Roots of Caribbean populations revealed with aid of new technique for DNA analysis

By Krista Conger

Those of us who want to learn about our ancestors—who they were, where they came from and how they mingled (or didn’t) with others around them—often turn to historical records or elderly family members for answers. But a new study by researchers at the School of Medicine and the University of Miami Miller School of Medicine indicates that the answers can also be found within our own genes.

The researchers compared patterns of genetic variation found in populations in and around the Caribbean, which has had a particularly tumultuous past since Christopher Columbus stumbled into the Bahamas in 1492. Not only did they identify an influx of European genes into the native population that occurred within a generation of Columbus’ arrival, but they also discovered two geographically distinct pulses of African immigration that correspond to the beginning and height of the transatlantic slave trade.

The study demonstrates how deciphering genetic echoes from the distant past can illuminate human history. But it also helps explain why members of some populations, like Latinos, who may be classified by medical researchers as a single group, display marked differences in susceptibility to diseases or responses to therapeutic drugs.

“If we don’t understand the origin of our genetic variants, we won’t be able to design personalized, or even population-level, medicine,” said Andres Moreno-Estrada, MD, PhD, a life sciences research associate at Stanford. “Until recently, Latinos have been considered as a single group of people, when in fact they are very heterogeneous. We wanted to know what are the roots of the Caribbean people. Where do they come from? Clearly the population history of the region is very complex.”

Moreno-Estrada is the lead author of the study, which was published Nov. 14 in *PLOS Genetics*. Carlos Bustamante is senior author of a study that shows how deciphering genetic echoes from the distant past can illuminate human history. Until recently, researchers have tried to extract this type of information from ancient DNA, which can be very difficult to find and to process that age and damage skin are impeded by dilute bleach solution, according to a new study by researchers at the School of Medicine.

The study was conducted on mice. But if shown to work similarly in humans, the inexpensive, widely available household chemical could provide a new way to treat skin damage caused by radiation therapy, excess sun exposure or aging.

Dilute bleach baths have been used for decades to treat skin damage in mice blocked by dilute bleach solution.

Study: Inflammatory skin damage in mice blocked by dilute bleach solution

By Krista Conger

Processes that age and damage skin are impeded by dilute bleach solution, according to a new study by researchers at the School of Medicine.

The study was conducted on mice. But if shown to work similarly in humans, the inexpensive, widely available household chemical could provide a new way to treat skin damage caused by radiation therapy, excess sun exposure or aging.

Dilute bleach baths have been used for decades to treat moderate to severe eczema in humans, but it has not been clear until now why they work. “Originally it was thought that bleach may serve an antimicrobial function, killing bacteria and viruses on the skin,” said Thomas Leung, MD, PhD, an instructor in dermatology at Stanford and a pediatric dermatologist at Lucile Packard Children’s Hospital. “But the concentrations used in clinic are not high enough for this to be the sole reason. So we wondered if there could be something else going on.”

Leung is the lead author of the study, which was published online Nov. 15 in *Journal of Clinical Investigation*. Seung Kim, MD, PhD, professor of developmental biology and a Howard Hughes Medical Institute investigator, is the study’s senior author.

“Dr. Leung relentlessly
Addressing faculty senate, dean shares vision for leading ‘biomedical revolution’

By Kathleen Sullivan

In his first presentation to Stanford’s faculty senate, Lloyd Minor, MD, dean of the School of Medicine, said the goal of the Campaign for Stanford Medicine is to “lead the biomedical revolution” by promoting fundamental, clinical and translational discovery, by transforming patient care and by training future leaders.

“We are the epicenter of innovation,” Minor said during his Nov. 8 presentation.

“We are drawn to the difficult problems, not the problems that can be solved with incremental solutions or approaches, but the problems that no one else tackles,” he said. “The problems that, at first, we don’t even know how to conceptualize and approach to solve them. And we develop the platforms and the paradigms that change the future.”

As an example, Minor cited the work of Karl Deisseroth, MD, PhD, a professor of bioengineering and of psychiatry and behavioral sciences, who led the multidisciplinary team that combined neuroscience and chemical engineering to develop a process that renders mice transparent.

Citing many facts and figures during his 15-minute presentation, Minor provided an overview of the School of Medicine. Currently, the medical school has 411 students studying to become doctors, 937 resident and clinical fellows, 713 PhD students and 1,277 postdoctoral research scholars.

Emphasizing the excellence of the school’s faculty, Minor noted that its ranks include six living Nobel laureates.

Turning to undergraduate education, he said that 19 percent of medical school courses are open to undergraduate students. Some of most popular are “Sleep and Dreams,” “Genetic Analysis,” “Cell and Developmental Biology” and “Economics of Health and Medical Care.”

Regarding patient care initiatives with Stanford Hospital & Clinics, Minor noted that the hospital developed the new Stanford HealthCare Alliance, a low-cost, high-quality health-care plan that will be available to Stanford employees and postdoctoral scholars in 2014.

Minor compared Stanford to 20 of its peer medical schools by looking at the number of faculty, medical students, residents and fellows, and hospital beds.

“Across the board, we’re small, and that is one of our greatest strengths,” he said. “Because we’re small, we’re nimble. We can respond. We can react. We can plan.”

“We can organize in ways that much larger institutions have a great deal of difficulty doing.”

Following the presentation, faculty members asked questions about the quality of patient care in teaching hospitals, the challenges facing the medical school and the quest to derive meaningful information about individuals and populations from massive databases.

“The minutes of the Nov. 7 meeting will be available on the faculty senate website. The minutes will include the questions and answers session that followed Minor’s presentation.”

Kathleen Sullivan is the university governance writer at the Stanford News Service.

Biolinnovate program established in Ireland

The Stanford Biodesign Program has selected Bio-Innovate Ireland, led by the Bio-Innovate Ireland-Galway, as its first global affiliate program. This alliance will lead to the joint development of new training programs that will provide mutually beneficial experiences for our fellows and students.

