Researchers at the School of Medicine have launched a first-of-its-kind iPhone app as an easy-to-use research tool that enables users to help advance the understanding of the health of the human heart.

The MyHeart Counts app collects data about physical activity and cardiac risk factors for Stanford scientists studying the prevention and treatment of heart disease.

The free app uses the new ResearchKit framework announced March 9 by Apple, which gives users a simple way to participate in the study, complete tasks and answer surveys from their iPhones. The app will deliver a comprehensive assessment of each user’s heart health and provide information on how to improve it. In the future, it will also be used to study various methods — designed to be both easy and fun — for using smartphones and other wearable devices to enhance heart-healthy habits.

“We are looking for everyone who is curious as to how healthy their heart is to download this app,” said Alan Yeung, MD, the Li Ka Shing Professor of Cardiovascular Medicine at Stanford. “Users will be able to see their activity and fitness levels, and their heart age. We’ll also be able to study what motivates people to improve their heart health.”

MyHeart Counts can be downloaded from the App Store. More information about the app is available at https://myheartscounts.stanford.edu.

So far, about 28,000 people have consented to participate in the study.

How is my heart?

Heart disease is the leading cause of death in the United States and around the world. It’s responsible for one in four deaths, according to the U.S. Centers for Disease Control and Prevention. A healthy lifestyle has been shown to improve one’s “heart age.”

Centuries-old DNA helps identify origins of slaves who died in Caribbean

By Krista Conger

More than 300 years ago, three African-born slaves died on the Caribbean island of Saint Martin. No written records memorialized their fate, and their names and precise ethnic background remained a mystery. For centuries, their skeletons were subjected to the hot, wet weather of the tropical island until they were unearthed in 2010 during a construction project in the Zoutsteeg area of the capital city of Philipsburg.

Now researchers at the School of Medicine and the University of Copenhagen have extracted and sequenced tiny bits of DNA remaining in the skeletons’ teeth. From this data, they were able to determine where in Africa the individuals likely lived before they were captured and enslaved.

The research marks the first time that scientists have been able to use such old, poorly preserved DNA to identify with high specificity the ethnic origins of long-dead individuals. The finding paves the way for a greater understanding of the patterns of the trans-Atlantic slave trade, and may transform the general practice of genealogical and historical research.

“Through the barbarism of the middle passage, millions of people were forcibly removed from Africa and brought to the Americas,’’ said Carlos Bustamante, PhD, professor of genetics at Stanford. “We have long sought to use DNA to understand who they were, where they came from, and who, today, shares DNA with those people taken aboard the ships. This project has taught us that we cannot only get ancient DNA from tropical samples, but that we can reliably identify their ancestry. This is incredibly exciting to us and opens the door to reclaiming history that is of such importance.’’

Researchers identify genetic basis of common skin disease

By Kimberlee D’Ardenne

Researchers at the School of Medicine, in collaboration with the genetics company 23andMe, have identified a genetic basis for rosacea, an incurable and poorly understood skin disease.

Treatment options for rosacea are not limited, but finding out what causes the disease could help scientists identify new targets for treatment and understand its link to other known diseases.

A paper describing the study’s findings was published online March 12 in the journal Investigative Dermatology. Rosacea causes skin on the face to redden and can result in acne-like bumps. “Rosacea is a very visible, inflammatory disease of the skin,” said Anne Lynn Chang, MD, lead author of the paper and an assistant professor of dermatology at Stanford. “It can lead to permanent scarring.”

According to the National Rosacea Society, the disease affects around 14 million Americans, or 5 percent of the population. In northern European countries, the prevalence is greater, at around 10 percent of the population. Rosacea is most visible in fair-skinned people but affects people of all skin types.

“It is one of the most common things we see in dermatology clinics that is incurable and not easily treatable,” Chang said.

Rosacea patients can also experience itching, stinging and burning sensations on the face. “Rosacea is a disease that causes skin on the face to redden and can result in acne-like bumps,” said Ravi Majeti, MD, PhD, an assistant professor of medicine and senior author of the paper. So finding potential treatments is particularly exciting.

Majeti and his colleagues made the key observation after collecting leukemia cells from a patient and trying to keep the cells alive in a culture plate. “We were throwing everything at them to help them survive,” said Majeti, who is also a member of the Stanford Cancer Center and the Stanford Institute for Stem Cell Biology and Regenerative Medicine.

Unusual metamorphosis

Postdoctoral scholar Scott McClellan, MD, PhD, a lead author of the paper, mentioned that some of the cancer cells in culture were changing shape and size into what looked like macrophages. Majeti concurred with that observation, but the reasons for the changed cells were a mystery until he researched an earlier research paper.
Basal cell carcinomas are uniquely dependent on the inappropriate activation of a cellular signaling cascade called the Hedgehog pathway. Blocking signaling along this pathway will stop the growth and spread of these tumors. The Hedgehog pathway plays a critical role in normal development. It’s also been found to be abnormal or active in many other cancers, including pancreatic, colon, lung and breast cancers, as well as in a type of brain cancer called medulloblastoma.

