Dean seeks dialogue in shaping the future of Stanford Medicine

By Susan Ipakchian

As an otolaryngologist, Lloyd Minor, MD, knows a thing or two about ears. And right now, his are getting a full-time workout.

Take the afternoon of Feb. 5. Minor, who became the dean of the School of Medicine on Dec. 1, held a town hall meeting attended by more than 500 faculty, staff and students. Minor invited them to “begin a dialogue with me about where we are and where we need to go in the future.”

He outlined and discussed what he sees as the three key priorities of the school: advancing innovation, empowering future leaders and transforming patient care. He then invited the attendees to share their thoughts with him.

The future was very much on their minds, judging from the questions they asked — questions ranging from the uncertainties surrounding federal research funding, to ways of making careers in primary care medicine professionally and financially rewarding, to the path ahead for students and trainees.

Lloyd Minor, dean of the medical school, spoke with a member of the audience after a town hall meeting Feb. 5. “I think one of the most active things that I do is to listen and process what I’m hearing,” he said.

Study: Immune system can ‘remember’ germs it has never been exposed to

By Bruce Goldman

It’s established dogma that the immune system develops a “memory” of a microbial pathogen, with a correspondingly enhanced readiness to combat that microbe, only upon exposure to it — or to its components through a vaccine. But a discovery by School of Medicine researchers casts doubt on that dogma.

In a path-breaking study published online Feb. 7 in Immunity, the investigators found that over the course of our lives, CD4 cells — key players circulating in blood and lymph whose ability to kick-start the immune response to viral, bacterial, protozoan and fungal pathogens can spell the difference between life and death — somehow acquire memory of microbes that have never entered our bodies.

Several implications flow from this discovery, said the study’s senior author, Mark Davis, PhD, professor of microbiology and immunology and director of Stanford’s Institute for Immunity, Transplantation and Infection. In the study, newborns’ blood showed no signs of this enhanced memory, which could explain why young children are so much more vulnerable to infectious diseases than adults. Moreover, the findings suggest a possible reason why vaccination against many types of treatment, for the disease’s resistance: The ability of the tubercle bacillus to infiltrate and settle down in a particular class of stem cell in the bone marrow. By doing so, the bacteria take advantage of the body’s own mechanisms of self-renewal.

“Cancer scientists have noted that self-renewing stem cells, like those in the bone marrow, have properties — such as natural drug resistance, infrequent division and a privileged immune status — that make them resistant to many types of treatments,” said Dean Felsher, MD, PhD, professor of oncology and of pathology. “Now it turns out that this ancient organism, Mycobacterium tuberculosis, figured out a long time ago that, for the same reasons, these cells are ideal hosts to invade and in which to hide.”

Not only did the scientists find genetic material from the bacteria inside the stem cells, they were also able to isolate active bacteria from the cells of human patients with tuberculosis who had undergone extensive treatment for the disease.”

The findings raise the possibility that other infectious agents may employ similar “well-in-stem-cell-clothing” tactics. And, although any new human treatments are likely to still be years away, they suggest a new possible target in the fight against tuberculosis, which infects nearly 2.2 billion people worldwide.

“We now need to learn how the bacteria find and infect this tiny population of stem cells, and what triggers it to reactivate years or decades after successful treatment of the disease,” said postdoctoral scholar Bikul Das, MBBS, PhD. Felsher is a co-senior author of the study, which was published online Jan. 30 in Science Translational Medicine. Das is the lead author. The study’s senior author, Mark Davis, PhD, professor of microbiology and immunology and director of Stanford’s Institute for Immunity, Transplantation and Infection.