“We are pleased and excited to see the growth of Bio-Innovate Ireland into a world-class training program in biomedical technology innovation,” said Paul Yock, MD, director of the Biodesign Program. “We look forward to this opportunity to share best practices in education and training, create new teaching materials and provide mutually beneficial experiences for our fellows and students.”

Jim Browne, DSc, president of NUI Galway, said, “This affiliation is further recognition of NUI-Galway’s commitment to biomedical excellence. The Bio-Innovate Ireland program enables collaboration across diverse fields to meet the needs of patients, clinicians and industry, and puts innovation at the forefront of what we do.”

The Bio-Innovate Ireland Fellowship is a medical device innovation training program modeled after Stanford Biodesign. It will train multidisciplinary teams on the process of identifying unmet clinical needs and then inventing and implementing biotechnologies to meet those needs. This is the third international alliance that Stanford Biodesign has initiated, the other two being BioInnovate Canada and BioInnovate India.

Bio-Innovate Ireland is led by NUI-Galway in collaboration with the University of Limerick, University College Cork and Dublin City University. Program support comes from Enterprise Ireland, Irish Medical Devices Association, Boston Scientific, Medtronic, Creganna Tactx Medical, Steripack, Aerogen and Zeus.

Hiromitsu Nakauchi, distinguished stem cell scientist, joins faculty

By Christopher Vaughan

Hiromitsu Nakauchi, MD, PhD, a renowned stem cell scientist, has been recruited to the faculty of the Stanford Institute for Stem Cell Biology and Regenerative Medicine.

Nakauchi, who previously directed the Center for Stem Cell Biology and Regenerative Medicine at the University of Tsukuba, is the first scientist recruited to Stanford with the assistance of a $6 million Research Leadership Award from the California Institute for Regenerative Medicine. The award is designed to help bring stem cell researchers from outside California to the state, and to allow them to pursue high-risk, high-reward research.

“We are very excited to be bringing Dr. Nakauchi to Stanford,” said Irving Weissman, MD, director of the medical school’s stem cell institute and a professor of pathology and of developmental biology. “He is one of the world’s leading stem cell scientists. His recent discoveries that tissues and organs can be developed from pluripotent stem cells of one species in the body of an animal of another species promise an important path to using stem cell biology to advance human regenerative medicine.

The recruitment marks a return to Stanford for Nakauchi. After earning a medical degree from Yokohama City University and a PhD in immunology from the University of Tokyo, Nakauchi studied immune cell genes as a postdoctoral scholar in the laboratory of the late Stanford geneticist Leonard Herzenberg, PhD.

Nakauchi then returned to Japan to study both and immune stem cells at the RIKEN Research Institute and at the University of Tsukuba. In 2002, he became professor of stem cell therapy at the Institute of Medical Science at the University of Tokyo. In 2008, he was appointed director of the newly created Center for Stem Cell Biology and Regenerative Medicine there.

Nakauchi said he is excited to be coming back to Stanford, this time as a faculty member. Although the university has been tremendously busy over the past few years, he said, “it’s open, friendly and innovative atmosphere does not seem to have changed.”

Nakauchi notes there are differences between the way science is done in Japan and in the United States. “My challenge will be to combine and to utilize the best parts of the systems in both countries to do innovative science and create innovative scientists,” he said.

Nakauchi’s research involves clarifying the mechanisms of stem cell self-renewal and exploring new medical therapies involving stem cells. One project explores the possibility of creating human organs in large animals. Currently, the options for patients in need of organs or diseased organs are limited because suitable donor organs often cannot be found. Some stem cell scientists have explored the possibility of creating new organs from stem cells in the lab, but fully functional organs are shaped by interactions with the organs and tissues during development.

Nakauchi has pioneered an approach that may allow a patient to become the seeds for new, genetically matched organs that are grown in large animals. Once mature, these organs could be transplanted into the patient. Such organs could also become model systems for drug or human health research.
Chris Webb, Martha Kessler honored for support of university’s research mission

By Kathleen J. Sullivan

Two staff members at Spectrum, the university’s home for clinical and translational research, were presented with 2013 Marsh O’Neill Awards on Nov. 14 for their outstanding support of the university’s research mission.

This year’s honorees were Martha Kessler, executive director of finance for Spectrum and director of finance for the Department of Health Research and Policy, and Chris Webb, PhD, executive director of administration for Spectrum.

Spectrum, an independent center at Stanford founded in 2008, supports health-related research activities across the university. Its goal is to accelerate and enhance medical research, from basic and translational research among university medical centers to clinical and observational studies. Inception, and were instrumental in Stanford earning a competitive site visit from the National Institutes of Health.

Kessler arrived at Stanford in 1999, when she became the educational and financial coordinator for the Stanford Brain Research Center. She joined the Department of Health Research and Policy in 2002 and then Spectrum in 2008.

Webb came to Stanford in 1999 as a senior scientist for the Genome Technology Center. One year later, he became the center’s associate director. He served as institutional proposal development manager for the medical school’s Office of the Dean from 2004 to 2008. He joined Spectrum in 2008.

In a letter nominating Webb and Kessler for the Marsh O’Neill Award, faculty and staff praised them for shepherding the development of many major grant proposals to advance the mission of the medical school, the Department of Health Research and Policy, and Spectrum.

“The letter said Kessler and Webb’s management of the recent $50 million proposal for a new Clinical and Translational Science Award from the National Institutes of Health resulted in a perfect score for Stanford — giving the proposal top ranking among the 30 applications from leading universities and other academic medical centers across the country,” said Branimir Sikic, MD, professor of medicine and co-director of Spectrum, praised Webb and Kessler in a nomination letter, saying they had been the administrative and financial leaders of the program from its inception, and were instrumental in Stanford earning a perfect score for its five-year application for continued NIH funding.

