Pilot program uses data-driven, integrated team approach to predict, prevent disease

By Amy Jeter Hansen

A Stanford Medicine pilot program combining cutting-edge tools of biomedicine with a collaborative, team-based method, offers a new approach to personalized health care that captures the promise of Precision Health: to predict, prevent and treat disease based on the individual patient.

Through the Humanwide project, primary care teams at Stanford Medicine’s Primary Care 2.0 clinic in Santa Clara, California, merged high-tech and high-touch interventions to provide a diverse group of 50 patients with care that treated the whole person based on his or her unique factors, from genetics to lifestyle. Over the course of a year, the program succeeded in identifying previously undiagnosed conditions and future health risks, setting patients on a path to avert serious medical problems, such as cancer and heart disease.

“Our vision of Precision Health is to predict, prevent and cure — precisely,” said Lloyd Minor, MD, dean of the Stanford University School of Medicine. “With Humanwide, we have begun to realize that vision in a clinical setting. The information gathered in this pilot suggests approaches to primary care that may ultimately benefit thousands of people.”

A paper published May 13 in *Annals of Family Medicine* outlines initial learnings from Humanwide. The authors are Megan Mahoney, MD, Stanford Medicine’s chief of general primary care, and Steven Asch, MD, vice-chief of primary care and population health. Mahoney, the lead investigator, said the Humanwide design shifts the focus of primary care to detecting disease earlier, strengthening the relationship between the patient and care team and deploying the latest health technologies.

“With Humanwide, we’re...” We refer you to page 7 for the remainder of the article.

Immune cells crucial to causing osteoarthritis, team of scientists finds

By Bruce Goldman

Scientists at the School of Medicine have definitively linked mast cells, a class of cells belonging to the immune system, to the development of osteoarthritis, one of the world’s most common causes of pain and immobility.

In a study published online May 14 in *eLife*, the scientists demonstrated for the first time that banishing mast cells — or blocking signals from the most common mast cells, a class of cells belonging to the immune system, to the development of osteoarthritis, one of the world’s most common causes of pain and immobility.

Mice aren’t people, but like us they become forgetful in old age. In a study published online May 13 in *Nature Medicine*, old mice suffered far fewer senior moments during a battery of memory tests when School of Medicine investigators disabled a single molecule dotting the mice’s cerebral blood vessels. For example, they breezed through a maze with an ease characteristic of young adult mice.

The molecule appears on the surfaces of a small percentage of endothelial cells, the main building blocks of blood vessels throughout the body. Blocking this molecule’s capacity to do its main job — it selectively latches onto immune cells circulating in the bloodstream — not only improved old mice’s cognitive performance but countered two physiological hallmarks of the aging brain: It restored to a more youthful level the ability of the old mice’s brains to create new nerve cells, and it subdued the inflammatory mood of the brain’s resident immune cells, called microglia.

Scientists have shown that old mice’s blood is bad for young mice’s brains. There’s a strong suspicion in the scientific community that something in older people’s blood similarly induces declines in brain physiology and cognitive skills. Just what that something is remains to be revealed. But, the new study suggests, there might be a practical way to block its path where the rubber meets the road: at the blood-brain barrier, through which the blood communicates deleterious signals to the brain.

“We may have found an important mechanism through which the blood communicates deleterious signals to the brain,” said the study’s senior author, Tony Wyss-Coray, PhD, professor of neurology and neurological sciences, co-director of the Stanford Alzheimer’s Disease Research Center and a senior research career scientist at the Veterans Affairs Palo Alto Health Care System. The lead author of the study is Hanadie Yousef, PhD, a former postdoctoral scholar in the Wyss-Coray lab.

The intervention’s success points to possible treatments that could someday slow, stop or perhaps even reverse that decline. Targeting a protein on blood-vessel walls may be easier than trying...
At the School of Medicine, has cared for thousands of patients in recent decades. A specialist in treating post-traumatic stress disorder, Jain has been part of an explosion in knowledge about the condition's biology and possible treatments. So it frustrates her when she encounters ignorance about PTSD, especially because she believes it stands in the way of people getting therapy for it. Though it's widely considered incurable, PTSD is treatable and, in some cases, can be prevented, said Jain, who is also medical director for integrated care at the Veteran Affairs Palo Alto Health Care System. Often, people with the disorder are unaware they have it, as are their friends and family, she said. PTSD is widely known for causing nightmares, flashbacks and extreme startle reactions, but the disorder has other, more subtle symptoms: It makes feelings of happiness, often leads people to withdraw and can result in damaging cellular changes that make pain harder to tolerate in the future, Jain said.

