Valve replacement via catheterization is gaining ground

By Tracie White

When Maryann Casey battled breast cancer more than 30 years ago, her doctors warned that the radiation therapy could damage her heart. Still, she was caught off guard when, after an echocardiogram in 2012, she was diagnosed with severe aortic stenosis, a potentially fatal heart-valve disease.

“They were telling me I could drop dead,” said Casey, 62, who lives in San Jose with her husband and 20-year-old daughter. Her local doctor said the key valve that carries blood out of the heart into the aorta had severely narrowed, obstructing blood flow and dangerously stressing her heart. “They said, you need to have open-heart surgery immediately.”

Despite that frightening warning, Casey, who retired after 24 years as a security manager in Silicon Valley, soon learned that open-heart surgery wasn’t her only option. After the shock of receiving her second diagnosis of a potentially fatal disease, she quickly made an appointment with her oncologist, the same Stanford physician who she credits with saving her life and who continues to give her yearly physical examinations and mammograms.

“I was told by my oncologist I would probably never heal correctly after open-heart surgery,” Casey said. “He knew about this new treatment and recommended I go talk to the heart doctors there.”

Casey was lucky. Her Stanford oncologist, Frank Stockdale, MD, PhD, the Maureen Lyles D’Amrogio Professor of Medicine emerita of oncology, who led the effort from 1993 until 2001 to design and build the center. “But we needed a building to reflect the way we already practiced,” she said. “It is an embodiment of our faculty and staff cast in bricks and mortar,” she said. “It is the vision of our faculty and staff cast in bricks and mortar.”

Rodin’s hand sculptures diagnosed as part of exhibit

By Tracie White

Eight of the 10 Rodin hand sculptures on display in a new exhibit have been diagnosed for malformations and diseases by a School of Medicine hand surgeon.

One of the sculptures has been “repaired” using virtual surgery by techies in the school’s Division of Clinical Anatomy. And with the help of more digital wizardry, viewers can see virtual blood and bone in the bronze hands.

Inside Rodin’s Hand: Art, Technology and Surgery, which runs April 9 through Aug. 3 at Stanford’s Cantor Arts Center, is a feat of interdisciplinary collaboration that celebrates the connection between sculptor Auguste Rodin’s fascination with the human form and medicine’s fascination with human anatomy.

“A deep and rich history

See VAl Ve, page 7

See tumoRS, page 6

Blood test could be accurate way to detect solid cancers

By Krista Conger

A blood sample could one day be enough to diagnose many types of solid cancers, or to monitor the amount of cancer in a patient’s body and responses to treatment. Previous versions of the approach, which relies on monitoring levels of tumor DNA circulating in the blood, have required cumbersome and time-consuming steps to customize it to each patient or have not been sufficiently sensitive.

Now, researchers at the School of Medicine have devised a way to quickly bring the technique to the clinic. Their approach, which should be broadly applicable to many types of cancers, is highly sensitive and specific. With it they were able to accurately identify about 50 percent of people in the study with stage-1 lung cancer and all patients whose cancers were more advanced.

“We set out to develop a method that overcomes two major hurdles in the circulating tumor DNA field,” said Maximilian Diehn, MD, PhD, assistant professor of radiation oncology. “First, the technique needs to be very sensitive to detect the very small amounts of tumor DNA present in the blood. Second, to be clinically useful it’s necessary to have a test that works off the shelf for the majority of patients with a given cancer.”

The researchers describe their findings in a paper that was published online April 6 in Nature Medicine. Diehn shares senior authorship with Ash Alizadeh, MD, PhD, assistant professor of medicine. Postdoctoral scholars Aaron Newman, PhD, and Scott Bratman, MD, PhD, share lead authorship.

“We’re trying to develop a general method to detect and measure disease burden,” said Alizadeh, a hematologist and oncologist. “Blood cancers like leukemia can be easier to monitor than solid tumors through ease of access to the blood. By developing a general method for monitoring circulating tumor DNA, we’re in effect trying to transform solid tumors into liquid tumors that can be detected and tracked more easily.”

Even in the

See TUMORS, page 6

Center celebrates 10 years as hub of cancer treatment

By Grace Hammerstrom

Cancer patients’ experience at Stanford was transformed with the opening of a state-of-the-art, 218,000-square-foot medical building in 2004.

For a decade, the ambulatory outpatient clinic has brought together all of Stanford Medicine’s cancer specialties under one roof. It has given physicians space to work and gather, and fostered a new level of collaboration. And it has done so in an environment designed to bring humanity to cancer care.

“Our goal is for Stanford to own the complexity of care coordination, and allow our cancer patients and their families to focus on the healing,” said Amir Dan Rubin, president and CEO of Stanford Hospital & Clinics. “This beautiful building and our superb faculty and staff are instrumental in us attaining that goal.”

As the Stanford Cancer Center celebrates its 10th anniversary of serving patients, many of those involved in its planning, construction and operation reflect on the milestone.

“Stanford already had an incredible multidisciplinary approach to cancer,” recalled Charlotte Jacobs, MD, professor emerita of oncology, who led the effort from 1993 until 2001 to design and build the center. “But we needed a building to reflect the way we already practiced.”