## Domino effect

Signaling cascades like the Hedgehog pathway can be imagined as a line of upright dominoes on the floor. Tapping one domino on the end causes a chain reaction down the line until all the dominos are toppled. In this way, signals from outside the cell are translated into the cell by the sequential activation of specific proteins until a particular action is accomplished. Vismodegib binds to and inactivates Smo, or Smoothened, a key protein in the Hedgehog pathway. In the domino analogy, Smo is one of the first tiles in the signaling chain. In 2012, vismodegib became the first Smo antagonist approved by the Food and Drug Administration to treat advanced and metastatic basal cell carcinoma. Smo is one of many members of a class of proteins called G-protein-coupled receptors. These receptors sit on the surface of the cell and translate external signals into inside-cell signals to control cellular processes like growth and division. However, it’s possible for the protein to develop mutations that allow it to escape the inhibitor. The researchers examined gene expression patterns in 44 vismodegib-resistant tumors and identified specific mutations in the protein that were resistant to treatment. They found that tumors with either class of mutations in the protein grew more quickly in the presence of vismodegib than did cells with unmutated Smo proteins. Furthermore, they found that physiotherapy works when the cell has been inactivated, or almost ‘on’ regardless of what signals it receives from upstream in the pathway. The researchers found four main classes of the protein in the resistant tumors.

Finally, the researchers grew both vismodegib-resistant tumor cells and their corresponding parental cells in the laboratory. They found that tumors with either class of mutations in the protein grew more quickly in the presence of vismodegib than did cells with unmutated Smo proteins. Furthermore, they found that physiotherapy works when the cell has been inactivated, or almost ‘on’ regardless of what signals it receives from upstream in the pathway.

The research was supported by the National Institutes of Health, the V Foundation, the American Skin Association, the Dermatologic Foundation. Oro and Chang are investigators in clinical trials sponsored by Genentech, Novartis and Eli Lily. Tang is a consultant for Genentech.

## Plans for personalized medicine

Oro and his colleagues are now using information about mutations in Smo as a way to guide therapy decisions for patients. “We’ve just started a personalized genomics clinic at the Stanford Cancer Institute,” said Oro. “Our expectation is that patients will come in, have their tumors sequenced and subsequently receive the best treatment for their types of cancer. Eventually we would like to do this for many types of skin cancers, including melanomas and squamous cell carcinomas.”

Other Stanford authors are postdoctoral scholars Ramon Whitson, PhD, Jiang Li, PhD, and Mina Ally, MD; Najib Kim, MD, assistant professor of pathology and of dermatology; technicians Geurim Kim and Melika Rezaee; and graduate student Catherine Yao.

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Stanford’s Department of Dermatology also supported the work.
Paul Kalanithi, neurosurgeon and writer, dies of cancer at 37

By Rosanne Spector

Stanford neurosurgeon Paul Kalanithi, MD, who wrote eloquently and movingly about facing mortality after being diagnosed with lung cancer, died of the disease March 4. He was 37.

Kalanithi, who had recently completed his neurosurgery residency at the Stanford University School of Medicine and become a first-time father, was an instructor in the Department of Neurosurgery and fellow at the Stanford Neurosciences Institute.

"We are all devastated by the tragedy of his sudden illness and untimely demise," said Gary Steinberg, MD, PhD, professor and chair of neurosurgery. "Paul spent seven years with us. He's very much part of our neurological family. It was a privilege to know him and work with him."

Kalanithi had recently completed his neurosurgery residency at the Stanford University School of Medicine and become a first-time father.

"Like a death in a closely knit family," Kalanithi's family wrote in a statement. "Kalanithi's words on transition from neurosurgeon to cancer patient to new dad touch millions of readers."

Construction services started operating again back in late 2013. At that time, I was Paul's shadow, learning and supporting him in his own role."

A reception will take place afterward at the Stanford School of Medicine's auditorium. A reception will take place afterward at the Stanford School of Medicine's auditorium. A reception will take place afterward at the Stanford School of Medicine's auditorium.

"We walked out of the operating room corridor together, toward the intensive care unit and I was telling Paul how much I appreciated being able to be with him and look at him in his satirical voice, 'You know I have lung cancer, right?' I looked up at him and said, 'I know,' and we both laughed, I said loud out, and I'll never forget what he said to me next. 'Don't forget what you do, and who you do it for. These are people who you can help, and you should not forget that.' Part of me, to the hero of all heroes.'"

Kalanithi is survived by his wife, Lucy Goddard Kalanithi, MD, FACP, a clinical instructor in medicine at Stanford, and by their baby; their three children — a son, Sujatha Kalanithi and A. Paul Kalanithi, MD; brothers, Suman Kalanithi, MD, and Jeewan Kalanithi; and Jeewan's wife, Emily Kalanithi, and their children, Eve and James.

A memorial service will take place at 2 p.m. March 31 at the Memorial Church on the Stanford campus. A reception will take place afterward at the Arrillaga Alumni Center at 526 Galvez St.