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when the cancer cells have a genetic mutation in the cell surface receptor to bombard the cells with the drug. We've found that treatment of these resistant cells with an antibody directed against KIT slows their growth in laboratory dish when compared to untreated cells. The KIT antibody expressed less KIT on their surface than did untreated cells. Furthermore, antibody treatment promotes engulfment and destruction of cancer cells, regardless of their sensitivity or resistance to imatinib. When they treated the cancer cells in living laboratory animals over time, they observed that antibody treatment induced killing of cancer cells and stimulated immune cells called macrophages to kill the rogue cells. Currently, people with GIST are often treated first with surgery and then with the drug imatinib, marketed as Gleevec — a small molecule that also targets KIT. The treatment, which was approved for GIST in 2002, has been remarkably successful. It has increased the average survival time of many people with advanced disease from about 18 months to about five years. It was the first targeted small molecule inhibitor that proved effective against a solid tumor, but its effect is temporary.

"Gleevec," or imatinib, marked a paradigm shift in our understanding about solid tumor, but its effect is temporary.

In lab tests, antibody hinders growth of gastrointestinal tumors that have become resistant to Gleevec, study says

By Krista Conger

An antibody that binds to a molecule on the surface of a rare but deadly tumor of the gastrointestinal tract inhibits the growth of the cancer cells in mice, according to researchers at the School of Medicine.

The effect remains even when the cancer cells have become resistant to other treatments, and the findings may one day provide a glimmer of hope for people with the cancer, known as gastrointestinal stromal tumor, or GIST. The scientists hope to move into human clinical trials of the antibody within two years.

The antibody’s target is a receptor called KIT, which is often mutated in patients with the cancer. When mutated, KIT sends a continuous stream of signals into the cancer cells that keep it growing uncontrollably. The Stanford researchers found that the antibody reduces the amount of KIT on the surface of the cancer cells that are genetically immune cells called macrophages to kill the rogue cells.

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Mystery disease unraveled by Stanford neurologist

By Sara Wykes

At first, Marc Laderriere thought that his decreasing energy was just age catching up to him. Cell loss is just the norm. But something about that explanation didn’t sit right.

“At one point, one of my doctors said, ‘This is definitely a little strange. I don’t know what you have, but it could be nerves,’” Laderriere recalled.

After a year and a half, his discomfort, that he was not in such great shape any more. He knew he should add exercise to his daily routine, but the fatigue he felt was overwhelming.

Laderriere, who lives in Paso Robles, started to consult local doctors. He had a variety of standard tests, with the thought that he might have developed diabetes. At first, Marc Laderriere thought that he might have developed diabetes. That was not the case. When he came to work he never got goose bumps. He was experiencing a set of symptoms that were unusual but did not strike him as significant. Hot weather sapped his strength and made him dizzy, but he was sweating less. In cool weather, he never got goose bumps.

The diagnosis of cancer had come, growing up in France, Laderriere had always been active. “I did a lot of skiing, a lot of swimming,” he said. When he came to work in the United States, as a director of wine sales for the Vina Robles Winery in Paso Robles, he said he became a workaholic. “I completely accepted that way of life,” he said.

The more he traveled for his job, the less time and attention he paid to his health until he recognized, with some discomfort, that he was not in such great shape any more. He knew he should add exercise to his daily routine, but the fatigue he felt was overwhelming.

Marc Laderriere, who works for Vina Robles Winery & Vineyards in Paso Robles, was about 50 when he began experiencing unusual symptoms.

“Although the tumors from the imatinib treatment have been partially eradicated, the source of a patient’s system disorders. But recognizing that such a disorder is the source of a patient’s symptoms allows doctors to treat those symptoms more effectively.

Marc Laderriere, left, diagnosed Laderriere with an autonomic disorder.