Indeed, when Stanford broke ground on the building on Sept. 4, 2001, Jacobs spoke of the achievement as being much more than a building. “It is the vision of our faculty and staff cast in bricks and mortar,” she said. “It is an embodiment of our cancer faculty. It reflects their multidisciplinary approach to cancer, their zeal for discovery, their superb clinical expertise and their dedication and concern for patients.”

Patients had long come to Stanford to receive care in multiple locations. Waiting rooms on the ground floor of the hospital were crowded, often standing-room only. There

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Scientists are working to solve a mystery: How does nature construct the different types of synapses that connect neurons?
One of the buzzwords at Stanford is collaboration. Faculty easily cross lines and work outside traditional departmental hierarchies. Why does that seem to flourish so easily here?

We are fortunate that our tradition of fostering collaborative research was established years ago and became official back in 1982, when then-provost Albert Hastorf signed a very forward-thinking policy that called for interdisciplinary institutes to promote collaboration. The first independent labs were mostly in the hard sciences, but others that followed shortly thereafter were what is now the Freeman Spogli Institute for International Studies, the Stanford Institute for Economic Research and Policy and the Stanford Humanities Center. These programs paved the way for us to take advantage of new opportunities for interdisciplinary research and scholarship that are all around us now.

An important element of the Stanford organizational structure is that the dean of research is designated as the cognizant dean for the independent institutes. Again, the policy is produced by the Office of the Dean of Research, with the cognizant organizational structure that the dean of research is designated as the cognizant dean for the independent institutes. The policy, with the cognizant organizational structure that the dean of research is designated as the cognizant dean for the independent institutes.

Another very specific historic reason collaboration succeeded at Stanford is the original organization of seven schools, including our professional schools, on one campus. Even though Stanford can seem like a very big place, if you connect with the places and people, you will always find a faculty from various disciplines to encounter each other, you can appreciate why it’s not so hard to overcome barriers to collaboration.

2 Even with faculty on one campus, disciplines have distinct cultures that can present their own barriers. How do you facilitate cross-campus collaboration?

Much of what we do through the institutes and with school-based centers that cross disciplines is provided to the community through remarkable places for faculty and students to get together, whether in a formal setting with talks by people who are coming to a problem from many different angles, such as the Uncommon Dialogues of the Woods Institute for the Environment, or in informal discussions where they learn approaches and ways of thinking that are relevant for their work. Of course, creating new collaborations is not an overnight thing. Researchers are finding that the analytical frameworks and the tools of one discipline are suddenly very relevant to other disciplines and revolutionizing the research that can be done.

Therapy programs at Stanford have found that being able to put together an interdisciplinary team is critical. Research often entails a creative tension. For example, the department of neurology and chemical biology institutes to continue this paradigm shift.

3 Why the increased focus on interdisciplinary research? Has disciplines become too specialized?

I don’t think the disciplines have become too specialized at all. I am a firm believer that discipline must be strong. But the intersections of disciplines are where new ideas emerge and innovative research happens. We are at a time in the history of science where the work that the disciplines have been doing is spilling out over the top of whatever silos we have had. Researchers are finding that the analytical frameworks and the tools of one discipline are suddenly very relevant to other disciplines and revolutionizing the research that can be done.

That’s why Bio-X [which bridges biology, the biomedical sciences, the physical sciences and engineering] was so groundbreaking when it was founded in 1998. Faculty who led this initiative had remarkable foresight about how these scientific disciplines would benefit from coming together in the Clark Center and through the networks created across faculty across the campus. The new Institute for Chemical Biology has also emerged from this tipping point. It connects people from chemistry and chemical biology in an interdisciplinary search that will have major benefits for human health.

Our students are another important reason to encourage and facilitate interdisciplinary research. In fact, the momentum to take these approaches often comes from students who are highly motivated by the potential for interdisciplinary opportunities. At the same time, we have to prepare our students to be able to function well in the new environment for research and scholarship, where the ability to cross boundaries is increasingly important for success.

4 The independent entities at Stanford often span many departments and schools. Are they ever at cross-purposes with the central administration?

Yes. It’s not always tidy. As deans, we have to really work together to balance objectives in which sometimes involves a creative tension. For example, the departments and schools have the authority over faculty appointments, which the dean of research does not have, except for some faculty in the policy-related institutes, or the deans of research. We are working to find more space for research where the faculty member’s program is located. But these challenges and the need to find creative ways to build and sustain these exciting new programs.

A structure of schools and departments with independent labs, centers and institutes mirrored across this university campus is very powerful. It allows us to manage a university, but I think it has been quite well accepted that the opportunities it creates are worth the effort.

5 How much do you worry about the unpredictable nature of federal funding for scientific research?

The fact that research funding is flat and has been so for several years now is very worrisome. Stanford faculty and students are fortunate to have some more diverse sources of support, including federal, corporate funds and other sources. We have found that being able to put together an interdisciplinary team is critical. Research involves a creative tension. For example, the department of neurology and chemical biology institutes to continue this paradigm shift.

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Protein in nerves plays key role in pruning brain connections

By Amy Adams

A newborn baby, for all its cooling cuddliness, is a data-acquisition machine, absorbing information to finish honing the job of brain wiring that started before birth. This is true nowhere more so than the eyes, which start life peering at a blurry world and within months can make out a crisp, three-dimensional image of a mobile dangling overhead.