Gifts in Kalanithi's memory may be sent to the Dr. Paul Kalanithi Memorial Fund at Stanford University, Development Services, P.O. Box 20466, Stanford, CA, 94309-0466. Gifts can also be made online; instructions are available at http://paulkalanithi.com/donate. The fund will be used to recruit and retain top neuroscience faculty in the pursuit of a transformative education, a cause Kalanithi cared deeply about. 11W

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For accomplished surgeon, it’s all in a (long) day’s work

Boy’s 26 artery strictures repaired in one fell swoop

The first five years of life for Jordan Ervin were an endless cycle of illnesses and medical appointments, from Illinois all the way to California. He’d been poked, prodded, X-rayed and scanned, and even had his chest cut open, but none of it knocked the perpetual smile off his face.

“Jordan is such a champ,” said his mother, Seville Spearman, of DeKalb, Illinois. “He’s always been just a really happy kid.”

Happy then, but even happier now. That’s because years of incorrect diagnoses and treatments are now over.

Jordan’s path to recovery started when, just before his fifth birthday, in 2013, a developmental pediatrician put together all of Jordan’s problems and diagnosed him with Williams syndrome, a rare chromosomal disorder that affects just 1 in 10,000 people worldwide.

The disease brings a host of medical issues, including learning disabilities and severe heart defects. But there’s a silver lining: Individuals diagnosed with the rare disease also tend to be gregarious and extremely social.

Sounds like Jordan.

“Jordan’s personality made the process easier to deal with,” Spearman said. “He never fretted about going to doctor appointments. He was always excited about getting to see the nurses, the woman at the front desk and everyone else in the waiting room.”

That good cheer, combined with the work of Frank Hanley, MD, cardiothoracic surgeon at Lucile Packard Children’s Hospital Stanford and Stanford Children’s Health, means that Jordan’s big heart is now a properly working heart.

Hanley, who also is a professor of cardiothoracic surgery at the School of Medicine, is known for tackling some of the world’s toughest and most complex pediatric heart surgeries. He led an eight-hour surgery Dec. 10 to repair the stenoses, or narrowings, in pulmonary branch arteries of Jordan’s lungs.

It was a complicated case. The stenotic arteries caused severe pulmonary hypertension. In less-than-acute cases, in which there is only one area of stenosis near or at the pulmonary valve, doctors can perform a fairly simple surgical catheter procedure that uses a tiny balloon to expand the artery. But Jordan had multiple narrowings: 12 in his left lung and 14 in the right lung. The balloon technique is much less effective in this scenario, and no other surgical techniques have been developed to treat these stenoses.

So Jordan would need a different approach.

Unifocalization

That approach was developed by Hanley, who receives referrals from all over the world. He’s the pioneer of a one-stage, fix-all-the-defects surgery called unifocalization.

In the last few years, Hanley has taken many of the unifocalization techniques and used them for the pulmonary artery reconstruction on Williams syndrome patients like Jordan and other patients with similar heart defects.

To explain Jordan’s operation, Hanley likened the boy’s pulmonary arteries to a large tree, starting with a trunk that goes to larger branches and then smaller branches.

Normally, the blood flows freely through these branches, but in Jordan’s case, the narrowings in his arteries made it harder for the heart to pump blood to the lungs. This resulted in pulmonary hypertension, a life-threatening condition. In a case as severe as Jordan’s, Hanley said a balloon catheterization procedure isn’t effective.

So, in December’s intricate operation, Hanley and his team placed Jordan on life support and set to work fixing the 26 stenoses. As a result of the procedure, Jordan’s pulmonary hypertension was cured.

“It was another of the more than 540 unifocalization surgeries Hanley has performed at Lucile Packard Children’s Hospital for patients with complex pediatric heart defects, and with great outcomes.

Hanley taps his operating-room stamina and experience to use this innovative, one-stage approach to decrease overall hospital time for patients, reduce the number of times a heart must be stopped and repair problems before they worsen or become impossible to repair.

“We’re definitely on the leading edge of this kind of surgery,” said Hanley, who holds the Lawrence Crowley, MD, Endowed Professorship in Child Health. “Jordan is going to have perfectly normal life expectancy.”

“Joyfully stunned”

For Jordan’s parents, it was the best gift they could have hoped for. “We were joyfully stunned,” said Charles Spearman, Jordan’s stepfather, thankful for Hanley’s skill and thrilled that Jordan could return home for Christmas to share that famous smile.

A first-grader at Tyler Elementary in DeKalb, Jordan, 6, is about a year behind his peers developmentally, according to his mother. With heart surgery over and she and her husband can now focus on helping Jordan with other challenges that come with Williams syndrome, including social and gross motor skills.

“Things just seem brighter again,” said Seville. “There was just a dark cloud hanging over us. I was trying to figure out if my son would still be here in six months or for his next birthday. Now I know he will be here. Everything is back to normal, but I will never take anything for granted again.”

Diana Walsh is a freelance writer for Stanford Children’s Health.

Opening envelopes, medical students glimpse their futures

By Becky Bach

The day they’d been waiting for dawned overcast and cool. But for the medical students gathered March 20 inside the Li Ka Shing Center for Learning and Knowledge, the atmosphere was anything but chilly.

Decorated with red balloons and streamers, the second floor of the center was packed with 77 anxious, soon-to-be-graduating medical students, who were nervously crammed against the windows of the cavernous hall.

