Scientists changed the spatial organization of DNA in cell nuclei, showing how physical relocation altered cell function.

By Tracie White

Titus Dzongodza, MD, was at the end of a long work day, throwing on his jacket to go home, when an 8-year-old girl gasping for breath walked through the doors of the new pediatric otolaryngology clinic at Harare Children’s Hospital in Zimbabwe.

Immediately, I knew we were in trouble,” Dzongodza, who was director of the clinic at the time, said in a Skype interview. “She looked obviously stressed and tearful.” Anoona (not her real name) had traveled all day with her mother by bus from their home in a rural village hundreds of miles away to reach the nearest hospital. It was spring of 2018, a year after the opening of the pediatric otolaryngology clinic, which treats disorders of the ear, nose and throat. “I could hear the grating sound in her shaky voice indicating the return of the viral warts on her larynx,” Dzongodza said. “I knew we’d have to gather the whole team together in a matter of minutes.”

After two years of planning, building, fundraising, training staff and scrounging for medical equipment, the new clinic opened its doors in March 2017. Within its first year, thousands of new patients were making daylong trips by bus to get treatment for neglected conditions. It was only the second such clinic in Africa. (The first was in neighboring South Africa.)

In a country of 14 million people, there are only eight otolaryngologists, also known as ear, nose and throat doctors. Many consider the subspecialty of pediatric ENT unnecessary because of Zimbabwe’s many other unmet health care needs.

“This was a bold dream for a full-scale clinic with audiol-

See ZIMBABWE, page 6

By Erin Digitale

Teens and young adults who use Juul brand e-cigarettes are failing to recognize the product’s addictive potential, despite using it more often than their peers who smoke conventional cigarettes, according to a new study by researchers at the School of Medicine.

The findings, from an ongoing Stanford project addressing the use and perceptions of tobacco products by California youth, was published Oct. 19 in JAMA Network Open.

Juul e-cigarettes pose addiction risk for young users, study reports

See JUUL, page 7

Upward of 100 patients with undiagnosed diseases find answers with network’s help

By Hanae Armitage

More than 100 patients afflicted by mysterious illnesses have been diagnosed through a network of detective-doctors who investigate unidentified diseases, reports a study conducted by scientists at the School of Medicine and multiple collaborating institutes.

The long-awaited diagnoses are the fruits of the Undiagnosed Diseases Network, a program created by the National Institutes of Health in 2014.

“Our goal is to take on the hardest cases in medicine — to find patients and families with conditions that no one has been able to solve,” said Euan Ashley, MD, professor of medicine at Stanford. “We wanted to provide a place that these people could come, so the Undiagnosed Diseases Network came together to try to answer that need.”

The group, made up of hundreds of doctors across the United States, has so far dealthed out 132 of 382 previously unknown ailments — roughly 35 percent. “Some of these patients had been waiting decades to put a name to their illness. They tell us how much of a relief it is simply to know what they were up against,” Ashley said. But what’s most exciting, he said, was that for 80 percent of the network’s diagnoses, they distilled actionable information, such as changes to patient therapy, adjustments to future diagnostic testing and recomman-

See NETWORK, page 7

Euan Ashley of Stanford is among the hundreds of medical scientists nationwide who make up the Undiagnosed Diseases Network.
Anti-inflammatory works for treating lymphedema symptoms

By Tracie White

For more than three decades, Lisa Hanson did her best to hide the unsightly fluid retention in her left leg that caused uncomfortable swelling and made her skin taut and thickened. At 17, when she was first diagnosed with lymphedema, she threw out her shoes and dresses and began a lifelong journey of wearing compression hose up to her thigh and using an electric sleeve-like pump every night to control the swelling. Now, with a new treatment in hand, she’s actually excited to tell people about this chronic condition, which, before she said, left her feeling “like a freak.”

“For a long time I couldn’t talk to people about my lymphedema without crying because it’s something weird and obscure,” Hanson said. “Now there is research for people like me with this disease.”

Hanson took part in one of two small clinical trials led by researchers at the School of Medicine which showed that ketoprofen, an inflammation-reducing drug available by prescription and currently approved by the Food and Drug Administration, can effectively reduce recurrent infection. It can also reverse lymphedema by making the skin healthier and more elastic, Rockson said. “It reversed the lymphedema,” he said. “It’s not a cure. It’s an improvement and makes it easier to take care of my leg.” She still pumps the rest of the day, but nightly pumping now takes just a fraction of the time it used to. Hanson, like other participants in the trial, was warned by researchers that past studies have suggested gastrointestinal and cardiovascular side effects from long-term use of ketoprofen in some patients, but she’s decided to keep taking the drug.

“For me, the choice of being comfortable and not having so much burden in my life was much more beneficial and outweighs the risk,” she said.

An inflammatory response

Just how ketoprofen was working at a molecular level, though, remained unclear. To further examine this while continuing his ketoprofen trials in humans, Rockson joined forces with Nicolls, whose lab had been studying the molecular pathways of inflammation in pulmonary hypertension.

“We were excited to finally figure out that the drug worked by blocking an inflammatory molecule called leukotriene B4, said Nicolls referring to a study published in May 2017. The researchers that found the breakthrough believe that inflammatory response within the tissue of the skin, not merely a “plumbing” problem, is in the lymphatic system, as previously thought. They discovered that the naturally occurring inflammatory molecule LTB4 is elevated in both animal models of lymphedema and in humans with the disease, and that at elevated levels it causes tissue inflammation and impaired lymphatic function.