Spurred to clear up misconceptions about PTSD, Jain has written her first book. The Unspoken Mind: Stories of Trauma and Healing From the Frontlines of PTSD Science. It's a portrait of the condition — in its history, treatment and repercussions for society — written to be accessible to the general public. Jain is the only psychiatrist to be a scholar at Stanford and has incorporated the science of PTSD over the past 20 years. She wanted to write a book that is accessible to the general public. It's a portrait of the condition — its history, biology, treatment and repercussions for society — written to be accessible to the general public.

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Researchers show how big data can be used for personal health

By Hanae Armitage

Scientists at the School of Medicine and their collaborators followed a cohort of more than 100 people over several years, tracking the biology of what makes them tick.

Now, after collecting extensive data on the group’s genetic and molecular makeup, the researchers are piecing together a new understanding of what it means to be healthy and how deviations from an individual’s norm can flag early signs of disease.

The results point to a need for a paradigm shift, said Michael Snyder, PhD, professor and chair of genetics.

“I would argue that the way medicine is practiced is deeply flawed and could be significantly improved through longitudinal monitoring of one’s personal health baseline,” said Snyder, who holds the Stanford W. Ascherman, MD, FACS, Professorship in Genetics. “We generally study people when they’re sick, rarely when they’re healthy, and it means we don’t really know what ‘healthy’ looks like at an individual biochemical level.”

Michael Snyder and a team of researchers tracked the biology of more than 100 people over several years to piece together a new understanding of what it means to be healthy and how deviations from an individual’s norm can flag early signs of disease.

Over the course of the study, the researchers uncovered more than 67 clinically actionable health discoveries that ranged from high blood pressure, arrhythmias, cardiomyopathy and early stage cancer detection, among others. The study interwove data from wearable technologies, genome sequencing and microbial profiles to establish a baseline of sorts for each participant. Every person’s broad swath of data painted a picture of their biological baseline, and as scientists tracked how that picture changed, they also kept tabs on any abnormalities that could signal the development of disease.

“What this paper really shows is that if doctors and scientists do more advanced profiling reasonably frequently, they’ll discover clinically actionable information for patient health at a broader scale than has ever been shown before,” Snyder said.

A paper describing the research findings was published in the May 8 issue of the journal Nature Medicine. The study’s senior author is W. Ascherman, MD, FACS, Professorship in Genetics. Other Stanford co-authors of the article are Kegan Haddad, MD, clinical associate professor of medicine, and co-senior authors: Sophia Miryam Rose, MD, PhD, and M. Reza Sailani, PhD; health educator Dalia Perelman; genetics research coordinator Melanie Ashland; clinical exercise physiologist Jeffrey Christle, PhD; life science researcher Monika Avina; former Stanford research coordinator Par Lima-Cocomo; graduate student Camilo Ruiz; Marilyn Tan, MD, clinical assistant professor of medicine and Tracey McLaughlin, MD, professor of medicine.

A range of change

In most clinical research, the cohort of participants has an underlying unifier — a shared disease or biologic peculiarity of some kind. In this study, the grounding factor was the long-term collection of big data, although many of the participants had a clinical actionable outcome. Some participants were tracked for as long as eight years. The average was about three years. Of the 109 participants, three-quarters of the group had a clinically actionable outcome. In some words, readout, be it from a blood test or smartwatch, flagged a potential health problem that was treatable or manageable. None of these issues had been detected before, Snyder said.

“We caught a lot of health issues because we noticed their delta, or their change from baseline,” he said. “For instance, we caught nine people with diabetes as it was developing by continuously monitoring their glucose and insulin levels.”

Through genetic sequencing, the team identified 13 disease-related findings, two of which were associated with serious heart defects. “The person was quite young, and we found that they had a mutation in a gene that puts you at risk for cardiomyopathy, which causes problems for the heart muscle,” Snyder said. “And sure enough, subsequent cardiac testing proved this person did indeed have cardiomyopathy.”

From data to detection

One of the more serious discoveries came from a participant who was found to have lymphoma after researchers noticed the person had an enlarged spleen, an organ in which lymphocytes spread, and molecular data consistent with lymphoma. The participant went on to receive therapy to successfully treat the disease.

The list goes on: 18 people discovered they had high blood pressure; two people had precancers. Multiple people found out they had low hemoglobin, and six people found out they had low blood pressure; two people had precancers. Multiple people found out they had an enlarged spleen, an organ in which lymphocytes spread, and molecular data consistent with lymphoma. The participant went on to receive therapy to successfully treat the disease.

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Aid continued from page 2

Newspapers by circulation in each of the 45 states and the District of Columbia were surveyed.

They found that the probability of populations holding a very favorable opinion of the United States was 19 percent points higher in the countries where and when U.S. donations for health care were highest, compared with countries where and when health aid donations were lowest. Using another metric, the researchers found that every additional $100 million in health aid was associated with a nearly 6 percent-age-point increase in the probability of registering a very favorable opinion of the United States.