It was Match Day, when medical students gather March 20 in the morning in California — to open envelopes delivered at the same time — which was 9 a.m. in California.

“Match Day is a clear milestone,” said Dean for Medical Education at the School of Medicine. “This is such an important transition.”

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“Match Day is a clear milestone,” said Charles Spearman, MD, senior associate dean for medical education at the School of Medicine. “This is such an important transition.”

Thousands of medical students gathered at the same time — which was 9 a.m. in California — to open envelopes assigning them to a residency for the next three to seven years. Nationwide, 35,000 U.S. and international medical students applied for 27,000 residency positions this year, according to the American Association of Medical Colleges.

At Stanford, Match Day kicked off with coffee and socializing before Prober assigned the students to separate rooms, where they would receive the all-important envelopes.

Calling home

For Rowza Tur Rumm, the day was both exciting and nerve-wracking. “I think it’s hard to not have the jambalaya of those issues in our minds,” she said.

Clutching her red envelope and a cell phone, she dialed repeatedly, trying to get in touch with her parents in Bangladesh to share the moment with them.

Finally, with her father on the phone, Rumm slid open the envelope and a relieved grin spread across her face. “We’re definitely on the leading edge of this kind of surgery,” said Hanley, who holds the Lawrence Crowley, MD, Endowed Professorship in Child Health. “Jordan is going to have perfectly normal life expectancy.”

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**Newborn with heart defect saved after 13-hour operation**

Five-month-old Jackson Lane has a large scar that looks like a giant zipper down the center of his chest. His father, Andy Lane, a former coach for the Chicago White Sox, calls it a baseball scar. That’s because it looks a lot like the seams of a hardball, and underneath the scar is a heart that some thought would never beat on its own.

Elyse Lane was 20 weeks pregnant in June 2014 when she went for a routine fetal exam at her doctor’s office in Phoenix. She and Andy knew they were having a boy and, based on earlier appointments, they didn’t expect any surprises at this one. But the ultrasound found something wrong with the baby’s heart.

The first specialist they saw told them the baby was missing his pulmonary valve and that the pulmonary artery was massive. The artery was so large — 10 times the size it should have been — that it was significantly and dangerously impeding the growth of his airway. Their doctor told them they should consider terminating the pregnancy. Even if the baby made it to term — and the doctor cautioned that it wasn’t clear he would — he likely would need mechanical assistance to breathe.

### Tetralogy of Fallot

“When we asked what the outlook was and what his life expectancy might be, we got vague answers,” Elyse said. “It was heartbreaking.”

Two days later, they took a red-eye flight to Boston in search of second opinion. The specialists told them their baby had a condition called tetralogy of Fallot, a rare heart defect affecting blood and oxygen flow. They explained the fact that he was also missing his pulmonary valve and one of his pulmonary arteries was detached. But the doctor also gave the distraught parents their first glimpse of hope. The baby appeared strong and active in utero, and, if he made it to term, there was a surgeon who said he could do what he needed to give the baby a fighting chance.

The baby’s condition was complicated by the fact that he was also missing his pulmonary valve and that the pulmonary artery was massive. But he also gave the distraught parents their first glimpse of hope. Elyse said, “He’s already made it through the biggest challenge.”

### Renewed hope

With renewed hope, the Lanes now had to find a way to make it all happen. Andy turned to his baseball roots, and contacted the Baseball Assistance Team to see if the league-affiliated organization could assist with his looming medical, lodging and travel expenses. Just before the delivery, they learned that BAT had approved a significant grant to help them out. Following their philanthropy on social media, ballplayers who were friends of Andy, as well as their wives, also got involved, raising additional money for a Jackson fund that they created.

When Elyse was 36 weeks pregnant, she and Andy packed their bags and flew to California, expecting to spend the first four weeks of her pregnancy near Lucile Packard Children’s Hospital, where she would deliver the baby and Hanley would perform the surgery. Two days later, however, with the baby’s heart rate fluctuating wildly, doctors told the Lanes they needed to intervene.

Six-pound, 5-ounce Jackson Lane arrived at 10 p.m. Oct. 10 — nearly four weeks early — in a room filled with a team of 13 care providers, including doctors and nurses. Hanley arrived “worst-case scenario,” said Hanley — unable to breathe on his own. The enlarged pulmonary artery had severely compromised his bronchial tubes, and he was whisked away to the neonatal intensive care unit, where he was put on full life support.

“Jackson’s presentation was about as dramatic as you can get,” said Hanley, a professor of cardiothoracic surgery at the School of Medicine. “A case of this severity only comes around once every four or five years.” Hanley decided he’d need to perform the surgery soon because the baby couldn’t breathe on his own.

When he was just 5 days old, Jackson underwent a 13-hour operation that would save his life. Hanley and his team did a complex overhaul of Jackson’s heart: They inserted a pulmonary valve, reduced the size of Jackson’s right pulmonary artery, and enlarged his small, disconnected left pulmonary artery. Hanley also used an innovative and intricate procedure known as the LeCompte maneuver, which moved Jackson’s right and left pulmonary arteries from the back of the heart to the front. This gave his severely compromised bronchial tubes — which had been compressed by the enlarged artery — room to grow and remodel after surgery was over.