Further research in mice revealed that using a drug to block LTB4 induced lymphatic repair and reversed the disease processes. This indicated that perhaps ketoprofen could reverse the negative impact of inflammation on lymphatic repair by targeting LTB4.

Other Stanford authors are postdoctoral scholars Wen “Amy” Tian, PhD, and Xingguo Jiang, PhD, who are also affiliated with the Palo Alto Health Care System; François Hadad, MD, clinical associate professor of cardiovascular medicine; Leslie Roche, RN, clinical research coordinator at the Stanford Center for Lymphatic and Venous Disorders; and Jinjia Kim, MD, PhD, a dermatological pathologist. **

Researchers reveal new mechanism for how animal cells stay intact

By Taylor Kubota

Almost eight years ago, Stanford bioengineer Manu Prakash, PhD, was looking for a way to watch every cell in a living, adult amphibian embryo in detail. He searched the catalog of life throughout its watery world. The Prakash lab found Tplax manages this feat through surprisingly fast contractions in its skin like “little paddles.” These contractions strong enough that they would ordinarily rip apart such delicate tissues.

In their first paper based on years-long study of this organism, published online Oct. 11 in Proceedings of the National Academy of Sciences, the researchers describe the ultra-fast contractions and propose a hypothesis for how this creature withstands the mechanical stresses of external forces in a marine environment. The findings could help inform not only the development of animal models but also the creation of an advanced material, called an active solid, that could dramatically and quickly modulate its own mechanical properties.

Moving without muscles

“Much of the rules of biology that we read in textbooks have been, so far, dictated by a few sets of ‘model’ organisms,” said Prakash, who is also a medical professor of bioengineering and senior author of the paper. “If we intend to be the gen- eration that truly understands biology, it’s extremely important to understand and appreciate the diversity of what has evolved on our planet and think much more holistically.”

OCTOBER 22, 2018           INSIDE STANFORD MEDICINE
By Lisa Trei and Nathan Collins

Stanford will accelerate the pace of discovery about the human brain and advance innovative, interdisciplinary brain science thanks to nearly $250 million in gifts from philanthropists who have long supported and envisioned the research and education missions of Stanford University.

In recognition of the lead gift from alumna Clara Wu and her husband, Joe Tsai, the Stanford Neurosciences Institute is changing its name to the Wu Tsai Neurosciences Institute.

The institute’s goal is to better understand how the brain works in health and disease, and to pave the way for new treatments for neurological and psychiatric diseases such as depression, anxiety and schizophrenia. The institute was established in 2013, provide support to scale up research initiatives; expand resources for faculty, students, postdoctoral scholars and new technologies; and complete an interdisciplinary research complex where scientists from across campus can meet and collaborate.

Stanford President Marc Tessier-Lavigne, PhD, a neuroscientist himself, said the gifts come at a pivotal time.

“We are on the threshold of a very promising era, as we make discoveries about the living brain that were previously unimaginable,” Tessier-Lavigne said. “Nearly 450 faculty members from a range of fields are already engaged in the neurosciences and brain-related research at Stanford, making it one of our most vibrant areas of impact on campus. These foundational advances uniquely position our scientific community and universitywide institute to advance new breakthroughs. I am deeply thankful for the vision and generosity of our partners.”

The Wu Tsai Neurosciences Institute is led by William Newsome, PhD, the Vincent V. C. Woo Director, who jointly led the working group for the 2015 campus-wide “Big Ideas” initiative. Newsome said that advances in the neurosciences have the potential to transform the 21st century in the same way quantum physics and the genetic code transformed the 20th century.

“Technologies invented in the last decade are making it possible for neuroscientists to acquire new information about the brain that, until recently, was the stuff of scientists’ dreams,” said Newsome, who also holds the Harman Family Provostial Professorship.

The Wu Tsai Neurosciences Institute and the other for intersecting buildings: One will serve as the hub for neurotheory collaborations involving computer scientists, statisticians, applied physicists and engineers who want to identify fundamental principles of nervous system computation, understand how the brain’s neural network of interconnecting neurons operates and also make sense of the vast quantities of new brain data.

Newsome said there has been an explosion of interest from young scientists in collaborative brain research and that the institute will need to raise funding for more fellowships to ramp up cross-disciplinary graduate and postdoctoral training programs. It will also support neuro-theory collaborations involving computer scientists, statisticians, applied physicists and engineers who want to identify fundamental principles of nervous system computation, understand how the brain’s neural network of interconnecting neurons operates and also make sense of the vast quantities of new brain data.

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New era for neurosciences at Stanford

The neurosciences institute marked its fifth anniversary Oct. 11 with a symposium titled “Natural/ Artificial Intelligence.” Future plans include launching an initiative in neuro-translation to help teams of scientists move discoveries from the lab into practical applications. It will also support neuro-theory collaborations involving computer scientists, statisticians, applied physicists and engineers who want to identify fundamental principles of nervous system computation, understand how the brain’s neural network of interconnecting neurons operates and also make sense of the vast quantities of new brain data.

