurse Jackie.* A former Stanford drama professor, she now teaches at New York University's Tisch School of the Arts.

The endowed lectureship was established in 1991 to bring attention to the importance of compassionate and humane care for all patients. It honors Jonathan King, who earned a master's degree and PhD in computer science at Stanford and who became an advocate for patients' rights after his diagnosis of cancer in 1989.

The Center for Biomedical Ethics sponsors the annual event. More information is available at http://bioethics.stanford.edu/events/king. **ISM**

OF NOTE

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

VICTOR CARRION, MD, professor of psychiatry and behavioral sciences, received a 2015 Excellence in Healthcare Award from the *Silicon Valley Business Journal* for his research on anxiety and mood disorders in children and teenagers.

STEVEN GOODMAN, MD, MHS, PhD, professor of medicine and of health research and policy, associate dean for clinical and translational research and co-founder and co-director of the Meta-Research Innovation Center at Stanford, has been named the 2016 Spinoza Chair in Medicine at the University of Amsterdam. Goodman will be in residence at the university for a week next May giving master classes on the foundation of scientific and statistical reasoning. He also will give a lecture on the causes of and cures for the current crisis in research reproducibility. The chair is named for the Enlightenment philosopher Baruch Spinoza.

FRANK LONGO, MD, PhD, the George E. and Lucy Becker Professor in Medicine and professor and chair of neurology and neurological sciences, has been named the inaugural winner of the Melvin R. Goodes Prize for Excellence in Alzheimer's Drug Discovery by the Alzheimer's Drug Discovery Foundation. Longo and his colleagues developed a way to identify and develop oral drugs that mimic the function of normal brain proteins that protect nerve cells. One of their experimental medications is now in clinical trials. Longo will receive $150,000 to support research to develop a second Alzheimer's drug candidate.

MARIA-GRAZIA RONCAROLO, MD, the George D. Smith Professor and professor of pediatrics and of medicine, and **SHERRI SPUNT**, MD, MBA, the Endowed Professor in Pediatric Cancer and professor of pediatrics, have been awarded a 2015 infrastructure grant from Alex's Lemonade Stand Foundation. The award provides $625,000 over five years to support phase 1 and 2 childhood cancer clinical trials. The grants are designed to support projects that have been deemed highly important but have not received National Institutes of Health funding.

KULDEV SINGH, MD, MPH, professor of ophthalmology, will receive the American Academy of Ophthalmology's Life Achievement Honor Award at the academy's annual meeting in November. The award recognizes individuals for their contributions to the academy and to ophthalmology.

Victor Carrion

Steven Goodman

Frank Longo

Maria-Grazia Roncarlo

Sheri Spunt

Kudlev Singh

AVNESH THAKOR, MD, PhD, was appointed assistant professor of radiology, effective Aug. 1. He is trained in both pediatric and adult interventional radiology. His research focus is developing molecular-guided therapies. His current work addresses the design and development of new nanoparticle platforms for both diagnosis and therapy. **ISM**

Child Health Research Institute awards $1 million to five projects through Transdisciplinary Initiatives Program

The Stanford Child Health Research Institute has awarded $1 million to five research projects through its Transdisciplinary Initiatives Program awards.

The TIP program supports innovative, heterogeneous groups of scholars working to inform one another's perspective on a child- or maternal-health problem.

Teams comprise scientists from preclinical, clinical and basic science fields in the School of Medicine, as well as one or more faculty members from the School of Humanities and Sciences, School of Engineering, School of Business, School of Education, School of Law and School of Earth, Energy and Environmental Sciences. Following are the titles of the projects and their transdisciplinary teams:

• "IPSC-derived cardiomyocytes to determine mechanisms by which beta-cardiac myosin mutations cause pediatric hypertrophic cardiomyopathy." PI: Daniel Bernstein, MD, pediatrics. Co-PIs: Beth Pruitt, PhD, mechanical engineering; James Spudich, PhD, biochemistry; Alexander Dunn, PhD, chemical engineering.

• "Measuring children's physical activity and sleep in the real world: Processing and analysis of high-dimensional accelerometry data using statistical learning techniques." PI: Manisha Desai, PhD, medicine. Co-PIs: Thomas Robinson, MD, pediatrics; Clete Kushida, MD, PhD, psychiatry and behavioral sciences; Scott Delp, PhD, bioengineering, mechanical engineering; Ram Rajagopal, PhD, civil and environmental engineering; Dennis Wall, PhD, pediatrics.

"Cerebellar circuitry in development, learning and clinical conditions." PI: Heidi Feldman, MD, PhD, pediatrics. Co-PIs: Brian Wandell, PhD, psychology; Bruce McCandliss, PhD, education; Kristen Yeom, MD, radiology.

"The NSD2 methyltransferase in pediatric ALL." PI: Or Gozani, MD, PhD, biology. Co-PIs: Julien Sage, PhD, pediatrics, genetics; Justin Dubois, PhD, chemistry; Norman Lacayo, MD, pediatrics.

"The role of ALDH2 genetic variation and aldehyde metabolism in hematopoietic stem cell biology and the pathogenesis of bone marrow failure." PI: Kenneth Weinberg, MD, pediatrics. Co-PIs: Daria Mochly-Rosen, PhD, chemical and systems biology; Eric Kool, PhD, chemistry; Matthew Porteus, MD, PhD, pediatrics.

For more information about the institute's Transdisciplinary Initiatives Programs, visit http://chri.stanford.edu/research/funding_opportunities. **ISM**

St. Baldrick's Foundation awards four researchers grants totaling more than $500,000 for projects on pediatric cancer

Four School of Medicine researchers have received awards totaling $510,000 from the St. Baldrick's Foundation to support separate research projects on pediatric cancer.

Avanthi Shah

Eric Sweet-Cordero

KARA DAVIS, DO, an instructor of pediatric hematology and oncology, received $115,000 to fund an additional year of her NetApp St. Baldrick's Scholar award. The previous funding helped Davis and her team identify features of cancer cells that put a patient at higher risk for relapse of the disease. Her project investigates how communication in cancer cells differs between children who are cured of acute lymphoblastic leukemia and those whose disease relapses.

KATHLEEN SAKAMOTO, MD, PhD, the Shelagh Galligan Professor in the School of Medicine and professor of pediatric hematology and oncology, received an award of $100,000 to study the role of a protein in the development of acute myeloid leukemia, an aggressive form of childhood leukemia.

AVANTHI SHAH, MD, a postdoctoral scholar in hematology and oncology, was named a Sweet Caroline St. Baldrick's Fellow. Shah received $195,000 to fund her efforts to design a tool to detect tumor-specific genetic alterations in the blood of pediatric sarcoma patients. She hopes this test could serve as a better way to measure tumor size and response to treatment than current imaging methods.

Kara Davis

Kathleen Sakamoto

ERIC SWEET-CORDERO, MD, associate professor of pediatric hematology and oncology, received the $100,000 Team Clarkie St. Baldrick's Research Grant for research into how a DNA mutation leads to a rare bone cancer known as Ewing's sarcoma. **ISM**