### Home in time for Christmas

“The benefit of moving it from behind to in front is that it takes the pressure off of the breathing tubes,” said Hanley, who is also the Lawrence Crowley, MD, endowed Professor in Child Health. It’s like driving a car; there are different routes you can take to get to the same destination. As long as the pulmonary arteries are re-routed in an unobstructed fashion, there is no downside to having it in front of the aorta.”

Incredibly, Jackson and his parents left the hospital just after Thanksgiving when their newborn was just 7 weeks old — four months earlier than anyone expected. Because of the surgery, Jackson’s airway tubes were wide open and he was breathing normally.

“Nobody in the hospital could believe how quickly he recovered,” said Elyse. “We are just so lucky that we found Dr. Hanley and that our son fought for his life.”

Jackson and his parents were thrilled to be home in time to celebrate his first Christmas. “We are so grateful. He’s our Christmas miracle,” said Andy.

“Other than a few tune-ups — he’ll need to have a heart valve replaced as he gets bigger — Jackson is now expected to have a long and normal life,” said Hanley.

When he was just 5 days old, Jackson Lane underwent a complex, 13-hour surgery to fix his heart. Other than a few tune-ups — he’ll need to have a heart valve replaced as he gets bigger — Jackson is now expected to have a long and normal life.

### Stories by Diana Walsh

“The purpose of this article is to help children from disadvantaged backgrounds,” said Hanley. “We are trying to reach underserved children in need, to help them get the care they need.”

### Match

**Match continued from page 4**

mer program in Bangladesh, where she helped implement and adapt a World Health Organization checklist of steps to reduce surgical complications.

Although at first she was too nervous to open the envelope, Mia Kanak also scored her first choice: a pediatrics residency at Boston Children’s Hospital. She was attracted to the program because it provides an opportunity to specialize in treating underserved children. Surrounded by her parents, who flew in from Tokyo, and her fiancé, from the East Coast, Kanak beamed: “I’m really excited.” She also has master’s degrees in public health and wants to help children from disadvantaged backgrounds.

“I feel like it’s very meaningful to take to care of a population that has a whole life ahead of them,” Kanak said.

### Crisscrossing the country

To nail these prestigious spots, both of the women and their peers, had to travel the country for several interviews: This year’s class completed more than 900, an average of 12 each. According to Neil Geandsheim, MD, MPH, associate dean for advising, the students and the residency program’s chief, the nonprofit National Resident Matching Program uses an algorithm to make the residency decisions.

Boston is a popular destination for Stanford medical students: 15 of them are bound for Massachusetts, but Stanford is also a favorite spot, with 19 students, or nearly a quarter of this year’s matriculates, staying put.

The most popular specialty was general medicine, with 12 students, followed closely by anesthesiology, with 10. With hugs all around and a few tears after the envelopes had all been opened, the students and their families gathered in Berg Hall, where glasses of champagne and a breakfast buffet awaited them.

“I want to say how proud all of us at Stanford Medicine are of your accomplishments today,” Lloyd Minor, MD, dean of the medical school, said. “And now, on behalf of everyone, a toast to your success, to the impact you’re going to have on the lives of so many people moving forward. Best wishes!”

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**Image:** Curtsey of The Lane Family

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**Image:** Curtsey of The Lane Family
Another month has passed since we last talked, and I still feel as if we've only just begun. Your recent post was wonderful, and I feel so grateful to have you as a friend. Your insights and encouragement have been invaluable to me.

As we continue our journey together, I want to share with you a few updates from my own life. I've been focusing on personal growth and self-care, and I've been exploring new interests that inspire me. I've also been spending more time outdoors, engaging in activities that bring me joy and help me connect with nature.

I hope you continue to find inspiration and solace in your writing. Your words have always had a special way of touching my heart. Keep writing, my dear friend, and know that you are always welcome to share your thoughts and experiences with me. Together, we can continue to support and uplift one another.

Warmest regards,

[Your Name]
Researchers unravel the secrets of shape-shifting bacteria

By Tom Abate and Chris Cesare

Sixty years ago, Nobel Prize-winning scientist Joshua Lederberg, PhD, first described a biological mystery. He showed how bacteria can lose their cell walls, take on new shapes and define their properties, potentially becoming less visible to the immune system, only to later revert to their original form and regain their full infectious potential.

Now, using time-lapse microscopy and other new techniques, K.C. Huang, PhD, professor of chemistry and biochemistry at Stanford, and colleagues here and at Princeton have created a forensic account of the ways bacteria pull off this shape-shifting trick.

In a paper published online July 23, 2014, in Molecular Microbiology, they describe the experiments, offering a step-by-step explanation of this curious behavior, and also shed light on one of the ways bacteria may develop antibiotic resistance. Huang is senior author of the paper, and Gabriel Billings, a graduate student in physics, is the lead author.

Huang’s team experimented with E. coli, one of the bacteria that can cause food poisoning. It’s also a favorite of lab oratory scientists, who have studied the organism for more than 100 years.

Their experiments focused on the rigid cell wall that gives E. coli its characteristi- cally rod-like shape.