“Process of refining the brain’s wiring involves cutting off some of the excess nerve connections we have at birth while strengthening connections we use all the time. Some estimates show that as many as half of the brain’s connections formed during development are clipped back as the final wiring takes shape. Carla Shatz, PhD, the David Starr Jordan Professor of Stanford Bio-X, and her team recently found a protein that is essential for the brain to remove those excess connections. The team specifically showed a role for the protein in the developing visual system in mice, but their findings, published online March 30 in Nature, appear to apply broadly across the developing brain. Shatz is senior author of the paper. Postdoctoral scholar Hanmi Lee, PhD, is the lead author.

Shatz said the discovery helps clear up something that has been a mystery to those who study brain development: How does the decision get made to eliminate some connections? It also settles a decade-long debate over whether the nervous system or the immune system is making those decisions. (Spoiler alert: It’s the nervous system.)

A single vision

“Vision is a challenging problem because you have two eyes and only one view of the world,” said Shatz, who is also the Sapp Family Provostial Professor and professor of biology and of neurobiology. “There’s a very beautiful set of wiring steps that makes sure the eyes are pointed at the same place and the two images get aligned.”

Shatz said the rule of which connections the brain cuts back to create that single vision follows a simple mantra: “Fire together, wire together. Out of sync, lose your link.” Or rather, if early in life the left sides of both eyes see the same duck motif wallpaper, those neurons fire together and stay linked up. When the top of one eye and bottom of the other eye form a connection, the nerves fire out of sync, and the connection weakness and is eventually pruned back. Over time, the only connections that remain are between parts of the two eyes that are seeing the same thing.

The ability to detect which nerves fire out of sync and should therefore lose their link requires the protein Shatz’s team reported, which goes by the name of MHC Class I D, or D for short. This protein is one that is famous for its role in the immune system, but only in the past decade has Shatz’s team started building a case for D’s independent role in the brain.

Two camps, one protein

In 2000, Shatz first published work suggesting that a group of immune proteins called MHC in mice and HLA in people played a role in the developing nervous system. At the time, this caused a stir among immunologists, who were surprised to find their proteins showing up in the brain. Lawrence Steinman, MD, professor of neurology and neurological sciences and of pediatrics at the School of Medicine, has followed Shatz’s work from the perspective of both a neurologist and immunologist. “One of the reasons that I think the research is so interesting is that it shows us that molecules thought to be the province of one group can be in another,” he said, adding, “It slowed the prevailing idea that people believed that some molecules were the domain of one camp.”

Bio-X includes faculty members and students from both immunology and the neurological sciences, and Shatz said that being able to talk about her work and collaborate with this mix of colleagues has helped break down barriers in thinking about her unexpected findings.

After the initial discovery, Shatz went on to show that two of those MHC proteins — D and its sister protein, K — seemed to be important in eliminating connections in the brain. Mice genetically engineered to lack both K and D had poorly functioning immune systems and also ended up with the visual system in a jumble, with unrelated parts of the two eyes forming connections. With D and K, the mice weren’t detecting which connections fired out of sync, so those connections didn’t lose their link.

After Shatz published that work, some immunologists argued that perhaps D and K were necessary for brain remodeling only because of their key function in the immune system. “They were saying that the immune system was telling the nervous system what to prune,” Shatz said. It was a theory, but not one Shatz agreed with. Her feeling was that just because D and K were first found in the immune system didn’t mean they couldn’t have a unique role in the brain. “The nervous system has just as much right to these immune proteins as the immune system,” Shatz said. Her most recent work makes that point clear.

D on the brain

Shatz and her group worked with the mice that were lacking D and K every where, then used genetic engineering tricks to add D back, but only in the neurons. These mice still had poorly functioning immune systems, but had perfectly normal eye connections. In these mice, the nerves were able to determine which connections to cut and which to keep, even without the immune system.

Steinman said the work settles the issue of whether D is acting in the brain separate from its role in the immune system. “If Carla had studied D with immune proteins before the immunologists, then we would consider them to be part of the nervous system. They clearly have major roles in both the nervous system and the immune system,” he said.

The group went on to show that the presence of D alters the composition of other proteins on the nerve cell surface that are in charge of receiving signals from other nerves. Her team thinks that it is this difference in how the nerve receives signals with or without D that makes the pruning process go awry. Essentially, without D, all nerve connections appear to be firing together and therefore they stay wired together.

Shatz said that in addition to explaining an important part of brain development, the work could also provide a new avenue for studying schizophrenia. Some studies have shown that people with mutations in the human genes related to D are more prone to the disease. Other studies have associated D and K with improper formed connections in the brain. Shatz suggested that this new role for D in the brain could mean that the pruning process has gone awry in schizophrenia. The group plans to explore this idea further, as well as to tease apart what D is doing to alter the composition of neurotransmitter receptors on the nerve cell surface. Other Stanford co-authors of the study are research associate Barbara Brott, PhD; medical student Sarah Chung; and postdoctoral scholar Akash Dwari, PhD. The study was funded by the National Institutes of Health, the G. Harold and Leila Y. Mathers Charitable Foundation and a National Science Foundation Predoctoral Fellowship.