“Chris and Martha deserve a lion’s share of the credit for the success of Spectrum, an achievement that has brought Stanford to the very summit of clinical and translational research among university medical centers,” Sikic said.

Harry Greenberg, MD, senior associate dean for research at the medical school and director of Spectrum, also commended Webb and Kessler, saying it had been an honor to have “two such able and dedicated colleagues” available to help him manage and improve Spectrum.

“Virtually all of our success can be related either directly or indirectly back to these two terrific individuals,” said Greenberg, who also is a professor of medicine and of microbiology and immunology, and the Joseph D. Grant Professor in the School of Medicine.

“Although they exemplify the traditional values of hard work, high integrity and complete reliability, perhaps their most unique skills are their ability, together, to work with both faculty and staff in a collegial way that seems to always result in progress and accomplishment of goals,” Greenberg said.

“Receiving and maintaining an NIH-supported Clinical and Translational Science Award is a badge of honor for any research-intensive biomedical research institution. Chris Webb and Martha Kessler have had a critical role in making this possible and in bringing this substantial honor and resource to Stanford.”

The award presentation — which includes a check for $5,000 for each winner — took place Nov. 14 at the Faculty Club.

The Office of the Dean of Research established the award in 2007 to recognize outstanding contributions to research at Stanford. Blythe Whimby, who chairs the University Postdoctoral Association, also is scheduled to give a presentation.

To download a complete transcript of the meeting notes, visit http://med.stanford.edu/senate.

Dean to hold town hall Dec. 6

A town hall meeting hosted by Lloyd Minor, MD, dean of the School of Medicine, is scheduled for 3 to 4 p.m. Dec. 6 in the Pacific Ocean Conference Room at 3160 Porter Drive in Palo Alto.

Seating for the event is limited, so please RSVP by Nov. 2 at http://gsi.TownHallRSVP.com.

Minor plans to devote part of the meeting to answering questions from faculty, staff and students, who may submit questions in advance by visit http://RSVP.im.

In addition, Nobel laureate Steven Chu, PhD, professor of molecular and cellular physiology and of physics, will discuss his views on interdisciplinary science and his reasons for returning to Stanford after a stint as U.S. Secretary of Energy.

Charles Proctor, MD, senior associate dean for medical education, will discuss the preliminary findings of the Liaison Committee on Medical Education’s recent site visit to the school. For those unable to attend the meeting, the URL for the streaming video will be emailed to members of the Stanford Medicine community as the event date approaches.

Faculty senate to meet Nov. 19

The next meeting of the medical school’s faculty senate is scheduled for 5:15 to 6:45 p.m. Nov. 19.

Laurence Baker, PhD, professor of health research design and editor-in-chief of the Stanford Postdoctoral Association, also is scheduled to give a presentation.

The medical school faculty can download the complete minutes of the senate meetings by visiting http://med.stanford.edu/senate.

For more information, visit http://med.stanford.edu/senate.

By Krista Conger

Recently some intriguing data has suggested that breast cancer patients whose tumors appear insensitive to a class of drugs known as anti-HER2 medications (the drug trastuzumab, marketed as Herceptin, is a well-known example) may somehow still benefit from treatment with the medication.

There’s an ongoing clinical trial to determine if trastuzumab, given in combination with other treatments, really is beneficial to more patients than previously thought. But the reason why it could be has been a mystery.

Now, a study from the laboratory of Maximilian Diehn, MD, PhD, assistant professor of radiation oncology, has started to answer some of these questions. The study was published online Oct. 31 in Cancer Research.

Typically, only tumors in which the cells express aberrantly high levels of a receptor molecule, HER2, on their surfaces — about 25 percent of all breast cancer cases — seem to shrink in the presence of the drugs, which bind to and inactivate the receptor. As a result, only these patients are given anti-HER2 agents.

“Trials of anti-HER2 agents like Herceptin in metastatic patients with HER2-negative tumors haven’t shown tumor shrinkage or improved outcomes, which is why these drugs are only approved for use in HER2-positive tumors,” Diehn said.

However, Diehn said that recent clinical studies have suggested the drugs may also help breast cancer patients with less-advanced tumors that don’t express high levels of HER2 — once most of the tumor has been treated with combinations of surgery, radiation and standard chemotherapy.

Although these patients don’t have visible tumors, microscopic numbers of cancer cells can remain and cause the disease to recur; treatment with anti-HER2 agents appears to improve their chances of survival.

Diehn and postdoctoral scholar Cleo Yi-Fang Lee, PhD, the lead author of the study, wondered why this could be. How could trastuzumab and other anti-HER2 agents effectively fight tumors that didn’t overexpress HER2? They hypothesized that perhaps the drugs were targeting only a few important cells in the tumor: the cancer stem cells. Also called tumor-initiating cells, cancer stem cells are able to both renew themselves and to generate all the cells of the original tumor. Killing them is vital to ensure that a tumor does not recur after seemingly successful treatment with chemotherapy, radiation or surgery.

Unfortunately, these cancer stem cells are uncom- monly resistant to normal radiation and chemotherapy.

“Our hypothesis was that the clinical observations described above could be explained if the anti-HER2 drugs work against microscopic deposits of cancer stem cells at least a subset of HER2-negative tumors,” Diehn said. “Patients with visible metastases of these types of tumors do not respond since only a small proportion of cells in the tumor deposits are cancer stem cells. However, if most of the tumor has been killed or removed through standard therapies, anti-HER2 agents may effectively target remaining cancer stem cells and possibly prevent recurrence.”

To understand how this could occur, Diehn, Lee and their colleagues studied breast cancer cells in mice and humans. They learned that, in a subset of tumors with only a few visible HER2-positive cells, the cells produce high levels of a molecule called neuregulin 1. Neuregulin 1 works by activating HER2 in these cancer stem cells to promote their growth and self-renewal.