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By Hanae Armitage

Stanford researchers have reworked CRISPR-Cas9 gene-editing technology to manipulate the genome in three-dimensional space, allowing them to ferry genetic snippets to different locations in a cell's nucleus.

The new technique, dubbed CRISPR-genome organization or simply CRISPR-GO, uses a modified CRISPR-Cas9 editing tool to reorganize genome compartments in three dimensions. If CRISPR is like molecular scissors, then CRISPR-GO is like molecular tweezers, grabbing specific bits of the genome and plunking them down in new locations of the nucleus. But it's more than just physical relocation: Displacing genetic elements can change how they function.

"The research shed new light on how the genome's spatial organization in the nucleus governs the function of the cell overall, and the question of why spatial organization in a cell matters is an important one, and it's also not one that scientists agree on," said Stanley Qi, PhD, assistant professor of bioengineering and of chemical and systems biology. "CRISPR-GO could provide an opportunity to answer that question by enabling us to target, move and relocate very specific stretches of DNA, and see how their new placements in the nucleus change the function they might have." 

Most mammalian cells contain a nucleus that houses more than 6 feet of DNA, if stretched out in a line. This genetic material determines the fate of the cells and, if out of place or damaged, can lead to disease. Previous studies have shown that DNA tends to clump up in certain areas in the nucleus. How that placement affects the DNA's function, however, is still unclear.

In the proof-of-principle study, Qi investigated three distinct subregions of the nucleus using CRISPR-GO, testing an overarching hypothesis: Do genes and other genetic elements behave differently in different zones of the nucleus?

So far, their data show that specific compartments and some free-floating bodies of proteins in the nucleus can sway the function of repositioned DNA. Depending on where the genetic materials are located, some nuclear regions repress gene expression and some accelerate telomere growth, and subsequently cell division. One protein body may even hold the power to suppress tumor formation.

A study detailing this research was published online Oct. 11 in Cell. Qi is the senior author. Postdoctoral scholar Haifeng Wang, PhD, is the lead author.

Bridging the gap

Demystifying the physical details of the genome has proved to be a tedious task, but there are some existing technologies that allow scientists to peer into the nucleus and see how their guts are physically organized. What's been missing is a way to tamper with this organization.

CRISPR-GO is the first to offer researchers a means to do so. By deconstructing the "cutting" mechanism of CRISPR-Cas9, the editing tool becomes more of a delivery system, which Qi used to deliver small stretches of DNA via a programmable guide RNA to a new location in the nucleus.

There are three essential parts of CRISPR-GO. First, there's what Qi calls the "address" of the genetic target — that's targeted with a complementary strand of binding RNA. Then, you need the destination address — the specific portion of DNA in a nuclear compartment to which you want to move the chromatin. Finally, there's the "bridge," which, in this case, is a catalyst that spurs the congealing of the target DNA to its new home in the nucleus.

"Kids often like to build little railroads to help trains get from one station to another," said Qi. "It's not so different from what we're doing here."

Different room, different function

Qi describes the functionalities of the nuclear compartments like the spaces of a house. In every room of your home, you do different things — in the kitchen, you cook; in the bedroom, you sleep. In the nucleus of a cell, the same concept applies. There are multiple compartments in the nucleus that all have specific roles in upholding cell functionality overall. Qi and his lab investigated three distinct areas of the nucleus, testing whether they could somehow shift the function of chromatin depending on where they moved it.

By using CRISPR-GO, the researchers observed that genes relocated to a part of the nucleus called the Cajal body, an amorphic and somewhat mysterious blob of proteins and RNA, stopped expressing proteins.

"We were super-excited to see this, it's the first time that researchers have evidence to show the Cajal body can have a direct gene-regulation effect, in this case repressing gene expression," Qi said. "It suggests that the Cajal body has some unexpected role in controlling transcription." That could be big, as transcription is an important process that synthesizes the "code" for protein production.

When Qi used CRISPR-GO to move the DNA of telomeres — the molecular caps of chromosomes that are associated with longevity — from the middle to the edge of the nucleus, the telomeres stopped growing, halting the cell cycle and reducing cell viability. The opposite, however, happened when telomeres were moved closer to the Cajal body: They grew and, in doing so, increased cell viability.

The third application used CRISPR-GO to form a promyelocytic leukemia body. This glob of proteins is known to suppress pro-tumor genes. By positioning it next to cancer-causing genes in the nucleus, Qi plans to test if it can help curb tumor formation.

"Another unique advantage of CRISPR-GO is that we can track the interactions between chromatin DNA and nuclear compartments in real time under a microscope," Wang said.

While the evidence shown by CRISPR-GO is exciting, the researcher is still in a pilot stage, and there's more work to be done before the findings can be confirmed, Qi said.

"We're very excited about the potential here and, while we've answered a couple questions, we've opened up about 20 more," Qi said.

It will be even more important to decipher why these location-based effects take place in specific nuclear compartments, and what the underlying cause is, he said. One day, Qi hopes, this line of research will come to bear on human health.

Other Stanford authors of the paper are postdoctoral scholars Xiaoshu Xu, PhD, Yantza Liu, PhD, Xueqiu Lin, PhD, and Timothy Daley, PhD; undergraduate student Cindy Nguyen; graduate students Yuchen Gao and Nathan Kipnis; and research scientist Marie La Russa, PhD.