In contrast, the researchers found, aid for governance, infrastructure, humanitarian and military purposes was not associated with a better opinion of the United States.

Bendavid, an infectious diseases physician and core faculty member of Stanford Health Policy, led the team to go out to conduct this research, he believed it would result in “a resounding thud” — that the “soft power” of health aid would have no impact.

“For me, the notion that this program — hatched and headquartered in the United States, with perhaps 4 million people in the United States and 300 million in India and Pakistan, seemed farfetched,” Bendavid said. “I was incredulous that it was even in place.”

The ‘America First’ agenda

The Trump administration’s “America First” agenda is calling for significant cuts to global health aid, particularly to the highly successful AIDS relief program, which was established by President George W. Bush. The administration’s budget, released in March, proposed a $860 million cut to the program. President Trump’s National Initiative is facing a $331 million reduction in federal funding. That’s a decline of 18%, 4%, respectively.

The U.S. contribu-

tion to the Global Fund to Fight AIDS, Tuberculosis and Malaria would also decline by 17% or $225 million, according to the Kaiser Family Foundation.

Yet beyond the reputational damage to the United States, such cuts could cause far greater setbacks. Improving health outcomes in developing countries, the researchers said. After all, HIV knows no borders, and having more resilient health care systems is instrumental in facing public health crises, such as the current Zika outbreak in the Democratic Republic of Congo, Jakubowski said.

The direct impact of cutting the United States’ health aid allocations is the potential to undermine or reverse gains that have been enabled by U.S. aid in curbing morbidity and the spread of HIV.

“There is a good scientific rationale for why we should make these investments,” said paper co-authors are Steven Asch, MD, MPH, professor of medicine, and former graduate student Don Mai.

Stanford’s Department of Medicine supported the work. 800
Neurosurgeons turn to basic science in fight against childhood brain cancer

By Krista Conger

Teresa Purzner, MD, PhD, is a hands-on, all-in physician.

As a neurosurgical resident at the University of Toronto in 2009, she rotated through a variety of specialties, including one in pediatric neurosurgery. During the three months of her pediatric rotation, she dealt with desperately ill children and their parents on a daily basis. Often, she participated in conversations that involved delivering bad news—telling the parents, for example, that their child, suffering from a deadly brain tumor called a medulloblastoma, might have a chance of being cured, but the chemo and radiation treatment was likely to cause permanent cognitive and neurological damage.

“It is a devastating conversation,” she recalled. “You’re basically delivering, and living in, every parent’s worst nightmare. One mother who lost her son shortly after diagnosis told me that she was thankful not to have had to put him through the treatment we were recommending.

When it all got to be too much, she and her husband, Jamie Purzner, MD, also a neurosurgeon trainee, just walked away from their residencies. Frustrated with the challenges of treating children with the tumors, they put their clinical careers on hold to tackle the root of the problem: the cells in the brain that run wild during the tumor’s development.

“A few brief conversations with the experts around us really sealed the deal,” Teresa Purzner said. “It was clear that medulloblastoma was a tangible and interesting problem, and that amazing strides had already been made in understanding the link between developmental biology and medulloblastoma.

The time was ripe, they felt, to bridge the gap between this new, conceptual understanding of the disease and the desperate need they’d witnessed in the path to this trial. We were all very dedicated to getting this step can kill medulloblastoma cells implanted into mice. It’s a remarkable achievement.”

Along the way, the pair faced many challenges, including the myriad difficulties of escorting a basic science finding through preclinical studies in animals to testing in humans. Teresa Purzner went on to test it in mice and to coordinate the launch of a phase-1 clinical trial that recently began enrolling patients. The two published their findings in *Science Signaling* in September 2018.

“Teresa and Jamie came up with an unbiased screen to identify a new component of a well-known developmental pathway, identified where in the pathway it functions and then showed that blocking this step can kill medulloblastoma cells implanted into mice. It’s a remarkable achievement.”

Teresa and Jamie Purzner came to Stanford to study medulloblastoma and search for a way to better treat the brain cancer.

“In the lab (and home) of Matthew Scott

Teresa and Jamie Purzner came to Stanford to study medulloblastoma and search for a way to better treat the brain cancer.

In 1984 discovery in fruit flies of a short DNA sequence called a homeobox, pointed the way to help these children.

The Scott lab then showed that during normal development, hedgehog signaling triggers growth of the cerebellum, the portion of the brain at the back of the head near the spinal cord. Loss of patched lets the normal growth signal happen when it should not. This explanation for the development of medulloblastomas piqued the Purzners’ interest.

but they needed to find the right place to do the necessary research.

The pair considered hundreds of laboratories in the United States and Canada. But rather than seek out labs and investigators experienced in translating existing research results into clinical applications—a bench-to-bedside approach—they focused on laboratories drilling into the nuts and bolts of biology.