Blocking HER2 or another molecule in the pathway, EGFR, together or separately inhibited the growth of breast cancer cells grown in the laboratory and after transplantation into mice. It suggested that the cells are particularly sensitive to the types of radiation used in cancer therapies.

The researchers hypothesize that a similar mechanism may exist in other types of cancers.

“Anti-HER2 therapies are already being used for esophageal and gastric cancers, and they have been explored for use in other cancers like those of the head and neck,” Diehn said. “It will be interesting to see if there is a similar dependence by cancer stem cells on HER2 signaling that would make these drugs even more effective in killing cancer stem cells in at least a subset of HER2-negative tumors.”

Contact Krista Conger at krista.conger@stanford.edu or by phone at 650-723-2283.

Maximilian Diehn

The award presentation — which

Chris Webb, Martha Kessler are recipients of the 2013 Marsh O’Neill Awards.

Kathleen Sullivan is university governance writer at the Stanford News Service.
While eating lunch, you notice an insect buzzing around your plate. Both its color and motion may influence how you respond. If the insect is yellow and black — the color of a bee — you may immediately jump up and scream. Conversely, you might simply be annoyed at the buzzing motion and shoo the insect away. You perceive both color and motion and decide based on the circumstances. Your brain makes such contextual decisions in a heartbeat.

The mystery is how it does so.

In an article published Nov. 7 in *Nature*, a team of Stanford neuroscientists and engineers delve into this decision-making process and report some findings that confound the conventional wisdom.

The neuroscientists believed that decisions of this sort involved two steps: One group of neurons would perform a gating function to ascertain whether motion or color was most relevant to the situation, and a second group of neurons would consider only the sensory input relevant to making a decision under the circumstances.

But in a study that combined brain recordings from trained monkeys and a sophisticated computer model based on that biological data, William Newsome, PhD, professor of neurobiology, and three other researchers discovered that the entire decision-making process may occur in a localized region of the prefrontal cortex.

In this region of the brain, located in the frontal lobes just behind the forehead, they found that color and motion signals converged in a specific circuit of neurons. In their experimental evidence and computer simulations, the scientists hypothesized that these neurons act together to make two snap determinations: whether color or motion is the most relevant sensory input in the given situation, and what action to take as a result.

“We were quite surprised,” said Newsome, who is also the Harman Family Provostial Professor and senior author of the paper. “Until now, neuroscientists believed that decisions of this sort involved two steps: One group of neurons would perform a gating function to ascertain whether motion or color was most relevant to the situation, and a second group of neurons would consider only the sensory input relevant to making a decision under the circumstances.”

The model predicts a very specific form of activity, while the neural network is very specific in what it is doing all of the time, Sussillo said. “If our model is correct, then almost all neurons in this biological circuit appear to be contributing almost all of the information to the selection and decision-making mechanism.”

“Newsome, who directs the Stanford Neurosciences Institute, put it this way: ‘We think that all of these neurons are interested in everything that’s going on, but they’re interested to different degrees. They’re multi-tasking like crazy.’”

Other researchers who were not directly involved commended the Stanford team.

“This is a spectacular example of excellent experimentation combined with clever data analysis and creative theoretical modeling,” said neuroscientist Larry Abbott, PhD, of Columbia University.

Christopher Harvey, PhD, a neurobiologist and medical school graduate student, said the paper “provides major new hypotheses about the inner-workings of the prefrontal cortex, which is a brain region that has frequently been identified as significant for higher cognitive processes but whose mechanistic functioning has remained mysterious.”

The Stanford scientists are now designing an experiment to ascertain whether the interplay between selection vector and line attractor, which they deduced from their software model, can be measured in actual brain signals.

“The model predicts a very specific form of activity under very specific circumstances,” Sussillo said. “If we can stimulate the prefrontal cortex in this way, and then measure this activity, we will have gone a long way toward proving that the model mechanism is indeed what is happening in the biological circuit.”

The work was supported by the Howard Hughes Medical Institute, the Air Force Research Laboratory, a Director’s Pioneer Award from the National Institutes of Health, and the Defense Advanced Research Projects Agency.

Tom Abate is the associate director of communications at Stanford Engineering.

After studying biological data and a computer model, scientists believe that neurons in the prefrontal cortex receive both color and motion data, and then screen out the irrelevant sensory input to make decisions.
Faculty’s artistic talent showcased at campus exhibition

By Holly MacCormick

Only last year, the walls of the Li Ka Shing Center for Learning and Knowledge were stark, bare, unexciting. For Paul Berg, PhD, professor emeritus of biochemistry, and Philip Pizzo, MD, then dean of the medical school, these empty walls were like a pristine canvas awaiting an artist’s touch.

“We decided we were going to do everything we could to find works we could hang that weren’t overly expensive,” Berg said, eliciting laughter from a crowd that had gathered Nov. 5 to celebrate the opening of School of Medicine’s fourth art exhibition at the Li Ka Shing Center.

Berg and Pizzo’s vision for the center led to the creation of the school’s art committee and the first art exhibition at the center in January 2012. According to Berg, as artists from the medical school began submitting their works, the committee realized that the exhibit was no longer just about designing on a budget. “Our role would also be to support the arts in the School of Medicine,” Berg said.

This fall, the exhibition features the photography and glasswork by four current and emeritus professors and one of their spouses. It’s a “sample of the remarkable talents of our faculty,” Berg said.

The exhibition also shows how the School of Medicine has inspired and encouraged each of these scientists to pursue the arts.

“It’s a career that snuck up on me,” said Ira Glick, MD, professor emeritus of psychiatry and behavioral sciences. Glick’s photos are proof of a foray into a world that he doesn’t normally venture into. “I’m a night photographer,” he said. “But I’m not a night person.”

Since Glick worked for Stanford during the day, many of his photos were taken at night in countries he visited. “My work with Stanford has gotten me there when the photo was taken,” he said. “It’s a way of prolonging the experience,” he said.