Qi is a member of Stanford ChEM-H, Stanford Bio-X, the Stanford Cancer Institute and the Stanford Neuroscience Institute.

The research was supported by the Pew Scholar Foundation, the Alfred P. Sloan Foundation, the National Institutes of Health and a gift from the Li Ka Shing Foundation.

Stanford's Department of Bioengineering, which is jointly operated by the schools of Medicine and of Engineering, also supported the work.

Scientists modify CRISPR to reorganize genome in cell nuclei

By Julie Greicis

A "chosen family" is how some of the speakers described their colleagues here during the first-ever Stanford Medicine LGBTQ+ Forum.

Too often those letters — which stand for gay, lesbian, bisexual, transgender, and queer/questioning — describe individuals whose sexual orientation or gender identity is kept hidden because it can be personally and professionally risky to be "out." But the visibility-themed event on Oct. 10 was an unmistakable declaration of LGBTQ+ pride. Stanford Medicine recognized the importance of the event, beginning with President Marcina协donado, MD, senior associate dean for medical education and outreach, and co-chair of Stanford Medicine’s LBGTQ+ Forum.

"I want to personally commit to each of you, to all of you, that I’m going to stand beside you, I’m going to make sure that we change the fabric and the culture not only of our institutions, but also together we can really have an impact on the fabric and culture of our society,”协donado said. “I think we have an innate responsibility — as an academic medical center, as a great research university — to celebrate and embrace diversity and inclusion in all of its aspects.

The event was founded by MD-PhD student Timothy Keyes, who spent more than a year organizing it with fellow members of the LGBTQ+ Meds organization and many other sponsors. Faculty supporters like Yvonne "Bonnie" Botnic-Malodonado, MD, senior associate dean for faculty development and diversity, recognized the importance of the event, because the LGBTQ+ community is what she called an "invisible minority." Keyes' effort was also championed by faculty sponsors Marcia Valiee, a deputy director of the Center for Comparative and Functional Genomics.

Valiee, with涂鸦

"The medical school is leading the way on issues of inclusion in many ways,” said Valiee. "It is so important to have this kind of venue here at Stanford Medicine, to celebrate the diversity and to be inclusive of all individuals here at our institution who are part of the LGBTQ+ community.”

Attendees gather at a rainbow balloon photo booth during the LGBTQ+ Forum on Oct. 10.
Researchers study head motion in high school football hits

By Erin Digitale

Scientists at the School of Medicine are collaborating with local high school football programs at three Bay Area high schools to understand how hits to the head cause concussions in young players.

In a study launched last month, a research team led by concussion experts David Camarillo, PhD, and Gerald Grant, MD, is outfitting the players with mouthguards that measure the motion of the head during impacts sustained in practices and games. About 100 football players from Menlo School and Sacred Heart Preparatory, which are in Atherton, and Archbishop Mitty High School, in San Jose, are participating in the first year of the study.

Camarillo’s team has previously studied concussions in Stanford athletes and NFL players, but never in younger players.

“This will be the first study in kids where we’ll be measuring rotation and full motion of the head during impacts,” said Camarillo, assistant professor of bioengineering and the co-principal investigator for the study. “It’s important to expand our research to the high school level and younger because that’s where there are the most athletes.”

While the NFL and college football comprise several thousand players, high school and children’s football programs account for around 4 million players nationwide, he said.

“Our goal is to focus first on high schools in the Bay Area and to deepen our level of understanding about how concussions may occur in one player but not another,” said Grant, professor of neurosurgery and the principal investigator for the study. “We’re going to gather prospective data on the players in the preseason, as well as during the season and postseason. This is also a pediatric neurosurgeon at Lucile Packard Children’s Hospital Stanford, where he treats young patients with head injuries.

High-tech mouthguards

The researchers are collecting preseason neurocognitive data that they will use as a baseline for comparison with post-injury data collected after any suspected injuries. During practices and games, players will wear mouthguards equipped with gyroscopic sensors that measure motion in three directions — up/down, left/right and front/back — as well as three types of rotational acceleration: roll, pitch and yaw.

Practices and games will be filmed so that researchers can confirm collisions and assess players’ severity of impact. Eye tracking data will be collected as part of an effort to understand whether erratic eye motions after a head impact indicate a concussion.

The researchers hope the data will illuminate exactly what types of collision lead to concussion so that coaches can better evaluate when players who have had collisions are at risk. Simply watching collisions from the sidelines often does not provide an accurate sense of whether a player’s brain could be damaged.

“It’s entirely possible that something that looks really dangerous may produce accelerations that are not very high, and may not be dangerous,” Camarillo said. “Conversely, hits that don’t look scary may be high-acceleration. It’s difficult to see.

Understanding which hits are dangerous might also help players and coaches learn how to prevent risky collisions, the researchers said.

“It’s very exciting to think about using this feedback for coaching,” Grant said. “We suspect some players may be at greater risk for concussion than others because of the way they tackle. We hope to use the data to give coaches the tools they need to teach an individual athlete how to play using the safest possible technique.”

The study will continue through the 2018 football season and will expand in 2019.

The research is being funded by local philanthropists Tad and Diane Taube through the Taube Stanford Concussion Collaborative.

(Top) Research assistant William Mehring (right) hands a mouthguard to Menlo School sophomore J.P. McKinney. (Right) Mehring with the mouthguards, which local high school football players will wear during practices and games. The mouthguards contain sensors that measure motion in three directions.