On the wild road through life, the cell wall exists to protect the bacterium, but it also sends out signals that can alert our immune system to its presence of a potentially infectious intruder.

“A bacterial cell that’s growing is also constantly shedding parts of its cell wall, similar to how a kale shed its leaves very so often,” Huang said. “If a bacte- rium could get rid of its cell wall, it could effectively go undercover and avoid giv- ing off the signals that its infected host might use to try to mount a response against this invader.

When the rigid cell wall is dissolved, the bacteria become a shapeless blob called an L-form.

Follow the proteins

In the 1950s, Lederberg, who later founded the Genetics Department at Stanford, showed that E. coli could sur- vive for a time as L-forms and then re- cede its way back to the shape of the parent cell.

Huang’s team created a molecular- level understanding of the process of the parent cell, as described by Lederberg first observed. They used high-resolution microscopes to record time-lapse images of rod-shaped E. coli cells, which became shapeless L-forms and then reverting to rod-shaped again.

E. coli’s cell wall is knit together by proteins, a class of molecules that work together to perform many biological functions. “It’s like an orchestra in which several musicians play a part that is required to build the cell wall,” Huang said.

Previous research has shown that one protein, MreB, acts like the conductor, coordinating the efforts of several other proteins. But those studies focused on normal, rod-shaped E. coli. In this experi- ment, Huang’s team wanted to un- derstand how MreB factored into the process by which L-forms reappeared.

Huang suspected that as the con- ductor of this orchestra during regular growth, MreB might also be critical for rever- sion,” Huang said.

Growing L-forms

Under the tireless gaze of their time- lapse images, the researchers grew E. coli cells dosed with the antibiotic cefsulodin. A relative of penicillin, cefsulodin prevents E. coli from building cell walls.

The cefsulodin did not kill the E. coli, but as the cells divided and created succes- sive generations, the bacteria lost their rod-shaped walls and became bloblike L-forms.

The bioengineers let the L-forms grow and reproduce for a few hours before flushing out the cefsulodin. All the while they kept these blobs under microscopic surveillance. As the cells continued to re- produce, the time-lapse images showed that later generations slowly regained their rod-like shape.

That experiment documented the process of reversion to standard form. But it did not prove that MreB was essential for the process.

To demonstrate the link between the rod shape and MreB, the engineers per- formed a variation on the earlier experiment. After adding cefsulodin and letting the rod-shaped E. coli reproduce to be- come L-forms, they once again flushed out the antibiotic. But this time, they added a different antibiotic that specifically suppressed MreB function. Two hours later, the cell walls returned, as a rigid structure pro- tecting the cell.

But this time the cells were still shaped like blobs, and eventually all of these misshapen cells died.

“What we found was very stark: MreB was critical for this reversion process to occur, and without MreB what would happen is that the cells would just expand in size without any notion of their normal shape,” Huang said.

In addition to offering fundamental insights into how cells maintain their structures, Huang said the findings could help researchers understand how some bacteria adapt to stressful environments.

MreB is essential, but MreB and other toxins, including penicil- lin, target the cell wall. But bacteria can lose their cell wall and then later recover their shapes. This process of reversion might explain how bacteria develop resis- tance to antibiotics and establish chronic infections. The populations that survive in L-form and revert to their original shape may not be as susceptible to the next dose of antibiotics.

“Better understanding of cell wall construction could lead to better anti- biotic strategies,” Huang said. “And I’m always amazed to discover ways in which biology is programmed so robustly.”

Other Stanford authors of the paper are former postdoctoral scholar Tristan Usseglio-Viretta, PhD, and research scholar Samantha Desmarais, PhD.

The study was supported by National Science Foundation and National Insti- tutes of Health.

Tom Abate is the associate director of com- munications for the School of Engineering, and Chris Cesare is a former science- writing intern for the school.

Tom Abate and Chris Cesare

Skeletons continued from page 1

A new tool

The researchers used a technique recently devised in the Bustamante laboratory called whole-genome capture to isolate enough ancient DNA from the skeletons to sequence and analyze. In this way, they learned that one skeleton was that of a man who had likely belonged to a Bantu-speaking group in present-day Nigeria and Ghana.

Bustamante is co-author of a paper describing the research. It was published online March 9 in the Proceedings of the National Academy of Sciences. The lead authors of the study are Hannes Schroeder, PhD, a molecular anthropologist from the University of Co- penhagen, and Stanford postdoctoral scholar Maria Avila-Arcos, PhD. The research was initiated in Den- mark, and the senior author of the study is Thomas Gil- bert, PhD, of the University of Copenhagen.

Bustamante is well-known for his studies of the eth- nic background of native Mexicans and Caribs, as well as for using genomics to study the patterns of human migration from North Africa to southern Europe.

“Several years ago, we were part of the team that sequenced the genome of Otzi, the iceman, and we were able to tell from his DNA if he lived today that he’d closely match him genetically are Sardinians,” said Bustamante. “This incredible precision was possible be- cause we, as a community, had invested lots of resources in understanding the African genetic variation and I started to talk about the ‘Otzi rule,’ or the idea that we should be able to do for all people alive today what we can do for a 5,000-year-old body. It’s a method and a platform.”