Litt said the unpredictable nature of glasswork is unlike her work as a physician. “As a physicist, everything had to be right,” Litt said. “As an artist, you go with the flow. Sometimes the outcome is better than you imagined.”

For Matthew Scott, PhD, professor of developmental biology, of genetics and of bioengineering, the exhibit was an important milestone in a lifelong pursuit of developmental biology, of genetics and of psychiatry and behavioral sciences.

“Iris Litt patterned a glasswork, left, on a photograph taken by her husband, Dale Garell, that hangs on the adjacent wall. Right: No Escape, a photo by Ira Glick.

Blood Center to hold annual ‘Rivals for Life’ drive Nov. 19

As the football teams from Stanford and UC-Berkeley prepare to face off Nov. 23 in the Big Game, the schools’ respective blood banks are getting ready for their own competition.

The Stanford Blood Center’s seventh annual “Rivals For Life” blood drive will take place at the Arrillaga Center for Sports and Recreation on Nov. 19 from 11 a.m. to 7 p.m. The event will be hosted by BeWell, the wellness-incentive program for Stanford employees.

Cal, in conjunction with American Red Cross and the UC-San Francisco Blood Center to hold annual ‘Rivals for Life’ drive Nov. 19

Each donor at the Stanford Blood Center drive will receive a commemorative T-shirt and be entered into a prize drawing for the chance to win a Sports Basement gift certificate.

Donors should be in good health with no cold or flu symptoms. They must eat well prior to donation, drink fluids and present photo identification at the time of donation. The process takes about an hour. For more information or to schedule an appointment, please call (888) 723-7831 or visit bloodcenter.stanford.edu.

Holly MacCormick is a writing intern for the Office of Communication & Public Affairs.

A photograph of Yosemite’s El Capitan, reflected in water, taken by Matthew Scott and on display as part of an art exhibition at the Li Ka Shing Center.
analyze, and can’t show the full range of Caribbean diversity,” Moreno-Estrada said. “We wanted to approach the question from the other end — starting from the present day and going back in time.”

The group, led by Bustamante and Martin, documented genetic variants found in 251 people of Caribbean descent — representing Cuba, Puerto Rico, Haiti, the Dominican Republic, Honduras and Colombia — living in South Florida, and 79 Venezuelans representing three native South American tribes. They then compared the genetic variants with those found in more than 3,000 Native Americans, Europeans and Africans.

“For us, this is a very important project,” Martin said. “Hispanics and Latinos are the second-largest ethnic group in the United States, with people tracing their national origins to more than two dozen countries. Yet they are largely underrepresented in medical genetic studies. An often-cited reason for this is that we do not know enough about genetic differences within and among groups to effectively design multi- and trans-population studies. Dr. Martin and I were very fortunate to receive NIH funding for the GOAL project [Genetic Origins and Admixture of Latinos], which develops novel medical and population genetic approaches that we hope will improve the design and, ultimately, the outcome of medical genetic studies in this group.”

To conduct the research, the team devised a new way of analyzing genetic differences to infer ancestry at a fine geographic scale. Using this approach, they were able to estimate not just what proportion of each individual’s genome was derived from each continent, but also to determine the closest ancestral group at a more regional level.

“The approach allowed the researchers to categorize regions of DNA as not just European, for example, but Iberian, or not just African, but West African. They could even estimate when each ancestral segment occurred by assuming longer segments had been incorporated more recently than shorter segments. That’s because, over time, our chromosomes randomly swap regions during cell division, revealing a type of genetic debris left behind from the ancient mixing events. This fine-grained view of history provides us with a way to better determine the geographic origins of specific genomic regions,” Moreno-Estrada said.

Estrada said. “We then looked within those segments to more precisely determine their geographic source within those larger groups. This approach allowed the researchers to categorize regions of DNA as not just European, but Iberian, or not just African, but West African. They could even estimate when each ancestral segment occurred by assuming longer segments had been incorporated more recently than shorter segments. That’s because, over time, our chromosomes randomly swap regions during cell division, revealing a type of genetic debris left behind from the ancient mixing events. This fine-grained view of history provides us with a way to better determine the geographic source within those larger groups.

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The two Shelbys met. The older one, 17-year-old Shelby, who, coincidentally, is also named Shelby, is a high school junior at South Miami Senior High. She was diagnosed with type 1 diabetes at age 9.

“She’s never once complained about her diabetes,” said her mom, Lisa.

“She is very, very tough. She is a fantastic athlete who plays soccer, tennis, and basketball. She is a great attitude towards the disease,” she said. “Her determination speaks volumes.”

The researchers found, for example, that the Caribbean was first populated by people from inland South America about 2,500 years ago. Their DNA mirrors that of Amazonian tribes in the interior of the continent, and this flow of genes matches what is known about how language spread across the region during that time.

The European component, which was introduced 16 to 17 generations ago (or about 500 years ago — roughly when Columbus reached the islands) matches, but does not exactly mirror, the range of genetic diversity in modern-day Iberia. This finding most likely indicates that a small number of Europeans settled in the Caribbean and contributed their DNA to future islanders. It also confirms that, after the initial colonization of the Caribbean islands, future waves of immigration from Europe primarily came to the mainland.

Finally, African genetic diversity was first introduced to the Caribbean population about 15 generations ago (about 1550), when the first enslaved Africans were brought to the islands. The second pulse occurred five to seven generations ago, during the late 18th century, at the height of the transatlantic slave trade. The origin of the first pulse arose from the north coast of West Africa, whereas the second originated from the central coast of West Africa.

“The transatlantic slave trade involved the brutal and forced migration of over 12 million people,” Bustamante said. “They were the ancestors to and kin of many people who now live in the Americas, Africa and throughout the world today. We have tried to understand for years what role, if any, DNA can play in reconstituting these voyages. Realistically, we are just scratching the surface and seeing that we can find genetic signals that corroborate historical research. We are cautiously optimistic that as technology improves we can delve deeper and help reclaim more of this critically important history.”