Forum

continued from page 4

Stefanick, PhD, professor of medicine and of obstetrics and gynecology, and James Lock, MD, professor of psychiatry and behavioral sciences.

Recalling a talk with Ben Barnes

In his remarks at the event, Keyes described a visit to Stanford before he had decided to attend. He had interviewed with the late neuroscientist Ben Barnes, MD, PhD, an openly transgender man, who asked Keyes an unexpected question.

“He said, ‘Oh, Tim, by the way, are you gay?’” Keyes recalled. “And I said, ‘Yes, of course. ’ He had noted something on my CV that was LGBTQ leadership-related. And he said, ‘Well … I just want to let you know that this is a very supportive community here. … You could come here and be as out as you’d like to be and not have to worry about anything.’”

It was the first time, Keyes said, that anyone had asked him about his sexual- ity in a positive way with regard to his career. “It was so meaningful,” Keyes said. “It made me feel really, really special and … really seen. And that’s why I con- cluded, but it’s one of the most im- portant, for Stanford because of the fabric of our community. We have to feel, every day, that who we are, inside, is a vital part of who we are as a member of our community,” Minor said. “At its heart and core, a place like Stanford is Stanford because of the community that we bring together.”

The journey toward visibility and inclusion may not be easy, the dean concluded, but it’s one of the most important for Stanford, whose accomplishments can be an example for the country and the world.

“Competent and compassionate care”

Benjamin Laniaka, MD, clinical as- sistant professor of medicine, described how sorely lacking the LGBTQ+ health training was when he was in medical school from 2009-13. In all four years, he said, it amounted to only a single HIV/AIDS diagnostic question on one exam. Today, Laniaka said, “All I want to be able to do is to have medical stu- dents feel armed with the knowledge and skills to provide appropriate LGB and transgender care, to provide this compe- tence and compassionate care. That’s it.”

About 350 people attended the after- noon, on-campus event, which included LGBTQ+ individuals and their allies and colleagues from the School of Medicine, Stanford Health Care and Stanford Chil- dren’s Health. Guests were treated to giveaways and food.

As much as the gender and sexual mi- nority members at the event were there to be part of a chosen family, their allies and colleagues had chosen to be part of that same family, too.

“In order for each of us to fulfill our potential, we have to feel a part of the fabric of our community. We have to feel, every day, that who we are, inside, is a vital part of who we are as a member of our community,” Minor said. “At its heart and core, a place like Stanford is Stanford because of the community that we bring together.”

“Take part in clinical research”

Stanford Medicine researchers are recruiting participants of all ages for a variety of clinical trials. They need people with specific health conditions, as well as healthy participants. For more information about clinical trials at Stanford, visit clinicaltrials.stanford.edu.
Zimbabwe continued from page 1

ogy and speech therapy services, as well as two operating rooms with a recovery room and beds for overnight care,” said Peter Koltai, MD, professor of otolaryngology and of pediatrics at Stanford, who was recruited three years ago as a volun-
teer adviser for the project. “Now we be-
lieve that this new clinic can be used as a role model to be duplicated across all of Af-
rica.”

The problem

The clinic was the vision of Clemence Chidziva, MD, an ENT surgeon and professor of otolaryngology at the University of Zimbabwe. Chidziva knew firsthand the effects of malnutrition, poverty, and a lack of medical facilities on viruses on his pediatric ENT patients. He also knew these problems reached far beyond Zimbabwe into other parts of Africa and the developing world.

“I wanted to build a clinic that could provide high-quality care for children and proper training for pediatric ENT surgeons as well,” Chidziva said in a Skype interview.

Central Hospital, in the coun-
try’s capital, comprises the children’s hospital and an adult hospital, maternity hospital and psychiatric hospital. Condi-
tions are poor. Prior to the opening of the new clinic, Chidziva’s pediatric ENT patients received care at the adult hospital. (They still undergo surger-
ies there.) When Koltai first trav-
eled to Zimbabwe in 2015, he stayed in the background, listening and learn-
ing about the problems he and Chidziva’s staff were facing.

“When I first arrived, I saw the fragil-
ity of this medical system,” Koltai said.

“The lack of supplies, questionable water and sanitation, and the surgical cleanliness outside of critical areas in the hospital. There were no fiber-optic capabilities — that is, medical equipment used for internal examination of the body — and no record-keeping for patients. But I also saw the potential, the good intentions of those who were working under conditions we would find almost intolerable at Stanford.”

The types of ENT problems Chidziva’s patients presented are similar to what Koltai would eventually assist with during his repeated visits to Harare over the years — not more serious than the gen-
eral population understands, Chidziva said. There’s a common misconception in Zimbabwe that ENT problems in chil-
dren are trivial. Parents think that con-
tinually running noses in their children, constant snoring and painful ear infec-
tions are just a way of life.

But, in fact, the list of serious prob-
lems is long: untreated ear infections that lead to perforated eardrums and ear-

dential deafness; HIV infections that cause repeated ear and throat disorders; con-

Tplax continued from page 3

laboratory lines and animals they caught themselves in Monterey, the group works in a wide variety of sizes and shapes, creating animals that are hundreds to millions of cells. This varia-
tion in size and shape lends itself into understanding how cellular coordi-
nation varies as the number of cells in-
creases.