Finding a cause

Another confusing factor is the range of triggers for autonomic system disorders. They can be a secondary symptom of diabetes, Parkinson’s disease and infections like tick-borne Lyme disease, or they can appear independently. Laderriere, it turns out, had Lyme disease without knowing it. Jaradeh treated Laderriere’s Lyme disease with an extended course of antibiotics to make sure that he did not still have an active infection. Sometimes, people who also develop an autonomic system disorder, Laderriere had gone so long without diagnosis that he began to notice what he felt going on in his body, Jaradeh said, adding: “He clearly has something real, but he was beginning to be concerned that he was imagining his symptoms.” Many patients may also go from doctor to doctor, looking for an explanation for a set of symptoms, which, in fact, Laderriere’s, seem simple and complex at the same time. It’s the reason your heart’s beating, Jaradeh said. “It’s the reason your reason you can hold your balance if you’re dizzy. It’s the reason that you shiver if you’re in a cold room and sweat if you’re hot. It’s the reason that you can’t find anything. Or it might be suspicious, the medication is changed. If nobody, somebody will realize that maybe it’s the blood pressure is changing. Then the blood pressure is measured by having the person gets up from a supine position, and that’s when someone realizes that the blood pressure has dropped — and that there’s something wrong with this person’s autonomic system.

Antibody

carried on from page 2

of mice, waited two weeks for the cancer cells to become established and then treated the animals with the anti-KIT antibody.

“Although the tumors from the imatinib plus an antibody that targets a cell-surface molecule called CD47 prev- iously identified in Weissman’s labora- tory, will further inhibit tumor growth. (Anti-CD47 treatment has been shown to block tumor growth) signal expressed by many types of cancer cells that prevents them from undergoing cancer by macrophages may provide a syn- ergistic effect against the tumor, the re- searchers believe. A similar approach was shown to cure aggressive non-Hodgkin’s lymphoma in mice in Westman’s lab in 2010.

Other Stanford researchers involved in the research included postdoctoral scholar Anne Vollmer, MD; instructor Jens-Peter Vollmer, MD; technician Kelli Montgomery; research assistant Humberto Contreras; and medical student Agnieszka Czechowicz, MD, PhD; and associate professor of pathol- ogy, Stanford’s autism center.

The research was supported by the National Institutes of Health, the Life Sciences Research Fund and the Ludwig Institute for Can- cer Research. The research was dedicated to Dr. J. Michael Lesley, PhD, a colleague of many of the authors who lost her life to GIST in 2011. The work also was supported by the Department of Pathology.

Another frustration for patients can be the slow rate of recovery. The auto- nomic system’s nerve fibers do not have a sheath that guides their growth and acts as a protective layer. Without that protection, they are more fragile; with- out that guide, they take longer to regain strength and normal behavior. “It doesn’t mean that regrowth won’t happen,” Jaradeh said. “It’s just a long tunnel before you get to the light.” There are yet no cures for autonomic system disorders. But recognizing that such a disorder is the source of a patient’s symptoms allows doctors to treat those symptoms more effectively.

Trusting in the future

From the various tests that Jaradeh conducts with each visit, Laderriere is showing signs that his system is “on the slope of recovery,” Jaradeh said. He has seen no further spread of disease within the autonomic system, and some areas have improved. “I think he will continue to regain function,” Jaradeh said.

For others with similar issues, “the horizon is very promising,” Jaradeh said. “The field is wide open, and the opportu- nities for interactions between phys- icians are very great and the choice of areas for research is unlimited.” Possibili- ties include focusing on what neurotrans-mitters in the brain are active in response to various levels of blood pressure, and connecting that to electrical activity in the heart. “Or you could focus on hor- mones,” Jaradeh said. “We see patients who are sometimes misdiagnosed with early menopause who are actually hav- ing an autonomic problem. The ultimate future would be to see if we can figure out something in terms of the genetics of these issues, the sky is the limit.” Laderriere is willing to be patient. He is working with Jaradeh to see which medications will mitigate as many of his symptoms as possible. “I still don’t sweat, so that’s going to be the next stage of recovery,” he said. “We’re going to have to discover more with Dr. Jaradeh about what’s to be done. He’s so bright and has so much information. I feel I am in good hands, there’s no doubt. We’ll get there.”

Sara Wykes is a clinical affairs writer at Stanford Hospital & Clinics.
Minor continued from page 1
ten and process what I’m hearing, and to come up with informed questions that bring us together in planning our future,” Minor said. “That is what I am engaged in now.”

It’s just the kind of approach that Bill Brody, MD, PhD, the former president of Johns Hopkins and a Stanford University trustee, would expect from Minor. “He’s a very good strategic thinker, and he will analyze a situation and look at all the options before deciding how to proceed,” Brody said.