But surely the skeletons today are as well-preserved as Otzi, and not all we should be able to do for all people alive today what we can do for a 5,000-year-old body. It’s a method and a platform.”

In the centuries of the Atlantic slave trade, the largest forced migration in history, more than 12 million en- slaved Africans were shipped to the New World to work on plantations in the Americas, the Caribbean, and parts of the eastern and southern United States. Although some records were kept detailing the slaves’ departure from West and Central African ports, they are often complete and, therefore, it is impossible to tell from the shipping records where in Africa individuals originated.

Researchers could tell from the skeletons found in the Zoutsteeg area that the three people were between 25 and 40 years old in when they died, and all had been in that position for centuries.

The skulls of each also bore teeth that had been filed down in patterns characteristic of cer- tain African groups. This process wasn’t enough to pinpoint where the individuals originated on the African continent.

Getting DNA from tooth roots

Schroeder and Avila-Arcos isolated DNA from the root tips of each of the skeletons. Although the tooth roots are relatively protected from the elements and from external contamination with unre- lated genetic material, the DNA was very poorly preserved and highly fragmented — likely due to the centuries of hot, humid conditions the skeletons had endured. Initial DNA sequencing efforts failed to obtain any usable data.

The researchers turned to the whole-genome capture technique developed by study co-author Meredith Carpenter, PhD, of the Bustamante laboratory, to fish out snippets of ancient DNA from the mixture. The approach exposes the DNA sample to a genome-wide panel of human-specific RNA sequences to which the degraded DNA in the sample can bind. The effect is somewhat like stirring a pile of iron- rich dirt with a powerful magnet to isolate the metal from the soil. The approach allows researchers to concentr- ate the ancient DNA for more efficient sequencing.

They then used a different technique called princ- icipal components analysis to examine DNA sequence changes in the skeletons of Africans with a reference panel of 11 West African populations to identify the distinct ethnic characteristics of each individual.

The findings illuminate a tumultuous period of time in the Americas and may provide insight into subsequent migration patterns and perceptions of identity.

They were able to determine that, despite the fact that the three individuals were found at the same site, and may even have arrived on the same ship, they had genetic affinities to different populations within Africa,” said Avila-Arcos. “They may have spoken different languages, making communication difficult. This makes us reflect on two things: the dynamics of the trans-Atlantic slave trade within Africa, and how these dynamic, ethnic mingling may have influenced communities and identi- ties in the Americas.”

The lead authors are graduate student David Poznik and former postdoctoral scholar Martin Sikora, PhD.

The research was supported by the Danish National Research Foundation, the Directorate General for Re- search and Innovation of the European Commission, the European Research Council, the U.S. National Sci- ence Foundation, the Swiss National Science Foun- dation, the National Institutes of Health, a Leverhulme Early Career Fellowship, the Ministerio de Ciencia e Innovacion, the Plan Nacional, the Ministry of Education and Innovation, the Argentine Science and Technology Ministry, the Lundbeck Foundation and the Danish Council for Independent Research.

Bustamante is the founder of IdentityGenomics LLC, and is also the scientific advisory board of Personal Genomics, as well as the medical advisory board of InVitae. Carpenter is now the chief scientific officer at IdentityGenomics.

Stanford’s Department of Genetics also supported the work.
In course, students focus on identifying with patient experience

By Julie Greicius

When Emily Ballenger of San Jose delivered her twins, Julia Burch and Carrie Belle, last August at Lucile Packard Children’s Hospital Stanford, she also was credited with helping train a medical student in the art of patient-centered care and relationship building. Early in her pregnancy, Ballenger was partnered with a medical student as part of an elective course at the School of Medicine. First-year medical student Sunny Kumar attended almost all of Ballenger’s prenatal appointments and learned lessons that can come only from time spent with a real patient. “This class stands apart as a unique experience, really following a single patient over an extended period of time,” Kumar said.

The course is designed to help preclinical medical students experience pregnancy from the patient’s point of view, providing a months-long opportunity to develop a relationship with a patient that can influence the work of future physicians no matter what field of medicine they choose. The students focus on identifying with the patient’s perspective rather than on their role as medical provider. The course directors are Yasser El-Sayed, MD, obstetrician in chief at Stanford Children’s Health and professor of obstetrics and maternal-fetal medicine at the School of Medicine, and Janelle Aby, MD, clinical associate professor of pediatrics.

Preeclampsia

Ballenger and her husband, James, planned to have Kumar attend their babies’ birth, as well as the first few weeks of their pediatric appointments, as patients in the program often do.

With several members of her family in, or preparing for, careers in medicine, Ballenger knew how valuable an educational partnership could be for future doctors. “Before I met him, I was nervous,” she said. “But then he showed up and we talked for about 20 minutes, and it was like making a new friend.”

Ballenger was 37 weeks into her pregnancy when she developed preeclampsia and was admitted to Lucile Packard Children’s Hospital Stanford for induction. She was in labor for 28 hours before delivering healthy twin girls on either side of midnight, resulting in two 9-lb, 10-oz. birthdays. Kumar stayed with the couple through the entire labor process.