“_tplax are really mysterious beasts,” said Matthew Bull, a graduate student in the Prakash lab and co-author of the paper, “but we use that to our advantage to find where our understanding of what it means to be part of the animal knot has been for decades. We try to play in the grass, causing uncontrollable bleeding.

“Many of these things are no longer problems in the modern world, but big problems in the developing world,” Dzongodza said. He is now on a fellowship in Melbourne, Australia, where he is training to become a certified pediatric otolaryngologist who will be the first physician with the certification in Zimbabwe when he returns to lead the clinic in July.

One of the most serious and common medical problems treated by the Zim-
babwean physicians is called recurrent upper respiratory papillomatosis, caused by the human papilloma virus, or HPV, that causes growths in the upper respiratory tract. The growths can cause difficulty breathing, damage the vocal cords and become life-threatening.

The condition often gets misdiagnosed as asthma, delaying treatment. Children first lose their voices and then struggle to breath until, as in the case of Anoona, the growths threaten to block respiration completely.

“As the growths on the unit met her, one after the other over the years,” Dzongodza said. “I often asked the senior col-
leagues would dig into their pockets to get her bus fare for the next journey back to the hospital.”

The clinic

To make his vision a reality, Chidziva started by raising funds for construction of the clinic from the Christian Blind Mission International, a charity commit-
ted to improving conditions of those liv-
ing in some of the poorest communities in the world. He involved Koltai and other surgeons to join his team. Koltai’s prior experience in helping to set up several pediatric ENT clinics in the United States and working for 10 years as the director of the pediatric otolaryngology program at Stanford, would prove invaluable, Chidziva said.

“Clemence had a vision, and I brought it into it,” Koltai said. This project resonated with my goals of seeing the footprint of pediatric otolaryngology spread far and wide. I would supply some of the experience, and Clemence supplied the leadership.”

Koltai has spent endless hours scanning eBay in an effort to scrounge up re-
usable medical equipment at affordable prices. He brought two decommisioned

surgical microscopes from Lucile Packard Children’s Hospital Stanford to Harare and has been instrumental in plans for the delivery of an ultrasound machine. The Jenkins family of Menlo Park, who had supported Koltai’s research work in the past, helped pay for the eBay pur-
chases and their shipping fees. Early on, he secured funding from Stanford’s De-
partment of Otolaryngology-Head and Neck Surgery to fly the physicians from the clinic, including Dzongodza and Chidziva, to the Bay Area, where they stayed with Koltai and observed him for a month at Stanford Medicine.

“Peter’s work, together with his Zim-
babwean counterparts, helping to stock the clinic with instruments and develop a novel training program for the surgeons was a terrific example of an equity part-
nership,” said Mi-
chele Barry, MD, director of Stan-
ford’s Center for In-
novation in Global Health. “Having 
worked on and off in Zimbabwe for al-
most 30 years, I can tell you that this acc-
accomplishment was no small feat.”

Over the years, Koltai has returned repeatedly to Harare to teach advanced surgical techniques, hold seminars and set up the previously nonexistent record-
keeping program. The record-keeping system will be essential for Chidziva’s long-range plan of creating a training ground at the clinic for future pediatric ENT sur-
geons, along with a research program to help advance academic appointments at the University of Zimbabwe. The first of these research projects on the docket, he said, will be a clinical trial to provide evidence of what appears to be the widespread scourge of the HPV disease.

“We feel that with scientific evidence to support us, we can get our govern-
ment to vaccinate for HPV to prevent this disease,” Chidziva said.

Still, the clinic remains a work in progress. Plans are moving ahead to open two operating theaters and add the clinic and dedicated to treating children with ENT problems. Fundraising efforts have been amped up to fill gaps in care caused by the tripling of the patient load following the opening of the clinic. Due to constant funding shortfalls, much of the equipment considered essential at Stanford, such as MRI or CT machines, remains out-of-reach luxuries in Harare.

“When we created this clinic, we did it to improve care for our patients,” Chidziva said. “But within the first year

of opening, we saw 3,500 patients, three times the average caseload. The struggle now continues to get them all onto an operating table in time.”

The future

In May, the team organized the first international symposium to advance pediatric otolaryngology across Africa, called PENTAfrika, held in Victoria Falls in Zimbabwe, with the goal of advancing pediatric ENT across Africa. Attended by otolaryngologists and other health care professionals from Africa, Europe and North America, the event launched the organizers’ long-range plan to use the new program as a model to provide great access to care across the continent.

“We’re hoping our new clinic will plant a seed in each and every country in Africa,” said Chidziva. “By July, with the return of Dzongodza from Australia and with the opening of the clinic’s operating wings, Chidziva will be working on opening a new child.”

For Dzongodza, training thousands of miles away in Melbourne, he still worries about her one way or the other over the years,” Dzongodza said. “I saw the child once more last winter. She had the HPV that causes the warts on her larynx. As a toddler, she had been mis-

diagnosed with asthma and aspirated at the hospital for the first time when she was 3 years old, gasping for breath. This time, though, she would be initially seen at the new clinic, with staff better trained to treat children, and operated on at the adjoining operating room and hospital.

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Scanning eBay for medical equipment.