Amy Adams is director of interdisciplinary life sciences communications at Stanford.

PTSD continued from previous page

the mobile platform to deliver mental health interventions,” Taylor said.

All participation will be done remotely; no in-person visit is required. Half of the participants will use the app for three months, while the other half for three months, while the other half will be directed to the app following completion of the three-month period. Both groups will fill out online surveys at the start of the study and at the three-month follow-up.

The research is funded by the Department of Veterans Affairs through its Clinic-in-Hand program. People interested in participating in the study should contact research coordinator Niyaya Kanuri at nknnuri@stanford.edu or 485-3465.

Brain teaser

High school students examine brain sections during Brain Lab, one of the classes held March 28 as part of Med School 101. The annual, day-long event brings local high school students to the School of Medicine to learn about medicine and medical research. The year it drew students from 10 high schools to campus for the opportunity to learn, among other things, about surgery, sleep disorders, bacteria, cancer, sports injuries, genes, food allergies and how the brain does what it does — oh, yes, and what it takes to get into medical school. One student said she was in seventh grade when she got the idea that she might want to be a doctor, but really solidified her plans in eighth grade. Where is she now? 10th grade, she said.
Three-dimensional scanning technology used to digitally map the external surface of Rodin's hand sculptures.
Center
continued from page 1
were long waits for exam rooms. The infusion room for bone marrow transplant patients resembled a walk-in closet. And there was no natural light in the radiation oncology area. “It was a warrent of dark rooms that did not address the inner needs and struggles of cancer patients,” said Philip Pizzo, MD, professor of pediatrics and of microbiology and immunology, and former dean of the medical school.

Beverly Mitchell, MD, director of the Stanford Cancer Institute, recognizes the foresight and vision of those who came before her. “There was the recognition that cancer patients deserved a special environment, and that Stanford needed to deliver on that,” said Mitchell, professor of obstetrics and gynecology and of hematology, who came to Stanford in 2005. “It has really improved the atmosphere for cancer patients to have this light-filled building, with music in the lobby and dedicated clinic space. It has made a huge difference for our patients.”

When the cancer center opened, Pizzo described it as having “gone a long way toward alleviating the fear, anxiety and discomfort associated with cancer care facilities.”

“Indeed, this new facility serves as a model for Stanford and for our community,” he said.

The building is the physical structure that initially brought together all the modality-based disciplines like medical, surgical and radiation oncology, said Douglas Blaney, MD, professor of oncology and the Ann and John Doerr Medical Director of the Stanford Cancer Center. “First and foremost, that was good for patients in terms of convenience,” he said. “But it was also good for patients because there were multiple specialists collaborating both in time and in space on their particular cancers.”

The center, by its design, allows professional interaction to occur between clinical faculty who work and consult in both ways. “This constant interaction between the physicians and the tremendous camaraderie that they have benefited any of us thought might happen,” Jacobs said. “That accelerated the level of patient care to a level we could not have anticipated.”

Patient-centered design

The team tasked with designing the Stanford Cancer Center recognized that cancer is not an individual disease, but a family affliction. “Giving space and time for the families to come together into one space that was designated for the treatment of their loved ones was a big, intangible benefit,” said Sridhar Seshadri, vice president of the center, who led the process excellence work for the initial center design team.

“We wanted to make it patient-centered,” Jacobs said. “We wanted to make it more comfortable for the patient.” The team spent a lot of time determining how the space would function for patients and physicians. They wanted to create a warm atmosphere, with quiet, intimate areas, but they also wanted a wow factor. Jacobs said, with a grand piano in the lobby and a fountain out front.

Equally important was the desire to provide patients with ease of access, a one-stop shop. Patients can go from the clinics on the first floor to the infusion treatment area on the second floor to radiation oncology on the ground floor. They can have prescriptions filled at the onsite pharmacy, and grab a bite to eat at the café between appointments.

Getting the building designed and built was a 10-year process. It started in 1994, when David Korn, MD, who was dean of the school at that time, asked Jacobs to coordinate the effort. She and Sarah Donaldson, MD, professor of radiation oncology, created a small working team that met regularly with clinicians in each cancer specialty, as well as with nurses, support staff and patients, and synthesized each group’s priorities into the vision and blueprint for the building. Former hospital president and CEO Malinda Mitchell’s expertise and leadership helped make the effort a success, Jacobs said.

In a show of unprecedented collaboration, the hospital administration and the School of Medicine faculty aligned around the belief that creating a defined place for cancer patients was critical.

Growing pains

The success of the cancer center and its programs over the past 10 years has led it to outgrow its space. “Because of our ability to give really excellent cancer care, we have increasing numbers of patients,” said Beverly Mitchell, who is also the George E. Becker Professor in Medicine. She estimated current growth at 10-plus percent a year. Already, the center has expanded to the Blake Wilbur Building, with the Stanford Women’s Cancer Center occupying the first floor, and the head and neck and cutaneous cancer specialties on the third floor. In January, Stanford opened a new infusion center in Redwood City, and will open a new cancer center in July 2015 in the South Bay. The Jill and John Fredenrich Center for Translational Research, which opened in 2012, also houses key components of the cancer program.