“He and James took turns talking to me and helping through the contractions and pain, and helped me decide what interventions and pain management I wanted,” Ballenger said. “Sunny was great and knew what my wishes were going into labor because we had talked about it throughout my pregnancy. He was an amazing advocate for me and helped us figure out what we wanted to do at each step.”

Patient perspective comes first

While many medical schools today have similar programs, Stanford has offered the course for more than 20 years.

“I encourage my patients to participate because it’s a win for obstetric and pediatric patients,” said Susan Crowe, MD, Ballenger’s obstetrician and a clinical associate professor of obstetrics and gynecology at the School of Medicine.

“I really believe that the patient-centered care we strive for can be better achieved if we train our physicians to learn from and listen to our patients themselves. One of the biggest strengths of the program is that the patient perspective comes first. It sets the groundwork for that way of thinking in terms of training medical students,” added Crowe, who directs Outpatient Breastfeeding Medicine Consultative Services at Stanford Children’s Health.

The extra support during pregnancy is a win for participating moms, too. “I just know I have the best care right now,” Ballenger said during her pregnancy. “I have every level of care looking out for my daughters.

Through the experience, Kumar said, he learned some valuable lessons about the importance of patient relationships. “I think the most important thing is that a patient connection is what really drew me to medicine,” he said. “And that’s something that I will continue to value throughout my career.”

Julie Greicius is a freelance writer for Stanford Children’s Health.

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OF NOTE

Sumbul Desai, MD, was appointed vice chair of strategy and innovation for the Department of Medicine. A former strategist for Disney, Desai returned to medical school following her mother’s illness.

Joseph Garner, PhD, associate professor of comparative medicine, was senior author of a paper that was “highly commended” by the National Centre for the Replacement, Refinement and Reduction of Animals in Research. The paper found many laboratory mice are cold, which could skew experimental results, and that adding nesting materials to their cages helps them regulate temperature. His research focuses on addressing issues in animal and human well-being.

Peter Kim, PhD, was elected to the 17-member governing council of the National Academy of Sciences. The Virginia and D.K. Ludwig Professor of Biochemistry, Kim is a structural biologist who discovered how proteins cause viral membranes to fuse with cells. He is working to create an HIV vaccine.

Thomas Krummel, MD, was awarded the 2014 Albion Walter Hewlett Award in the Department of Medicine. Krummel has served as chair of the Department of Surgery for about 15 years. He is the Emile Holman Professor in Surgery and the Susan B. Ford Surgeon-in-Chief at Lucile Packard Children’s Hospital.

Gianna Laport, MD, professor of medicine, was awarded president-elect of the American Society of Blood and Marrow Transplantation. She is the associate director for education at the Stanford Cancer Institute and specializes in blood and marrow transplant clinical trials.

Emmanuel Mignot, MD, PhD, professor of psychiatry and behavioral sciences, received the 2015 National Sleep Foundation’s Lifetime Achievement Award. The award recognizes researchers in the field of sleep medicine for their leadership and productivity over years of work. A dinner honoring Mignot was held March 16 at the Arrillaga Alumni Center.

Darius Moshefighi, MD, was promoted to professor of ophthalmology, effective Jan. 1. He develops telemedicine techniques to identify and preserve childhood blindness. He founded the Stanford University Network for the Diagnosis of Retinopathy of Prematurity and is working on the Newborn Eye Screen Testing Program that is following newborns to determine the long-term effects of birth pathology. Ultimately, he hopes to promote universal eye screening in infants.

Denise Monack, PhD, associate professor of microbiology and immunology, was elected to the American Academy of Microbiology in January. She focuses on host-pathogen interactions and uses bacterial toxins to understand how microbes have evolved to evade and manipulate commensal bacteria in the gut and immune system during chronic infections.

Philip Sunshine, MD, professor emeritus of pediatrics, was named a Legend of Neonatology at NEO: The Conference for Neonatology. He is considered one of the founders of the neonatology discipline and led Stanford’s neonatal team for several decades. He specialized in neonatal and developmental gastroenterology and nutrition.

Dolly Tyan, PhD, professor of pathology, was awarded the 2015 Paul I. Terasaki Clinical Science Award for her contributions to the fields of transplantation, histocompatibility and immunogenetics.

Immunology center seeks pilot-project applicants

Stanford’s newly established Gates Center for Human Immune Systems Immunology is soliciting applications from Stanford faculty, senior postdoctoral scholars, clinical fellows, research associates and instructors for pilot projects aiming to advance research on HIV; tuberculosis; malaria; neglected infectious diseases, such as Dengue; and pathogens that cause pneumonia or enteric diseases in the developing world.

Funding for successful applications will be supplied by the Bill and Melinda Gates Foundation, a nonprofit charitable organization dedicated to curing and preventing infectious diseases. The amount of funding available for faculty-directed projects is $50,000-$200,000 over a two-year period, with a possibility of further support for a third year; as much as $50,000 over two years is available for postdoctoral scholars and clinical fellows, research associates and instructors.

Applications are due by 5 p.m. April 6.

Questions about the request for applications may be directed to Michele King at mking@stanford.edu.