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Juli
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“I was surprised and concerned that so many youths were using Juul more frequently than other products,” said the study’s senior author, Bonnie Halpern-Felsher, PhD, professor of pediatrics. “We need to help them understand the risks of addiction. This is not a consumers market, but they need to make informed decisions about products. They may need help understanding that even if they like Juul, it can still contain an enormous amount of nicotine—at least as much as a pack of cigarettes.”

The data show a worrisome disconnect between children’s perceptions of their Juul use and actual addiction, the researchers said. “We ask, ‘Do you feel addiction?’ And they say yes. If they’re using Juul, it’s your problem if that feels right way,” Wheeler said. “Lactic acidosis can also cause your acid-base balance to be out of whack, and when people have severe acid-base disturbances, they’re at risk for arhythmia or death.”

It wasn’t clear why the patient was experiencing these symptoms, which seemed to be prompted by a cold or flu. After giving the patient the full gamut of tests and analyzing sequencing information, a team of Stanford scientists found the culprit: a single mutation in the gene ATP5F1D, which is involved in the function of mitochondria, the cell’s powerhouse. The genetic oddity and symptoms had never been classified together officially, but from connections within the network and in some instances word of mouth, the scientists found that other doctors around the world had treated patients plagued by the same finding. What is causing the mutation is the syndrome—called mitochondrial complex V deficiency, nuclear type 5—network collaborators on the study developed animal models to those causally

Continuing the search
This is a new type of scientific odyssey,” Ashley said. “We’re learning about biology in a way that could help just not one family, but potentially dozens, even hundreds of other families.”

“Some cases are solved simply because we know more today than we did a year ago,” Ashley said.

Asking those questions about the epidemic’s drivers is the study’s senior author and Splinter is the lead author. The New England Journal of Medicine’s syndromes.

The study was funded by the NIH.

Stanford’s Department of Medicine also supported the work.

Other research on e-cigarettes
Also publishing Oct. 19 is a commentary by Halpern-Felsher about a tobacco-prevention curriculum developed by Juli. The commentary, which will appear in Journal of Adolescent Health, expresses concern about several aspects of Juli’s curriculum. Juli provides schools with a free e-cigarette sampling kit and use its curriculum and does not follow best practices in adolescent tobacco education, according to the commentary. For example, the curriculum does not discuss the role of industry in marketing tobacco- or nicotine-containing products to youths, makes little mention of Juul by name, and does not discuss why young people use e-cigarettes or mention that e-cigarettes are significantly less harmful than traditional cigarettes. Juli argues that flavored products such as Juul may be especially appealing to them. The co-author of the commentary is Jessica Liu, PhD, a research associate at the Stanford Cancer Institute who completed a summer internship in Halpern-Felsher’s lab.

Earlier this month, the researchers also published a study in Addictive Behaviors exploring teens’ perceptions of advertising for flavored e-cigarette liquids. “The results showed that kids are not well informed about the impact of Juul use on teenagers and young adults. We’ve never had a research study to ask about Juul as part of a tobacco-use study they have been doing in 10 California counties since 2014,” said Splinter, who conducted the study, completed in 2014 and 2015, more than 700 students in ninth or 12th grade answered questions about their use and perceptions of tobacco products. The new findings come from follow-up questionnaires completed by 445 participants who were in 12th grade or younger when the new data were collected.

Participants answered questions about whether they had ever tried Juul; if and how often they used conventional cigarettes, Juul or other e-cigarettes; their use of flavored e-cigarette products; their perceptions of the social acceptability of using different products; and their perceptions of the products’ risks and benefits. The researchers analyzed their responses to identify which factors may encourage Juul use.

Across the study, 17 percent reported they had used Juul, 15.6 percent had used the brand. Other e-cigarettes were used by 30.4 percent of participants, while conventional cigarettes were smoked by 24.3 percent. Participants who had used two-thirds of the participants who used these products used more than one type of product: some combination of Juul, other e-cigarettes and conventional cigarettes.

Participants reported using Juul about twice as often as smoking conventional cigarettes when asked about use of tobacco products over the past seven or past 30 days.

Believed to be harmful
Participants thought Juul e-cigarettes were less harmful or addictive than other products mentioned in the survey. However, when asked about who they thought used Juul, 38.8 percent reported that they had used Juul within the last 30 days. More than half of those who had used other e-cigarettes or conventional cigarettes, 30.1 percent and 28.3 percent, respectively, reported using within the last 30 days. This was the most striking difference between Juul users and users of other e-cigarettes and conventional cigarettes.

Researchers from Harvard University, the NIH Clinical Center, and the Pacific Northwest National Laboratory, led by Juul. The commentary, which will appear in Journal of Adolescent Health, expresses concern about several aspects of Juli’s curriculum. Juli provides schools with a free e-cigarette sampling kit and use its curriculum and does not follow best practices in adolescent tobacco education, according to the commentary. For example, the curriculum does not discuss the role of industry in marketing tobacco- or nicotine-containing products to youths, makes little mention of Juul by name, and does not discuss why young people use e-cigarettes or mention that e-cigarettes are significantly less harmful than traditional cigarettes. Juli argues that flavored products such as Juul may be especially appealing to them. The co-author of the commentary is Jessica Liu, PhD, a research associate at the Stanford Cancer Institute who completed a summer internship in Halpern-Felsher’s lab.