In addition to managing future projected growth, the cancer center’s leadership team is turning its attention to transforming cancer care at Stanford. The Stanford Cancer Transformation sets out to “create a new cancer care model that is comprehensive, multidisciplinary, highly coordinated and structured around the unique needs of each patient,” Seshadri said. Other goals include creating new diagnostics and therapeutics, increasing the number of clinical trials and hiring more physician-scientists.

Stanford aims to be a national model for efficient and patient-centered cancer treatment by combining leading-edge science with smart, compassionate care, said Lloyd Minor, MD, dean of the School of Medicine. “Too often cancer care is not coordinated, not patient-centered and not evidence-based,” Minor said. “Our highly innovative model for cancer care delivery and research is going to change that by transforming the patient experience and bringing the best science to every patient.”

Grace Hammerstrom is a freelance writer for Stanford Hospital & Clinics.

Researchers survey protein family that helps the brain form synapses

By Tom Abate

Neuroscientists and bioengineers at Stanford are working together to solve a mystery: How does nature construct the different types of synapses that connect neurons, the cells that monitor nerve impulses, control muscles and form thoughts.

In a paper published in the Proceedings of the National Academy of Sciences, Thomas Südhof, MD, professor of molecular and cellular physiology; and Stephen Quake, a professor of bioengineering, describe the diversity of the neurexin family of proteins.

Neurexins help to create the synapses that connect neurons. Think of synapses as switchboards or control panels that connect specific neurons when these brain cells must work together to perform a given task. Neurexins play a key role in the formation and function of synaptic connections. Past genetics studies have linked neurexins to a variety of cognitive disorders, such as autism and schizophrenia.

Südhof, who shared the 2013 Nobel Prize in Medicine, has spent years studying the many different forms, or isoforms, of neurexins proteins. He has postulated that different isoforms of neurexins may help to create different types of synaptic connections with distinct properties and functions, and thus enable neurons to do so many complex tasks.

But Südhof had no way to know exactly how many isoforms of neurexins existed until he sat down last year with Quake, the Lee Ottesen Professor in the School of Engineering. Quake has pioneered new ways to sequence DNA, the master blueprint that nature follows when making proteins.

The study published in PNAS represents the results of a year-long collaboration between neuroscientists and bioengineers to better understand how different neurexin proteins affect the behavior of synapses and, ultimately, normal brain functions and neurological conditions such as autism.

Though this will not be the last word on the subject, the findings help illuminate how the brain works and improve our understanding of neurological disorders.

Inside cells, a molecular machine unzips a double-stranded DNA molecule to create an RNA molecule. The RNA molecule is a copy of all the genetic instructions encoded into the DNA. But only specific regions of this RNA molecule contain instructions for making a specific protein. The cell has ways to remove the unnecessary regions and splice the protein-coding regions into a shorter RNA molecule called messenger RNA or mRNA. Thus, each mRNA contains the full instructions for making a specific protein.

To begin this experiment, Ozgun Kiziloglu, a Stanford graduate student, and research is going to change that by transforming the patient experience and bringing the best science to every patient.”

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Inside cells, a molecular machine unzips a double-stranded DNA molecule to create an RNA molecule. The RNA molecule is a copy of all the genetic instructions encoded into the DNA. But only specific regions of this RNA molecule contain instructions for making a specific protein. The cell has ways to remove the unnecessary regions and splice the protein-coding regions into a shorter RNA molecule called messenger RNA or mRNA. Thus, each mRNA contains the full instructions for making a specific protein.

To begin this experiment, Ozgun Kiziloglu, a Stanford graduate student, and...
absence of treatment, cancer cells are continuously growing and dying. As they die, they release DNA into the bloodstream, like tiny genetic messages in a bottle, which scientists can then track and analyze — and to pick out the one in 1,000 or 10,000 that come from a cancer cell — can provide clinicians with a way to quickly and noninvasively monitor the volume of tumor, a patient’s response to therapy and even how the tumor mutations evolve over time in response to treatments or other select pressures.

“The vast majority of circulating DNA comes from normal, non-cancerous cells, even in patients with advanced cancer,” Bertman said. “We needed a way to isolate and analyze the circulating DNA from blood and detect the rare, cancer-associated mutations. To boost the sensitivity of the technique, we optimized methods for extracting, processing and analyzing the DNA.”

The researchers’ technique, which they have dubbed CAPP-Seq, for Cancer Personalized Profiling by deep Sequencing, is sensitive enough to detect just one molecule of tumor DNA in a sea of 10,000 healthy DNA molecules in the blood. Although the researchers focused on identifying mutations in small-cell lung cancer (which includes most lung cancers, including adenocarcinomas, squamous cell carcinoma and large cell carcinoma), their method may be applicable to many different solid tumors throughout the body. It’s also possible that it could be used to track the progress of a previously diagnosed patient, but also to screen healthy or at-risk populations for signs of trouble.

Tumor DNA differs from normal DNA by virtue of mutations in the nuclear DNA of cells. Some of the mutations are thought to be cancer drivers, responsible for initiating the uncontrolled cell growth that is the hallmark of the disease. They can evolve and accumulate randomly during repeated cell division. These secondary mutations can sometimes confer resistance to therapy; even a few tumor cells with these types of mutations can expand rapidly and evade the face of seemingly successful treatment.