Trading scrubs for lab coats

“Basic science is where fundamental discoveries occur,” Teresa Purzner said, “and basic science can tell you whether a specific potential treatment is likely to be helpful. The basic science is often understood at its core, but not in its backstory. It’s a kind of morbid logic that if this scientist is publishing this, it must be true. So it was surprising to learn that in the last few years, the field of developmental biology has exploded with implications for medicine.”

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Good brain cancer

are bleak and include whole brain and spinal radiation in combination with chemotherapy for as long as a year. Children are particularly susceptible to damage from these therapies because their brains are developing.

About 25% of all medulloblastomas are caused by mutations in genes for proteins that control the hedgehog pathway, including patched. Although drugs that inhibit the pathway can often temporarily shrink tumors in patients, the cancer cells rapidly become resistant to the treatment when the cells develop mutations that reactivate the pathway. Targeting the very last step — the moment when the proteins reach the nucleus and bind to the DNA to turn genes on — should leave the cancer cells fewer options to wiggle out of the treatment, researchers believe.

But how to do that?

The Purzners focused on the granule neuron precursor cells in the brain that give rise to hedgehog-associated human medulloblastomas. In mice, GNPs rapidly multiply by day seven with those of GNPs isolated at day 14. This increases the chance that the cells will accumulate additional mutations and become cancerous. Learning why this happens might be the key to stopping the rapid increase in medulloblastoma cells, the Purzners reasoned.

A chance encounter with Joshua Elias, PhD, assistant professor of chemical and systems biology, whose laboratory was one floor above Scott’s, gave the Purzners an idea of how to start. The Elias lab focuses on the study of all aspects of proteins in a cell or tissue to learn how cells and tissues develop and function. For example, a cell often adds or removes small chemical tags, called phosphate groups, from proteins to control their function. A phosphate group in one location on a protein may cue it to bind to a second protein, move to another part of the cell or latch onto a cell receptor to activate certain genes, whereas a tag in a different location on the same protein could trigger another set of biological outcomes. Conversely, removal of these phosphate groups can quickly inhibit the protein’s activity.

The cell’s ability to toggle a protein’s activity in this way allows the cell to react quickly and appropriately to changing conditions or developmental stages. For researchers, the ability to chart changes in the patterns and locations of phosphate tags across a panel of proteins over time can provide an intimate look at the workings of a cell during development or disease progression.

Combining expertise

Teresa Purzner decided to compare the pattern of phosphate tags, or protein phosphorylation, on GNP proteins isolated from the brains of newborn mice at day seven with those of GNPs isolated at day 14 and day one. Jamie Purzner, in contrast, focused on sussing out changes in which proteins are expressed at different cell stages. Although Teresa Purzner’s approach yielded more immediately promising results, she remained closely involved in each other’s projects.

“It was pretty darn fun combining our expertise and solving those tricky problems together from two perspectives,” she said.

The Purzners found that the protein phosphorylation pattern changed rapidly from day seven GNPs cells more closely resembles that of medulloblastoma cells than that of GNPS cells on day one or day 14.

Further detective work homed in on a phosphate-adding protein called CK2 that is likely responsible for many of the phosphate-tagging events observed in day seven cells — including some that are critical to the last steps in the hedgehog pathway.

Blocking CK2 activity in mice during days three to seven left the animals with significantly fewer granule neurons than control animals had, the Purzners found. Furthermore, a CK2 inhibitor slowed or stopped the growth of mouse medulloblastoma cells implanted in mice — even cancer cells resistant to other hedgehog pathway inhibitors.

“We put these angry medulloblastoma cells into the flanks of mice and see complete tumor regression when CK2 was inhibited,” Teresa Purzner said. “When we transplanted the medulloblastoma cells into the cerebella of mice, we found that, although the control animals had to be euthanized within 17 days due to cancer progression, 43 percent of mice treated with a CK2 inhibitor for 30 days lived past 100 days — basically until the experiment was terminated.”

“This was astonishingly effective,” Scott said. “The kinase acts very late in the hedgehog pathway, so it’s difficult for the cancer cells to mutate around it. It’s really a great example of the application of basic science. The Purzners didn’t start off looking for a protein involved in the hedgehog pathway. But once they did, Teresa Purzner embarked on shepherding this finding all the way from a basic science invention to preclinical tests that have now launched a clinical trial.”

Getting to the clinical trial wasn’t easy, however.

What to do next

“I had this beautiful, targeted small molecule inhibitor of CK2 that works in animals,” Scott said. “But I had absolutely no idea how to go from there to get it to patients. This was far outside my realm of experience.”

Enter Stanford SPARK. The program matches academic researchers with volunteers from the pharmaceutical, biotech and financial industries to streamline the process of getting a promising drug to the clinic.