Minor’s childhood experiences shaped his outlook and values. He grew up in Little Rock, Ark., amid the tumultuous efforts to desegregate public schools and enforce civil rights in the South. Minor experienced first-hand the disparities in educational opportunities when he was bused to a previously all-black junior high school.

His interest in otolaryngology took root during an undergraduate bioengineering class at Brown University that took as a model the vestibular system in the inner ear, which helps us sense motion and maintain balance. The opportunities to help patients suffering from balance and hearing problems as well as conduct research to better understand such disorders cemented his decision to specialize in the field.

As a medical student, resident and research fellow, Minor consistently sought ways to broaden the scope of his work.

Kathleen Cullen was doing her PhD work in neurobiology at the University of Chicago and was sharing lab space with Minor during his postdoctoral fellowship there. “My first week with the group, we had a little difference in opinion about a maze of wires running through the lab, and I may have approached Lloyd in a less than collegial manner about the problem. Even at that point in his career, he was good at managing crisis situations,” she said with a laugh.

Minor and Cullen quickly became collaborators and friends, a relationship that continues to this day. They even played together on Chicago’s Committee on Neurobiology “Mind Over Bassball” softball team. “He’s not a particularly good softball player and we weren’t a great team, but we had fun,” Cullen said.

Their scientific collaboration continued for the next 20 years as they investigated the physiology of vestibular function. “I had trained as an engineer and he had a clinical background, and we were able to generate a greater appreciation for the clinical impact of my work,” said Cullen, who is now a professor of physiology at McGill University in Montreal and directs the aerospace medical unit there.

Minor helped to make Cullen feel comfortable at a time when female neuroscientists were still relatively rare. “Chicago was very male, and Lloyd made the environment in the group very collegial for me,” she said.

“He lets me do surgery on one of his animals, and it gives me more confidence and would make me a better surgeon. He’s very good at giving people wings to fly — seeing what they’re capable of and letting them demonstrate their skills,” Cullen said.

He completed his training, eventually moving to a faculty position at Johns Hopkins in 1993. Several years later, Minor saw a patient with an unusual complaint: Loud noises made him dizzy. Later he would see other patients with related complaints, such as hearing the sound of their own voice as disturbingly loud. Through both his work with patients and his research, he made groundbreaking discoveries by identifying the problem as a tiny opening in the bone overlying an inner-ear balance canal. Minor named the condition superior canal dehiscence syndrome and developed a method of diagnosing the problem as well as a surgical procedure to essentially plug the opening in the bone overlying an inner-ear canal.

“It’s widely acknowledged that his work changed the image of his work. He’s very careful in picking his patients, which I honor and respect,” she said.

“Then she read a paper by Mi nor about superior canal dehis cence syndrome and was sure she had it. After contacting him and getting the highly sensitive CT scan he needed, she eventually journeyed to Hopkins for a con sultation where “in two seconds he diagnosed me,” she said.

After a thorough round of testing, Minor discussed the risks of the surgery with Hirsch and her husband. “He’s very careful in picking his patients, which I honor and respect,” she said.

Comforted by Minor’s empathetic manner and the quality of his published research, Hirsch went ahead with the surgery. A scant two months later, Hirsch had rejoined the world, painting her living room and dining room and returning to work. “Now, I’m cured,” she said.

Hirsch expressed disappointment that more patients wouldn’t benefit personally from the compassionate care she received from him.

“But if anything ever happens to my other side — not that there’s any indication that it will — I’m calling him at home,” Hirsch said with a laugh. “I will show up at his doorstep at Stanford.”

Lloyd Minor, an otolaryngologist and former provost of Johns Hopkins University, became dean at the School of Medicine on Dec. 1.