As exciting as it is to use genetics to answer age-old historical mysteries, it’s the potential contribution of this knowledge to medicine that has captured the researchers’ interest.

“All this affects what we call a genetic-mapping strategy to identify disease variants specific to population subgroups,” Moreno-Estrada said. “For example, those individuals with more European influence may be at increased risk for certain diseases because that genetic contribution was made by only a few individuals. Or, perhaps Caribbean with more African ancestry may share an increased risk of diseases with others from West Africa. We’re not yet at the point where we are able to say which populations are most likely to have specific diseases, but now we can begin to figure out the important components.”

Other Stanford co-authors include former postdoctoral scholar Simon Gravel, PhD; former graduate student Fouad Zakaria, PhD; postdoctoral scholars Jake Byrnes, PhD, and Karla Sandoval, PhD; graduate student Patricia Ortiz-Yello; senior research scientist Paul Norman, PhD; and Peter Parham, PhD; professor of structural biology and of microbiology and immunology.

The research was supported by the National Institutes of Health, the Stanford J. Clauer Foundation and the George Rosenkranz Prize for Health Care Research in Developing Countries.

The Department of Genetics also supported the work.

Diabetes

“It can be hard to manage and really frustrating at times, but it is something that you can control,” Payne said. “I have found that there are people who do not have type 1 diabetes. They don’t feel the same way. They feel like they can’t live their lives. I feel like I can live my life.”

“I think little Shelby just has such a great attitude towards the disease,” said DelSalvo. “That inspiration works both ways, according to Shelby Payne. She’s a positive role model in dealing with the disease, showing them the insulin pump she uses instead of a syringe, and sharing tips on how she manages training for soccer with diabetes.”

If she can be, facing a lifetime of needles and pumps, knowing you’ll always have to pay attention to your diabetes.

But after talking with Shelby Payne, the Stanford team, when Shelby Payne had a chance to pick a new number on her team, the DeAnza Force, she opted for 6 — the number worn by Shelby Payne. Young Shelby has also decided she wants to attend Stanford and play on its women’s soccer team.

“Shelby, her parents and the Payne sisters have all joined TrialNet, an international collaboration of institutions, including Packard Children’s and Stanford, running clinical trials on the development of type-1 diabetes in families, its prevention and early treatment. I think having a role model to look up to, someone with type-1 diabetes who has really succeeded in life, in sports and in academia, really gave Shelby some peace of mind about her disease and helped her do a good job of managing her diabetes,” said DeSalvo.

That inspiration works both ways, according to Shelby Payne.

“I think little Shelby just has such a great attitude towards the disease,” she said. “When I see a little girl like her doing anything she wants to, working hard, playing soccer every day, that attitude is infectious. She inspires me.”

Infectious.
Drug trial seeks participants with autism spectrum disorder

By Louis Bergeron

Researchers at the School of Medicine are seeking participants for a study examining the effectiveness of vasopressin, a neuromodulator, in treating children with autism spectrum disorder.

Difficulty with social interactions is characteristic of people with autism, who often have problems interpreting facial expressions or maintaining eye contact while talking with someone. There are currently no effective medicines available to treat social problems in people with autism.

Neuropeptides, such as vasopressin, are molecules stored by neurons in the brain to communicate with one another. Vasopressin has been shown to facilitate social interaction in animals.

Animal studies have also shown that when the proper functioning of vasopressin is interfered with, animals develop a variety of social deficits, including impaired memory for peers and a reduced interest in social interaction.

Researchers found that when vasopressin was administered to mice with a genetically induced form of autism, their social behavior became more normal.

Vasopressin is already approved by the Food and Drug Administration for use in humans, and has proved to be a successful treatment for some common pediatric conditions, including bedwetting. It also has the potential to improve social cognition and memory in people who do not have autism.

The researchers will test the effects of vasopressin on social impairments in 50 high-functioning boys and girls with autism, ages 6 to 12. The study will last four weeks.

Participants will be randomly chosen to receive either vasopressin or a placebo. At the end of the study, those who received the placebo will have the option of participating in a further four weeks of treatment during which they will be given vasopressin.

Stanford is the only site for the study. Participants do not need to live locally but will need to come to the Stanford University Department of Psychiatry and Behavioral Sciences for at least three visits. They will be provided with a $20 payment for each completed study visit and will be given general results from autism diagnostic assessments and neuropsychological tests.

Karen Parker, PhD, assistant professor of psychiatry and behavioral sciences, and Antonio Hardan, MD, professor of psychiatry and behavioral sciences, are principal investigators of the study.

This investigation is funded in part by the National Institute of Mental Health and by the Child Health Research Institute at Stanford University.

For more information visit, http://med.stanford.edu/principal/trials/NTCT01962870. To apply to participate in the trial, contact Robin Lliboe at 736-1235 or rlliboe@stanford.edu.

Memorial for Anthony Felsovanyi, clinical professor emeritus, Nov. 23

A memorial will be held for Anthony Felsovanyi, MD, an adjunct clinical professor emeritus of medicine, at 4 p.m. Nov. 25 in the Stanford Faculty Club.

Felsovanyi, an internist, died Oct. 7 at his home in Menlo Park. He was 98.

“As a community physician and an academic teacher, he embodied the characteristics to which we all strive,” said Kelley Skeff, MD, PhD, the George DeForest Barnett Professor in Medicine. “Showing dedication over many decades, he represented a level of commitment to and love of internal medicine that was unaissled by age and unclouded by changes in the health-care system.”

Felsovanyi first came to the School of Medicine as a fellow in cardiology shortly after World War II. He later became an adjunct faculty member, a position he held for decades. Skeff described him as a revered community physician who, into his 90s, continued to attend medical conferences, as well as to teach on Stanford Hospital wards, where he inspired trainees and colleagues throughout his career.