“It’s so exciting,” Purzner said. “This took hundreds of hours and dozens of people to accomplish in many ways what we put together. There were at least two or three times I thought, ‘This could be the end. All of our work could be for nothing, and these kids are never going to get to see this drug.’

Scott said, “This was an absolute triumph of the translation of a series of basic science findings into a clinical trial. In 1980, we identified the first mutations in hedgehog and patched in fruit flies. “Sixteen years later we reported a connection with cancer; 16 years later we had our first FDA-approved drug targeting the hedgehog pathway in basal-cell carcinoma. So it took 32 years from pure, curiosity-driven ‘Huh, that’s interesting’ — when we found some genes that control patterning in fly larvae — to a point where patients were being treated. Now, 32 years is either way too long, or not too bad in the big picture of drug development. But Teresa did it in five,” he said.

The Purzners have returned to Canada to complete their neurological residencies.

It remains to be seen whether the CX-4945 will be safe and effective in children with hedgehog-dependent medulloblastoma. A success in mice doesn’t always translate to humans. But Teresa Purzner’s intensive approach to solving the problem has led to a promising new target in the field.

“Having my own children gave me a very sobering perspective about what these families are going through,” she said. “I didn’t fully grasp just how heart-wrenching it would be to have a child with a serious medical issue until I had my own children. Getting to this clinical trial has been very emotional. And I’m not emotional person. It is just such a huge relief to get to this point and know that I did what I came to do.”
Osteoarthritis continued from page 1

in human cells and tissues. Osteoarthritis, by far the most frequently occurring variety of arthritis, is characterized by cartilage breakdown and inflammation in joints, which can be further aggravated by excess bone growth called osteophytes.

Some 30 million Americans have symptomatic osteoarthritis. By the time you’re 60, your chances of exhibiting osteoarthritis symptoms exceed 30%. By age 80 or 90, your risk has risen to nearly 100%.

The classic trigger for that activation is the binding of an antibody to the immobilized IgE. The antibody is called a Fc receptor and is found on specialized receptors abounding on mast cells. The evolutionary purpose of IgE, as mentioned earlier, is to combat infectious pathogens and are essential to the healing process. When the investigators depleted old mast cells residing in the joints of humans with arthritic symptoms, it was definitively identified as risk factors for osteoarthritis.

Protection from the disease

In the study, Robinson’s group used electron microscopy to show that mast cells are the crucial and secretory agents of the immune system in the generation of cartilage-degrading enzyme they released when activated — protected mice from developing osteoarthritis.

Not just wear and tear

Osteoarthritis has traditionally been thought to be an inevitable result of wear and tear: the breakdown of cartilage over many years, ultimately resulting in grinding, bone-on-bone contact and degeneration in the affected joints. But the new study shows the essential involvement of the immune system in the genesis of osteoarthritis, while paying open a window through which researchers can see a way to design drugs to prevent it. At present, there are no drugs that can prevent, slow or cure it.

“Even though the vast majority of us will develop osteoarthritis at some point in our lives, we don’t have any disease-slowing therapies,” Robinson said.

The chances of actually reversing damage to joints are slim, he said. Today’s treatments for the pain and mobility-distress of patients like Iuprofen, naproxen and acetaminophen; walkers; canes; and knee or hip replacements. Mast cells are best known as the culprit’s tunes the histramines and other molecules responsible for allergic symptoms, ranging from the itch of eczema to the mucous explosions of hay fever to the throat constriction of asthma or food-triggered anaphylaxis. But mast cells also produce a degradative protein, tryptase, that can cleave other molecules that form the cartilage in joints.

Mast cells usually reside quietly within tissues throughout the body. But when they become activated, they secrete granules containing histamine, tryptase and other inflammatory substances. Since his lab first began reporting several years ago that mast cells have the capacity to jump the blood-brain barrier — but, in this case, would no longer transmigrate before. “Many of all of us will ultimately suffer from osteoarthritis if we live to be old enough,” said William Robinson, MD, PhD, professor of immunology and rheumatology, who is the study’s senior author. Lead authorship is shared by research associate Qiao Wang, MD, PhD; former MD-PhD student Christina Lepus, MD, PhD; and former postdoctoral scholar Harin Raghur, PhD.

Different way of reaching the brain

The researchers focused on the mouse hippocampus, a well-studied brain structure that’s essential to memory and learning and whose architecture and function are similar in mice and humans. The hippocampus is also one of the very few sites in the adult mammalian nervous system where neurogenesis, the creation of new nerve cells, occurs; those new cells are critical to the formation of new memories.

From his lab’s first report several years ago that unknown factors in old blood can accelerate cognitive decline and, conversely that factors in young blood can rejuvenate old brains, Wyss-Coray, the D.H. Chen Professor II, has sought to identify those factors. But he had and his colleagues took a different tack in the new study. He said the roughly 400 miles of blood vessels that pass through the human brain differ from those elsewhere in the body in one important respect: They’re much more selective about what gets in and what comes out.