In 2003, Minor was appointed chair of the Department of Otolaryngology–Head and Neck Surgery and otolaryngologist-in-chief at Johns Hopkins Hospital. Brody, who was then the university president, characterized the department as “very distinguished, but not performing up to its potential” prior to Minor’s appointment as chair, and so he was curious to see how Minor would respond to the challenges. Brody said he was struck by Minor’s ability to “run silent, run deep,” quietly listening and devising his plans. “He has a fortitude that is very focused,” Brody said. “He took the department to new highs in its research performance, clinical outcomes and financial outcomes.” Under Minor’s leadership, the department achieved a 50 percent expansion in research funding and a 30 percent increase in clinical activity.

Ronald Peterson, president of The Johns Hopkins Hospital and Health System and executive vice president of Johns Hopkins Medicine, said that while Minor built clinical service volumes and quality in otolaryngology, “he will be best remembered for bringing the science in the department to the next level. At the same time, he was extremely attentive to the fiscal affairs of the department and left it in very good condition on his departure.”

In addition, Minor wanted to address the lack of women on the faculty. Sandra Lin, MD, an associate professor of otolaryngology, said, “At the time, I was the only female clinical faculty member on the main campus in our department, and there was one other female clinical faculty member at the Bayview campus.”

Minor asked Lin to head the department’s diversity and inclusion efforts. They created a committee and began talking with faculty members to identify the barriers and devise remedies. “We found out that a lot of things that were important to women were important to men on the faculty as well, but everyone had been afraid to speak up,” Lin said. Many of these issues fell in the area of balancing work and home responsibilities, such as being able to attend their children’s school or sporting events in the evenings.

“Our department used to have meetings after the end of the business day, and that systematically excluded people who had evening responsibilities outside of work,” Lin said. “Right away, Lloyd moved our department meetings so that they took place early in the day, which the faculty collectively felt would be a more manageable time in order to balance work and outside responsibilities.”

The department implemented mentorship programs, actively recruited women and underrepresented minority faculty in both the clinical and research ranks, and added a clerkship that was available to minority medical students interested in doing an otolaryngology rotation at Johns Hopkins Hospital.

One result was that the number of female clinicians
and basic scientists in the 36-person department grew from three to nine under Minor’s leadership. There were promotions to associate professors by the time he became provost. Those efforts have continued to bear fruit; Lin said currently about 40 percent of the department’s residents are women, as are one-third of its faculty.

“Lloyd is a person of action and results. He really wanted change,” Lin said.

While chairing the otolaryngology department, Minor also expressed an interest in working more broadly on university-wide initiatives. Although Brody had left the university in 2008 to become president of the Salk Institute for Biomedical Research, he recommended that Hopkins consider Minor as a candidate for provost in 2009, and the two men spoke frequently by phone after Minor got the job. “I wasn’t sure how someone from oto-laryngology would take to dealing with the classics department, the applied physics department, the philosophy department,” Brody said. “I was really astounded at how quickly he grasped not only the vernacular and the strategic issues, but also the local cultural ethos and the peculiarities of various parts of the university. As provost and in his own research and clinical work, Lloyd was highly integrative and interested in bringing together various disciplines.”

Minor was overseeing the university’s nine schools and leading its budgeting process, Minor reinforced and expanded the university’s efforts to recruit and retain a diverse faculty. He also bolstered the university’s educational efforts, implementing programs to increase student satisfaction and to enhance introductory science courses at the undergraduate and graduate levels. He led the development of a board to promote excellence in doctoral education.

Perhaps one of his greatest accomplishments was providing opportunities and incentives to draw the university’s nine schools closer together, said Jonathan Bagger, PhD, the vice provost for graduate and postdoctoral programs who is currently serving as interim provost.

“Historically, Johns Hopkins has had a low-profile and reactive provost’s office. When Lloyd arrived, he set out to change that by building the support of the president,” Bagger said. “He was constantly finding ways to use his position to engage faculty from across the university — both with the central administration and with each other.”