“Theing was one of the highlights of my professional career and lasted some 40 years,” Felsovanyi said in a 2011 interview. “The students were very inspiring to me, and their enthusiasm egged me on.”

In 2006, Felsovanyi was awarded the title of Master of the American College of Physicians, which is bestowed for “personal character, positions of honor, contributions towards furthering the purposes of the ACP, eminence in practice or medical research, or other attainments in science or in the art of medicine.”

He is survived by his wife, Shirley; children Andrea and Steven; and a grandson, Stan Felsovanyi.

In lieu of flowers, donations can be made “In memory of Dr. Anthony Felsovanyi” for medical scholarships. Checks should be made payable to Stanford University and sent to Development Services, P.O. Box 20466, Stanford, CA 94309.

Bleach continued from page 1

followed his hunch that an antimicrobial effect of dilute bleach might explain the whole story,” Kim said. “And his work has revealed new mechanisms for targeting inflammatory pathways with this versatile small molecule. It has also identified new possible clinical applications.”

Leung and his colleagues knew that many skin disorders, including eczema and radiation dermatitis, have an inflammatory component. When the skin is damaged, immune cells rush to the site of the injury to protect against infection. Because inflammation itself can be harmful if it spirals out of control, the researchers wondered if the bleach (sodium hypochlorite) solution somehow played a role in blocking this response.

To find out, they homed in on a molecule called nuclear factor kappa-light-chain-enhancer of activated B cells, or NF-kB, which is known to play a critical role in inflammation, aging and response to radiation. When activated by signaling molecules, it enters the cell’s nucleus and binds to DNA to control gene expression. When inactive, it is sequestered in the cytoplasm, away from the DNA.

Leung wondered if there could be a link between the effect of the dilute bleach solution and NF-kB’s role in skin. He exposed human keratinocytes, or skin cells, to 0.0055 percent bleach for one hour before treating them with a signaling molecule that normally activates NF-kB function. He found that exposure to the solution blocked the expression of two genes known to be regulated by NF-kB. The effect was reversible, however, 24 hours after the bleach treatment restored NF-kB’s ability to regulate expression of the target genes.

Further investigation divulged how this happens.

“We found that the bleach solution oxidizes and inhibits an activator necessary for NF-kB to enter the nucleus, essentially blocking NF-kB’s effect,” Leung said. When the researchers mutated the activator to be oxidation-resistant, NF-kB’s gene targeting activity was unwound.

Next, the researchers turned to potential clinical applications. Radiation dermatitis is a common side effect of radiation therapy for cancer. While radiation therapy is directed at cancer cells inside the body, the normal skin in the radiation therapy field is also affected. Radiation therapy often causes a sunburn-like skin reaction. In some cases, these reactions can be quite painful and time consuming to treat, interrupting radiation therapy courses and preventing the skin to heal before resuming treatment. However, prolonged treatment interruptions are undesirable.

“It could be easy, safe and inexpensive,” Leung said. “An effective way to prevent and treat radiation dermatitis would be of tremendous benefit to many patients receiving radiation therapy,” said Susan Knox, MD, PhD, associate professor of radiation oncology and study co-author.

Leung and his colleagues tested the effect of daily, 30-minute baths in bleach solution on laboratory mice with radiation dermatitis. They found that the animals bathed in the bleach solution experienced less severe skin damage and better healing and hair regrowth than animals bathed in water.

They then turned their attention to old — but healthy — laboratory mice.

Multiple research studies have linked increased NF-kB activity with aging,” Leung said. “We found that if we blocked NF-kB activity in elderly laboratory mice by bathing them in the bleach solution, the animals’ skin began to look younger. It went from old and fragile to thicker, with increased cell proliferation.” The effect diminished soon after the dilute-bleach baths were stopped, indicating that regular exposure is necessary to maintain skin thickness.

The researchers are now considering clinical trials in humans, and they are also looking at other diseases that could be treated by dilute-bleach baths. It’s possible that, in addition to being beneficial to radiation dermatitis, it could also aid in healing wounds like diabetic ulcers,” Leung said. “This is exciting because there are so few side effects to dilute bleach. We may have identified other ways to use hypochlorite to really help patients. It could be easy, safe and inexpensive.”

Other Stanford co-authors of the study were Lilian Zhang, a life sciences research assistant; senior researcher Jing Wang, MD; and research associate Shoucheng Ning, MD, PhD.

The study was supported by the Dermatology Foundation, the National Institutes of Health and the Howard Hughes Medical Institute.

Information about Stanford’s Department of Dermatology, which also supported the work, is available at http://dermatology.stanford.edu.
1. I wanted to begin by asking you about the use of the terms “war on cancer” and “race for the cure.” You don’t think that these terms are especially helpful, do you?

MITCHELL: I feel a lot of type of language is misleading. “War” implies something with a beginning and an end and that we are going to win. It’s really about a long-term, multifaceted effort to improve the quality of care. It’s really about a long-term, multifaceted effort to make cancer treatment less toxic and better tailored to individual patients. Beverly Mitchell, professor of medicine and director of the Stanford Cancer Institute, recently discussed these trends, as well as new initiatives at Stanford Medicine aimed at transforming care for cancer patients, with Paul Costello, chief communications officer at the medical school. Mitchell is also the William and Flora Hewlett Professor of Medicine.

2. What are some of the biggest myths that people have about cancer?

MITCHELL: There is a lot of fear that a cancer diagnosis means a fatal diagnosis. Of course it can be a devastating disease, but we have the ability to significantly improve the outcomes of many people with cancer. We can help demystify cancer by educating patients about the specifics of their disease and involving them in their care decisions.