“The blood-brain barrier excludes most bloodborne substances that are in some way directly related to vascular function. Topping the list was a circulating form of a protein constantly produced within endothelial cells and displayed on their surfaces. The protein, called VCAM1, is essential to the adhesion of immune cells. It’s a docking station for circulating cells of the immune system in the brain’s otherwise tightly closed border. In all, the scientists were able to get into the brain itself.

In this study, the researchers showed that VCAM1’s abundance on the endothelial cells comprising blood vessels in the mouse brains rises in old age, as well as in the brains of younger mice that are given infusions of old mice’s plasma. Circulating VCAM1, though, wasn’t the source of the protective effect. Rather, it was the product of mast cells residing in the joints of humans with arthritic symptoms were.

Several types of genetically altered lab mice whose mast cells were deficient or absent were highly resistant to the development of osteoarthritis features including joint inflammation, osteophyte development and joint breakdown after undergoing an experimental procedure that mimics the conditions of these, the researchers found.

The researchers also proved that impairing the action of tryptase, which is secreted almost solely by mast cells, had a similar protective effect. And they further demonstrated that depleting IgE or other molecules responsible for allergic reactions and disabling their receptors’ subsequent signaling to components within mast cells, all protective.

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The chances of actually reversing damage to joints are slim, he said. Today’s treatments for the pain and mobility-distress of patients like Iuprofen, naproxen and acetaminophen; walkers; canes; and knee or hip replacements. Mast cells are best known as the culprit’s tunes the histramines and other molecules responsible for allergic symptoms, ranging from the itch of eczema to the mucous explosions of hay fever to the throat constriction of asthma or food-triggered anaphylaxis. But mast cells also produce a degradative protein, tryptase, that can cleave other molecules that form the cartilage in joints.

Mast cells usually reside quietly within tissues throughout the body. But when they become activated, they secrete granules containing histamine, tryptase and other inflammatory substances. Since his lab first began reporting several years ago that mast cells have the capacity to jump the blood-brain barrier — but, in this case, would no longer transmigrate before. “Many of all of us will ultimately suffer from osteoarthritis if we live to be old enough,” said William Robinson, MD, PhD, professor of immunology and rheumatology, who is the study’s senior author. Lead authorship is shared by research associate Qiao Wang, MD, PhD; former MD-PhD student Christina Lepus, MD, PhD; and former postdoctoral scholar Harin Raghur, PhD.

Different way of reaching the brain

The researchers focused on the mouse hippocampus, a well-studied brain structure that’s essential to memory and learning and whose architecture and function are similar in mice and humans. The hippocampus is also one of the very few sites in the adult mammalian nervous system where neurogenesis, the creation of new nerve cells, occurs; those new cells are critical to the formation of new memories.

From his lab’s first report several years ago that unknown factors in old blood can accelerate cognitive decline and, conversely that factors in young blood can rejuvenate old brains, Wyss-Coray, the D.H. Chen Professor II, has sought to identify those factors. But he had and his colleagues took a different tack in the new study. He said the roughly 400 miles of blood vessels that pass through the human brain differ from those elsewhere in the body in one important respect: They’re much more selective about what gets in and what comes out.

“The blood-brain barrier excludes most bloodborne substances that are in some way directly related to vascular function. Topping the list was a circulating form of a protein constantly produced within endothelial cells and displayed on their surfaces. The protein, called VCAM1, is essential to the adhesion of immune cells. It’s a docking station for circulating cells of the immune system in the brain’s otherwise tightly closed border. In all, the scientists were able to get into the brain itself.

In this study, the researchers showed that VCAM1’s abundance on the endothelial cells comprising blood vessels in the mouse brains rises in old age, as well as in the brains of younger mice that are given infusions of old mice’s plasma. Circulating VCAM1, though, wasn’t the source of the protective effect. Rather, it was the product of mast cells residing in the joints of humans with arthritic symptoms were.

Several types of genetically altered lab mice whose mast cells were deficient or absent were highly resistant to the development of osteoarthritis features including joint inflammation, osteophyte development and joint breakdown after undergoing an experimental procedure that mimics the conditions of these, the researchers found.

The researchers also proved that impairing the action of tryptase, which is secreted almost solely by mast cells, had a similar protective effect. And they further demonstrated that depleting IgE or other molecules responsible for allergic reactions and disabling their receptors’ subsequent signaling to components within mast cells, all protective.

Not just wear and tear

Osteoarthritis has traditionally been thought to be an inevitable result of wear and tear: the breakdown of cartilage over many years, ultimately resulting in grinding, bone-on-bone contact and degeneration in the affected joints. But the new study shows the essential involvement of the immune system in the genesis of osteoarthritis, while paying open a window through which researchers can see a way to design drugs to prevent it. At present, there are no drugs that can prevent, slow or cure it.