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After compassionate-use exemption, girl undergoes unusual heart surgery
By Erin Digitale

When Lizneidy Serratos’ mother took her to the hospital at 1 a.m. Aug. 4, she thought wildfire smoke near the family’s Reno home was why the 12-year-old was struggling to breathe. But after a series of tests, doctors said Lizneidy’s heart was failing.

“She’s heart function was only at 10 percent,” said Lizneidy’s mom, Maricela Alvarado-Lazarit. “It was a shock.”

And she couldn’t walk because her heart was failing.

Identifying the problem

In late July and early August, as wildfire smoke drifted into Reno, Lizneidy’s family noticed she was breathing less easily. Then, just after midnight on Aug. 4, Alvarado-Lazarit found Lizneidy sleeping in a strange position. “I was cross-axes apple sauce, with my head down at my feet,” Lizneidy said. People with heart failure can often breathe better if they sleep sitting up, but Alvarado-Lazarit did not yet know about the diagnosis. Alarmed, she woke her daughter and took her to the nearest emergency room. Doctors transferred Lizneidy to the pediatric intensive care unit at another Reno hospital, Renown Children’s Hospital, which has a pediatric specialty care partnership with Stanford Children’s Health. Then, Lizneidy was transferred by an emergency medical flight to Packard Children’s.

Lizneidy received medications that stabilized her for a few days. But her heart was not recovering. As in most cases of dilated cardiomyopathy, the physicians did not know why her heart failed.

“It appeared she was getting worse and was going to need a ventricular assist device,” said Christopher Almond, MD, associate professor of pediatric cardiology at the School of Medicine. A ventricular assist device is a surgically implanted pump that helps a patient’s failing heart move blood through the body.

Almond told the family that Lizneidy would probably need a heart transplant, and that she would receive surgery to implant the pump that could keep her alive until a donor heart became available.

The best pump

The Packard Children’s cardiology team wanted to give Lizneidy a pump called the HeartMate 3, which is small enough to implant in the chest. Patients with the pump must wear an external battery pack, but can leave the hospital, walk freely and perform many normal activities.

However, the HeartMate 3 had one drawback in Lizneidy’s case. To implant it, Maeda needed to create a hole in the girl’s left ventricle, the largest pumping chamber in her heart, and suture a washer-like device called a sewing ring onto the heart to anchor the pump. But the sewing ring that had been approved by the FDA was too big for Lizneidy. There was a smaller ring, but it was approved only in Europe. “The problem with the larger sewing ring is that Dr. Maeda would have had to sew across one of her most important coronary arteries,” Almond said. In rare cases heart pumps allow children’s hearts to get enough function to avoid a transplant. Closing the artery would have permanently severed the blood supply to part of Lizneidy’s heart muscle, cutting off this option.

“Because she had a chance of recovery, we didn’t want to sacrifice the main artery supplying blood to her heart,” Almond said.

So on Aug. 9, Almond began the process of asking the FDA for a compassionate-use exemption. He wrote a letter to the FDA and the device manufacturer, Abbott, requesting permission to use the smaller, unapproved sewing ring: contacted Stanford’s ethics team to get its permission for the unusual surgery; and arranged for another cardiologist to provide an independent second opinion to the FDA. On Aug. 10, as hours ticked by and paperwork stacked up, people in several locations across the country — including PDA staff — stayed late at work to help.

“The process for getting compassionate-use approval is a bit complex,” Almond said, noting it can take days or weeks. By 9 p.m. Pacific time on Aug. 10, the approval was complete. In one more bit of serendipity, Almond learned that the smallest sewing rings — which were commercially available only in Europe — are manufactured 30 miles from Packard Children’s, in Pleasanton, California. The sewing ring arrived at the hospital the following morning. That evening, Lizneidy was getting worse again. It was time for surgery.

Becoming a medical pioneer

On Aug. 12, Lizneidy’s family came to Lucile Packard Children’s Health, where she was wheeled into the operating room, listening to favorite songs on her phone. The small sewing ring worked just as the doctors had hoped. In the five-hour surgery, Maeda kept Lizneidy’s coronary arteries intact. Lizneidy became the first person in the United States to receive a small sewing ring and, at the time of her surgery, the youngest and smallest person in the country to get the HeartMate 3 ventricular assist device. The pump made an enormous difference. Lizneidy’s breathing tube was removed the next day, and she soon began eating again.

“Having her just talking and laughing, and getting something for food was great,” Alvarado-Lazarit said. “When she started being able to get up, it felt like, ‘She’s going back to normal.’”

Since the surgery, the smaller sewing ring has received FDA approval for commercial use, enabling more patients to benefit from the device.

Lizneidy’s family is now staying at the Ronald McDonald House at Stanford. Her medical team plans to monitor her for a few months before deciding whether to add her to the waiting list for a heart transplant.

In the meantime, Lizneidy is relaxed and comfortable, attending seventh grade at the hospital school and taking in stride new challenges, like swallowing lots of pills, which are intended to give her heart every opportunity to recover, if it can. The battery pack for her heart pump is always at her side, housed in a tote bag she wears over her shoulder.

“Her heart function returned to normal,” Almond said. “It’s like an annoying best friend, always there,” Lizneidy said. “But I’m OK with it.”

Twelve-year-old Lizneidy Serratos at the Dunlevie Garden at Lucile Packard Children’s Hospital Stanford.