“Cancer is a genetic disease,” Alizadeh said. “But unlike Down syndrome, for example, this is not a single gene or a single mutation that causes cancers. For most cancers it’s very difficult to identify any one particular genetic aberration or mutation that is found in every patient. Instead, each cancer tends to be genetically different from patient to patient, although sets of mutations can be shared among patients with a given cancer.”

So the researchers took a population-based approach. National databases such as The Cancer Genome Atlas contain DNA sequences of tumors collected from thousands of patients — and pinpoint places in which the cancer DNA differs from normal DNA. Although the significance of each individual change is not always clear, it’s becoming possible to generate a mutational fingerprint for each patient — including changes, insertions or deletions of short pieces of genetic material and translocations that shuffle or break chromosomes in certain regions. Although no patient will have all the mutations, nearly all will have at least some.

The group began by using a bioinformatics approach to collect information from the atlas on 407 patients with non-small-cell lung cancer, looking for mutations in enriched regions for cancer-associated mutations. “We really looked at which genes are most commonly altered, and used computational approaches to identify what we call the genetic architecture of the cancer,” Alizadeh said. “That allowed us to identify the part of the genome that would be best to identify and track the disease.”

They identified 139 genes that are recurrently mutated in non-small-cell lung cancer and that represent about 0.004 percent of the human genome. Next, the team designed oligonucleotides, panels of short pieces of DNA, bracketing these regions. The oligonucleotides were then used to perform deep sequencing (meaning each region was sequenced about 10,000 times) of the surrounding DNA. “By sequencing only those regions of the genome that are highly enriched for cancer mutations, we were able to reduce costs down and identify multiple mutations per patient,” Dieln said.

In contrast, other methods of tracking circulating tumor DNA have relied on single, well-known mutations that inevitably are not present in every patient with a particular cancer. Tracking more than one mutation increases the sensitivity of the approach and allows researchers to take advantage of the flexibility in seeing how the cancer changes over time.

“There are a large number of biomarkers available for lung cancer patients, which is the most common cancer to develop and treat,” Dieln said. “We are very excited about our findings because a personalized, clinically useful biomarker could revolutionize how we monitor and manage this devastating disease.”

Next, the researchers used these oligonucleotides to selectively sequence tumor samples from patients with the disease and identify specific mutations in each patient’s tumor. Starting with a predefined panel of oligonucleotides allowed the researchers to quickly home in on patient-specific mutations that could be used to tailor the type of therapy a patient would receive. “This approach could, theoretically, work for any tumor,” Alizadeh said.

“Of most interest, we found that we could track just one mutation from a small level of circulating tumor DNA in one patient that was highly enriched and detected just before disease recurrence and ultimately died,” Newman said. “We’ve developed statistical methods to suppress the background noise in a sample. This allows us to identify even the most minute quantities of cancer DNA in a blood sample.”

When the researchers applied the technique to patients with non-small-cell lung cancer, they found they could detect disease in all patients with stage-2 or higher disease, and in half of those with stage-1, the earliest stage of disease. Furthermore, the absolute levels of circulating tumor DNA were highly correlated with tumor volume estimated by conventional imaging techniques such as CT and PET scans. This suggests CAPP-Seq could be used to monitor tumors at a fraction of the cost of commonly used imaging studies.

“CAPP-Seq may also be useful as a prognostic tool, the researchers found. The technique detected small levels of circulating tumor DNA in one patient thought to have been successfully treated for the disease; that patient experienced disease recurrence and ultimately died. Conversely, scans of a patient with early stage disease showed a mass that was thought to represent residual disease after treatment. However, CAPP-Seq detected no circulating tumor DNA, and the patient remained disease-free for the duration of the study.”

Finally, CAPP-Seq was also able to identify the presence in one patient of a minor population of tumor cells with a mutation that confers resistance to a drug commonly used to treat non-small-cell lung cancer. “If we can monitor the evolution of the tumor, and see the appearance of treatment-resistant subclones, we could potentially add or switch therapies to target these cells,” Dieln said. “It’s also possible we could use CAPP-Seq to identify subsets of early stage patients who could benefit most from additional treatment after surgery or radiation, such as chemotheraphy or immunotherapy.”

The researchers are now working to design clinical trials to see whether CAPP-Seq can improve patient outcomes and decrease costs. They are also aiming to extend the technique to other types of tumors.

Screening healthy but at-risk populations is another goal of the researchers. “It may be possible to develop assays that could simultaneously screen for multiple cancers,” Dieln said. “This would include diseases such as breast, prostate, colorectal and lung cancer, for example.”

“This approach could, theoretically, work for any tumor,” Alizadeh said. “We expect it to be broadly applicable across cancers.”

Other Stanford co-authors of the study are clinical research assistants Jacqeline To and Jacob Wynne; former undergraduate student Neville Echov; medical student Leslie Modlin; research associate Chih Long Liu, PhD; assistant professor of medicine Joel Neil, MD, PhD; associate professor of medicine Heather Wakesle; MD; acting assistant professor of thoracic surgery Robert Merritt, MD; professor and chief of thoracic surgery Joseph Stratagel, MD; and assistant professor of radiology Billy Loo Jr., MD, PhD.