“Even though the vast majority of us will develop osteoarthritis at some point in our lives, we don’t have any disease-slowing therapies,” Robinson said.

The chances of actually reversing damage to joints are slim, he said. Today’s treatments for the pain and mobility-distress of patients like Iuprofen, naproxen and acetaminophen; walkers; canes; and knee or hip replacements.
New tool enables powerful molecular analysis of tissue samples

By Christopher Vaughan

Single-cell RNA sequencing is emerging as a powerful technology in modern medical research, allowing scientists to examine in detail the unique molecular signatures and behaviors in diseases like cancer. But the technique, which can’t be applied to the vast majority of the world’s patients, is expensive and can’t be done at the scale required to be part of routine clinical treatment.

In efforts to address these shortcomings, researchers at the School of Medicine invented a computational technique called CIBERSORTx, which the RNA of individual cells taken from whole-tissue samples or data sets. “We believe this technique has major implications for biomedical discovery and precision medicine,” said Aaron Newman, PhD, instructor professor of biomedical data science.

A paper describing their method was published online May 6 in Nature Biotechnology. Newman is the lead author of the paper; Ash Alizadeh, MD, PhD, associate professor of medicine, is the senior author.

Pinpointing cells and their states

CIBERSORTx is an evolutionary leap from the technique the group developed previously, called CIBERSORT. “With the original version of CIBERSORT, we could take a sample of tumors and analyze it by analyzing the frequency with which certain molecules were made, could tell how much of each kind of cell was in the original mix without having to physically sort them,” Alizadeh said.

“We realized that it was like analyzing a fruit smoothie,” Newman said. “You don’t have to see what fruits are going into the smoothie, you can put a banana, a lot of apple, a little banana and see the red color of some strawberries.”

CIBERSORTx takes that principle much further. The researchers start by doing a single-cell RNA analysis of a small sample of tissue. They might take a cancerous tumor, for instance, separate the cells in the tumor and look closely at the RNA (and therefore the proteins) from a tumor can give us insights into the mix of cells and their health state in these tumors, and how we might be able to address these defects for cancer therapy.

Being able to identify not only the types of cells, but also the state or behavior in particular environments, could lead to dramatic new biological discoveries and provide information that could improve therapies, the scientists said.

The group analyzed over 1,000 whole tumors with the technique and found that not only were cancer cells different from normal cells, as expected, but immune cells infiltrating a tumor acted differently than circulating immune cells — and therefore different RNA bar code — than the same kind of immune cells circulating in the blood.

“What CIBERSORTx does is let us not only see how these cells are doing in the smoothie, but how many are Granny Smiths, how many are Red Delicious, how many are Stem Cells, and which ones are bruised,” Alizadeh said. “Similarly, starting with a mix of RNA barcodes that each cell makes. From this they produce a “bar code,” a pattern of RNA expression, that identifies not only the kind of cell they are looking at, but also the subtype or mode it’s operating in. For instance, Alizadeh said, the immune cells infiltrating a tumor act differently and produce different RNA and proteins — and therefore a different RNA bar code — than the same kind of immune cells circulating in the blood.

“Another important finding involved small cell lung cancer. The group used new techniques to analyze single-cell RNA expression in small cell lung cancer tissues and stored in paraffin, which is true of most of the cells from each other. This makes single-cell RNA analysis impractical or impossible for most large studies and clinical trials, where information about how cells are behaving is crucial.

The researchers also tested the tool’s diagnostic power by analyzing melanoma tumors. One of the most effective therapies for melanoma and many other cancers are drugs that block the production of proteins called PD-1 and CTLA4, which stops T-cells from attacking tumors. But these “checkpoint inhibitor” drugs work well in a minority of patients, and researchers have often resorted to trial and error that will show which ones are being used correctly.

“PD-1 and CTLA4 are important for cancer growth, they said. “It took 30 years to identify these two proteins, and we can’t just jump out of the data when we’re looking at CIBERSORTx to see the gene expression of cells in tumors with treatment outcomes,” Alizadeh said.

Another interesting finding that could prove interesting,” Newman said. “It’s a treasure trove.”

As with the original tool, the scientists plan to let researchers from all over the world use CIBERSORTx’s algorithms on computers at Stanford through an internet link. Newman and Alizadeh think they will see a lot of online traffic. “We expect to see smoke coming out of the computer room,” Alizadeh said.

Reaching new people

From the paper, Mahoney and Asch noted that the Humanwide pilot demonstrated the value of a comprehensive, patient-centered, data-driven environment, and that both patients and health care providers are receptive to exploring new tools and data streams to transform primary care. Mahoney added that the project offers insights for the future use of personal health data to benefit individual patients.