3. Why are there forms of cancer so treatable and some still so intractable?

MITCHELL: It relates to the biologic basis of different types of cancer. We deal a great deal about the causes of some cancers. For example, the vast majority of cervical cancer cases result from the papillary smear frequency, which prevents the infection and thereby greatly reduce cancer incidence, which is exciting. Other cancers, such as lung and pancreatic, result from multiple different genomic abnormalities, which make them hard to treat as one disease. Often, these tumors don’t respond very well to our traditional therapies, or recur after an initial positive response. Understanding the genetic characteristics of these more resistant cancers is increasingly the focus of our research.

4. What progress is being made to reduce the toxicity and side effects for the current cancer treatments, particularly chemoradiotherapy?

MITCHELL: The biggest concern with traditional chemotherapy has been nausea and vomiting, and we now have drugs to address that in most cases. Of course, side effects are still a big problem, so our goal is to develop new, more targeted therapies that cause fewer side effects. This is another reason that we are so interested in developing drugs that seek out the genetic markers found only in cancer cells and not healthy cells. We are also working on strategies to empower patients’ own immune systems to more effectively kill cancer cells without having to use harsh toxins like radiation and chemotherapy.

Patients often feel overwhelmed by conflicting advice and have trouble navigating a very complex health-care system. There’s a major new initiative under way at Stanford that’s just begun to transform this aspect of cancer care and the patient’s experience. Could you talk about that?

MITCHELL: We believe that we can improve every aspect of how we treat cancer patients, and not just the therapies we provide. A better experience starts with improving access to more people and delivering comprehensive, compassionate care to each patient. It involves specially trained multidisciplinary coordinators who anchor a decision-making team that includes the primary physician, the patient and a family member. It also includes our improved use of communications technologies so that patients can have instant information and assistance when they need it, more conveniently and for lower costs. We understand that having cancer is tough enough for patients and their families, so we are committed to using every resource at our disposal to provide the best possible care in the most efficient and humane way we can.

Gary Shaw, DrPH, professor of pediatrics and associate chair for research in the Department of Pediatrics, has received the March of Dimes Agnes Higgins Award for outstanding achievements in the field of maternal-fetal nutrition. The award was presented at the annual meeting of the American Public Health Association. Shaw is co-principal investigator of the March of Dimes Prematurity Research Center at Stanford University.

Kipp Weiskopf and Aaron Ring, were awarded top prize in the graduate student division of the 2013 Colleague of the Year Awards, given to an individual who has made outstanding contributions to promoting justice in medical education and health-care equity in the United States. This year, Glover co-led the Stanford University Minority Medical Alliance Conference and co-chaired the course, “Rural and American Indian Health Disparities,” which included a trip to the Rosebud Sioux Reservation in South Dakota. He received a $5,000 award and the Nickens Lecture at the AAMC’s annual Diversity Policy and Programs unit, is given to an individual who has made outstanding contributions to promoting justice in medical education and health-care equity in the United States. This year, Glover co-led the Stanford University Minority Medical Alliance Conference and co-chaired the course, “Rural and American Indian Health Disparities,” which included a trip to the Rosebud Sioux Reservation in South Dakota. He received a $5,000 award and the Nickens Lecture at the AAMC’s annual Diversity Policy and Programs unit, is given to an individual who has made outstanding contributions to promoting justice in medical education and health-care equity in the United States.

Jennifer Lee, MD, has been appointed associate professor of medicine, effective Nov. 1. Her research focuses on the microenvironment of tumor cells and its role in cancer progression and tissue remodeling within the tumor microenvironment and the tumor-stroma interactions that have important clinical implications.

Christopher Gardner, PhD, has been appointed professor (research) of medicine, effective Nov. 1. He conducts research on nutrition and preventive medicine, with a particular focus on plant-based diets; cardiovascular disease; cancer; obesity; dietary response to weight loss diets by insulin resistance status; the link between dietary behavior and social changes; stealth nutrition; and food marketing.

Heng Zhao, MD, has been promoted to professor (research) of neurosurgery, effective Oct. 1. His work focuses on understanding the microenvironment that regulates the effective expression and postconditioning and remote reconditioning against stroke.

Ciaran Phibbs, PhD, has been appointed associate professor (research) of pediatrics, effective Nov. 1. His research interests include perinatal and neonatal care and how hospital competition interacts with costs, demand and outcomes.

Julia Salzman, PhD, has been appointed associate professor of biochemistry, effective Nov. 1. The goal of her research is to use experimental and statistical tools to construct a high-dimensional picture of gene regulation, including various ways of controlling the full repertoire of RNAs expressed by cells. Currently, her lab focuses on studying the biogenesis and function of circRNA. It can be tricky, but you get a good sense of what drives more or less efficient physician behavior, including organizational features of workplace design, financial and social incentives, and the use of information technology.

Kenneth Mahaffey, MD, has been appointed professor of medicine, effective Oct. 1. His primary research interest is the design and conduct of multicenter clinical trials and analyses of important clinical cardiac issues using large patient databases. He also serves as vice chair of clinical research in the Department of Medicine.

Yair Blumenfeld, MD, has been appointed assistant professor of obstetrics and gynecology, effective Nov. 1. His research interests include prenatal diagnosis, genetics and clinical obstetrics. Blumenfeld also serves as medical director of delivery at Lucile Packard Children’s Hospital.

Jennifer Lee, MD, has been appointed associate professor of medicine, effective Oct. 1. Her research focuses on the microenvironment of tumor cells and its role in cancer progression and tissue remodeling within the tumor microenvironment and the tumor-stroma interactions that have important clinical implications.

Beverly Mitchell, on advances in cancer care

In the past few years, there have been dramatic advances in the use of genome analysis, molecular biology, imaging technologies and data management to make cancer treatment less toxic and better tailored to individual patients. Beverly Mitchell, professor of medicine and director of the Stanford Cancer Institute, recently discussed these trends, as well as new initiatives at Stanford Medicine aimed at transforming care for cancer patients, with Paul Costello, chief communications officer at the medical school. Mitchell is also the William and Flora Hewlett Professor of Medicine.

Following is an edited transcript of their conversation.

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