The research was supported by the Department of Defense, the National Institutes of Health Director’s New Innovator Award Program, the Ludwig Institute for Cancer Research, the Radiological Society of North America, the Association of American Cancer Institutes’ Translational Cancer Research Fellowship, the Siebel Stem Cell Institute, the Thomas and Stacey Siebel Foundation and Doris Duke Clinical Sciences Development Awards.

Stanford’s Department of Radiation Oncology and Department of Medicine also supported the work.  

Neurexin

continued from page 5

“Gokechi Koyejo is a postdoctoral scholar in the lab of Stanford’s Dr. William Bachtell, who studies the brain’s synapses, the places where neurons communicate.”

The mRNA molecules of neurotransmission molecules were retained, which is not the case in other studies. From this large pool of RNA, they identified the mRNAs for neurexins. They then used messenger molecules to create a sequence of chemical instructions for making a specific isoform in the neurexin family of proteins. “This was a very laborious process,” Gokechi said. “It involved using new instruments that allow researchers to read the long sequence of chemicals in an mRNA strand, making it possible for them to access every possible messenger sequence by attaching to the cell’s protein-making machinery.”

“This experiment couldn’t have been done even a few years ago,” Treutlein said.

The mRNAs for neurexins are very long chains of nucleotides — the chemicals that encode genetic information. Only recently have instruments been capable of reading the entire sequence of such long nucleotide chains.

The ability to read the entire sequence of each neurexin mRNA to identify the presence of a given neurexin allows scientists to more robustly understand how proteins are made. “We now have a complete, high-resolution view of the diversity of synaptic connections that neuroscientists are trying to understand,” Gokechi said. “This is the first time we have been able to see the diversity of splicing and variation of the neurexin mRNA families.”

“Neurexins are the constituent parts. But not all of these parts are used each time neurons produce a copy of the protein. Isoforms of neurexins have tens of different combinations of these 25 possible components. This experiment was designed to discover how many isoforms of neurexin exist and how prevalent each one is in the brain.”

The researchers analyzed more than 25,000 full-length neurexin mRNAs. They found 450 variants. Each variant omitted one or more of the 25 possible components. Most of these isoforms occurred infrequently. A handful accounted for the predominant isotypes.

Although the Stanford scientists sequenced 25,000 mRNAs to discover 450 variants, they believe that if they were to sequence even more mRNAs they would discover more isoforms — their estimate is that at least 2,500 isoforms of the neurexin family exist.

“Of most significance is that we can now use the full repertoire of neurexin isoforms to address key questions in neuroscience,” Treutlein said. “Now we have a complete, high-resolution view of the diversity of synaptic connections that neuroscientists are trying to understand,” Gokechi said. “This is the first time we have been able to see the diversity of splicing and variation of the neurexin mRNA families.”

“One key advantage of our approach is that we can also track many different classes of mutations, and integrate information from all of them to get a much stronger signal,” Newman said. “We’ve also developed statistical methods to suppress the background noise in a sample. This allows us to identify even the most minute quantities of cancer DNA in a blood sample.”
At the recommendation of Stockdale, she went to the Stanford Transcatheter Heart Valve Clinic, where she was seen by Stockdale as well as the study’s investiga- tor of medicine and director of interventional cardiol- ogy, and by Fischbein. Her doctors categorized Casey as being at high risk for surgery because of the ra- diation therapy she underwent in her 30s. The radiation, which prob- ably caused thinning of the muscles and skin of her chest to to 80s or older. Typical TAVR candidates are much more weakened by the valve narrowing, which impedes the flow of blood to the skin and muscles of her chest and to the heart muscle.

Casey’s fast-growing, inflammatory form of breast cancer had required especially high doses of radiation, which likely caused additional long-term damage to the skin and muscles of her chest and to the heart muscle. After 5,000 American patients suffer from de- terioration of the valve, which forces the heart to work harder to pump blood, often leading to heart failure and sometimes even death. In 2011 there were 7,000 U.S. patients with severe aortic stenosis were treated with transcatheter valve replacement. Doctors are increasingly interested in them because the obvious appeal of a less invasive procedure should not be the overriding factor in choosing a treatment plan for severe aortic stenosis doctors categorized Casey as being at high risk for complications or death from open-heart surgery, the valve would not require an incision in the center of the chest, which meant an easier recovery. And because the heart muscle was rejuvenated to full function throughout the procedure, no heart- lung machine would be required.

I was scared about the skin healing, having my chest broken open so that it can heal properly, the longer recovery,” Casey said. “My doctors showed me the valve. I took a picture of it. I thought this might be a better way to go.”

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Trial aims to understand why one diet doesn’t fit all

By Ranjini Raghunathan

Researchers at the Stanford Prevention Research Center are seeking participants for a 12-month weight-loss study aimed at understanding why people on the same low-fat or low-carbohydrate diet have different rates of success.

The study, titled One Diet Does Not Fit All, will also help identify traits that account for these differences — factors such as genetic influences, insulin resistance, gut microbes, sleep- ing and eating habits, and depression or other psychological issues.