Asch, who led evaluation of the pilot, used a survey and a focus group to assess how patients evaluated their experience. The study evaluated their individual physiologic response to medications based on their genetic makeup.

Used mobile monitoring devices, including a glucometer, pedometer, scale and blood pressure cuff, to regularly upload to their electronic health records for remote monitoring by their health care team.

Worked with a certified health coach to identify wellness goals and create a plan for achieving them.

Through these initial assessments, regular interactions and continuous monitoring, health care teams gathered data on each patient on a variety of factors known to influence health: activity, behaviors, biometric measurement, genetic factors, biomarkers, markers, care-utilization algorithms on single-cell RNA data from previously tested fixed samples. They confirmed the diagnostic power of analyzing melanoma tumors. One of the most effective therapies for melanoma and many other cancers are drugs that block the production of proteins called PD-1 and CTLA4, which stops T-cells from attacking tumors. But these “checkpoint inhibitor” drugs work well in a minority of patients, and researchers have often resorted to trial and error that will show which ones are being used correctly.
Tobacco, e-cig promotions spark teens’ use of nicotine products, study finds

By Erin Digitale

Owning items that promote e-cigarettes and other alternative tobacco products doubles the likelihood that a youth will begin to use them, a new study led by the School of Medicine has found. The finding illustrates the influence of such marketing on teenagers. The study, which was published online May 17 in JAMA Network Open, followed 757 California teens for a year. At the beginning of the year, participants had never used alternative tobacco products, including e-cigarettes, chewing tobacco, cigars, cigarillos, pipes and hookahs.

But some participants owned marketing materials for these products, such as coupons, samples and branded hats or T-shirts. “We wanted to see how owning promotional materials would affect young people’s use later on,” said the study’s lead author, Hoda Magid, PhD, a postdoctoral scholar in health research and policy. Among teens, cigarette smoking rates have dropped in recent decades, but their use of e-cigarettes and other tobacco products has risen sharply. “The increase in use of alternative tobacco products poses a threat to the decades of hard work that public health experts have done to reduce tobacco use,” Magid said. "We also looked at trajectories of use of alternative tobacco products," said the study’s senior author, Bonnie Halpern-Felsher, PhD, professor of pediatrics. Understanding how youth start using such products is important for stemming the tide of addiction to them, she said.

Restrictions on conventional smokers

While marketing to minors and providing samples is illegal for all tobacco products, providing coupons and branded promotional items such as T-shirts and hats is illegal for all tobacco products, providing coupons and free samples or other marketing materials is strongly associated with more tobacco use, the teens who owned promotional items — such as coupons, free samples, T-shirts, posters and hats — for any type of nicotine product. The researchers asked similar questions about the use of cigarettes and alternative tobacco products a year later and analyzed changes in the teens’ use of e-cigarettes and other tobacco products as a function of owning or receiving promotional materials.

At the start of the study, 81 of the 757 participants owned items that promoted tobacco products, including 52 who owned promotional items for e-cigarettes. Over the course of the study, 129 participants, or 17 percent, began using alternative tobacco products but not traditional cigarettes. Twelve participants began using traditional cigarettes alone or in combination with alternative tobacco products. Before adjusting for confounding factors, teens who owned promotional items were found to be 2.23 times as likely to try alternative tobacco products as those who did not own such items. After adjusting for age, gender, race/ethnicity, maternal education level and baseline alcohol and cigarette use, the teens who owned promotional materials were 2.13 times as likely as their peers to begin using alternative tobacco products. When teens who had tried both alternative tobacco products and cigarettes during the year were included in the analysis, the influence of promotional materials did not reach statistical significance.

Study finds strong association

The findings provide evidence that ownership of marketing materials is strongly associated with more young people using e-cigarettes and other alternative tobacco products, the researchers said. The findings clearly show that no tobacco company, including any e-cigarette company, should be allowed to provide coupons, free samples or other marketing materials to teens, and suggest that the FDA should further restrict and enforce such marketing techniques, Halpern-Felsher said.

“Manufacturers say they’re not marketing to teens, but teens are owning these promoting materials, and they’re reporting use of alternative tobacco products,” Magid said. Current restrictions and laws that make marketing cigarettes and other tobacco products to minors should be enforced for all nicotine-containing products, she added. Halpern-Felsher is a member of Stanford’s Maternal & Child Health Research Institute and the Stanford Cancer Institute. Researchers from the University of California-Berkeley and the University of California-San Francisco also contributed to the study. Magid was a graduate student at UC-Berkeley at the time the research was conducted.

The research was supported by grants from the National Cancer Institute and the Food and Drug Administration. Stanford’s Department of Pediatrics also supported the work.

“We need to know trajectories of use of alternative tobacco products.”