Participants will be assigned randomly to either a very low-fat or very low-carbohydrate diet for the entire year.

They will be required to attend weekly classes at Stanford for the first three months, once every other week for the following three months, and once a month for the remainder of the study.

Participants must be willing to have their fasting blood samples drawn four times during the 12-month period and participate in online and written surveys. They will receive all test results at the end of the study.

Men and women (only pre-menopausal) who are overweight or obese, in general good health and between the ages of 18 and 50 are eligible to par- ticipate in the study, which is part of a five-year project funded by the National Institutes of Health and the Nutrition Science Institute. Last year, 208 partici- pants were enrolled in the study. This year, the research team hopes to recruit an additional 135 participants for their spring cohort.

Participants will have extensive support and guidance from a team of Stan- ford health professionals and learn about healthy diets that may help their weight- loss efforts.

Christopher Gardner, PhD, professor of medicine, is the principal investigator. Gardner and his colleagues have investigated the poten- tial health benefits of vari- ous diets for decades. Some of their previous research indicated that some people have more success on one diet over the other, possibly because factors such as genetic influences and insu- lin resistance. For example, people with high insulin re- sistance appeared to fare better on a low- carbohydrate diet. The researchers want to find out if this knowledge can be used to predict what diet would work best for an individual.

They also hope to determine what factors drive a person to stick to a spe- cific diet and succeed at losing weight while on it. Such factors might include counseling and smartphone applications that track what they eat.

For a complete list of inclusion criteria, visit https://med.stanford. edu/clinicaltrials/trials/NCT01826591. To de- termine eligibility for this study, complete a brief online survey at https://www.surveymonkey.com/s/ OneDietDoesNotFitAll-WeightLossStudySurvey.

For more information, contact Jenni- fer Robinson at 650-498-7946.

The study is also supported by the NIH’s National Institute of Diabetes and Digestive Kidney Diseases.

Geoffrey Guntern and Joseph Woo appointed to endowed professorships

GEOFFREY GUNTER, MD, has been appointed the Johnson & Johnson Distinguished Professor in Sur- gery II, effective Feb. 11.

Gunter’s research examines how physical stim- uli (mechanical and chemical) alter the human response to injury, especially in the context of im- paired wound healing and fibrosis.

The professorship was established through the transfer of funds from the existing Johnson & Johnson Distinguished Professorship in Surgery fund and supplementation from the Department of Surgery. The Johnson & Johnson professorship was established at the School of Medicine in 1978. It was one of six chairs provided to medical schools by Johnson & Johnson to support the activities of surgery departments in patient care, research and teaching.

JOSEPH WOO, MD, has been appointed the Nor- man E. Shumway Professorship in Cardiovascular Surgery, effective Feb. 11.

Woo serves as professor and chair of the Depart- ment of Cardiothoracic Surgery. His research is focused on investigating new paths to myocardial repair through angiogenesis — the process through which new blood vessels form from pre-existing vessels — stem cells and tissue engineering. His clinical expertise is in the fields of valve repair, ven- tricular assist devices and cardiac transplantation.

The professorship was established in 1976 through a gift from Frances and Charles Field, longtime Stanford volunteers and supporters. The professorship honors the late Norman Shumway, MD, who performed the first successful human heart transplantation in the nation.

Four medical school faculty members awarded Sloan Research Fellowships

Four School of Medicine faculty members are among 126 American and Canadian scholars to re- ceive 2014 Sloan Research Fellowships.

The faculty members are MARIA BARNAI, PhD, as- sistant professor of genetics and of developmental biology; ANSHUL KUNDAJA, PhD, assistant professor of genomics and of computer science; JULIA SALZ- MAN, PhD, assistant professor of biochemistry; and LIANG FENG, PhD, assistant professor of molecular biology and cellular physiology.

Each fellow will receive $50,000 for research-related costs.

Fellows are selected by an independent panel of senior scholars on the basis of their independent research accomplishments, creativity and potential to become a leader in their fields. The fellowships have been awarded by the Alfred P. Sloan Foundation since 1955.

The Stanford Child Health Research Institute awards $1 million to 5 projects

The Stanford Child Health Research Institute has awarded $1 million to each of five research projects through its transdisciplinary initiatives program.

The program aims to foster innovative, interdis- ciplinary child-health research and training initia- tives that engage faculty from at least two different schools at Stanford.

Following is a list of the projects and their prin- cipal investigators:

• “Transforming growth factor beta induced protein in- vasive tumors and their microenviron- ments, and art and musical performances by Stanford medical students.

Hosseini will be in conversation with Paul Costello, chief communications officer for the medical school.

The annual medical school event, which is free and open to the public, starts at 5:30 p.m. April 16 in Berg Hall of the Li Ka Shing Center for Learning and Knowledge. RSVPs are requested by send- ing an email to mmsdm@stanford.edu or calling 725-3448.

Jong Yoon

Jong Yoon, MD, assistant professor of psychiatry and behavioral sciences, is the recipient of the David Ma- chief communications officer for the medical school.

Sensitive 29x556 to 124x659

Response to injury, especially in the context of im- paired wound healing and fibrosis.

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