For example, he created a fellowship program in the provost’s office in which faculty members spend 20 percent of their time working on projects they’ve proposed. One such project involved improving premedical education for undergraduate students and strengthening efforts to recruit and retain premedical students from minority groups. Another involved developing social networking tools to better connect faculty and students. “I appreciate the dialogue he sparked with the faculty,” Bagger said, adding that his admiration for Minor has increased since temporarily taking on the provost’s duties. “In a job like this, where so many issues come across the desk, what really matters are one’s values. A lot of these issues don’t have clear answers, and there isn’t always time to research every angle. What it comes down to is the person’s values — and Lloyd are impeccable. His commitment to integrity, both personal and institutional, is extraordinary.”

After Philip Pizzo, MD, announced that he would be stepping down as dean of Stanford’s medical school after 12 years, Minor learned about the opening and was intrigued by the possibility. Though he had spent most of his academic career at Johns Hopkins, he recognized that the two institutions both were respected internationally for their emphasis on interdisciplinary research and on strong relationships between basic science and clinical care.

“One thing Stanford has done exceptionally well is drawing bridges across disciplines,” said Alan Garber, PhD, who was a professor of health research and policy at Stanford until moving to Harvard to become provost.

In 2011, the two men got to know each other as fellows, and Garber said he believes Minor’s background will serve him well at Stanford.

“At Hopkins, he moved from being a successful researcher in one field of medicine to being a department chair to having to think about a wide range of issues for the whole university,” Garber said. “That kind of experience makes you think of the academic enterprise as a whole in a different way.”

Minor, who was promoted to associate dean of Stanford’s medical school after 12 years, Minor learned about the opening and is stepping down as dean of Stanford’s medical school.

Lucy Shapiro, PhD, professor of development biology, added, “He has had an incredible career as a physician, as a basic scientist and as an educator, serving as provost at a very great university, Johns Hopkins University, so that he has the experience of dealing with people from many parts of our campus.”

Despite the many challenges facing academic medicine today, Minor is undaunted. “As a leader, sometimes you’re going to make the wrong decision. Sometimes you’re going to get challenges head-on — and taking advantage of the opportunities they present — is the only way that we as institutions can adapt,” he said.

He is planning more town hall meetings like the one on Feb. 5, in addition to meeting with a variety of faculty, students and other constituents as he continues to work with his leadership team to formulate his plans for the future of Stanford Medicine around his priorities of advancing innovation, empowering future leaders and transforming patient care.

“It’s the same methodological process that has served him well throughout his career, and one that he believes will make the medical school firmly on the right track.

“A year from now, if we are moving forward with a number of priorities that we’ve identified from our current cam- paign planning process, if we are seeing our clinical programs strengthened, if we are collectively building on the strength of our programs and the way that integrates our clinical programs with our educational mission and our basic research — if we are moving forward on all those fronts, that will have been a successful year,” Minor said.

Cells can predict onset of graft-versus-host disease, study finds

By Bruce Goldman

School of Medicine investigators have identified a clutch of cells that — if seen early enough — could signal the onset of chronic graft-versus-host disease, or cGVHD. In this devastating syndrome, the patient’s tissues come under a vicious and enduring assault by the transplanted cells.

“The overwhelming majority of patients who die from cGVHD either have or will develop cGVHD within one to three months,” said David Miklos, MD, PhD, assistant professor of medicine and senior author of the new study, which was published online Feb. 6 in Proceedings of the National Academy of Sciences. Until now there have been no good predictive indicators for the onset of cGVHD, he said.

“The discovery of this easily measured marker in the blood could help guide new therapies designed to mitigate or prevent this potentially life-threatening adverse outcome of transplantation of bone marrow from one person to another,” Miklos said.

Mesenchymal stromal cells are most commonly used to treat leukemia and lymphoma, conditions incurred when a blood or immune cell, respectively, becomes cancerous and proliferates. To get these cells, account for 50,000 to 75,000 new cases annually in the United States.

“Donor bone marrow transplantation involves first clearing a patient’s body of his or her own immune cells and then transplanting bone marrow from the source of all blood-and immune-forming cells, from a tissue-matched donor. The new cells, which are free of cancer, repopulate the entire body. The immune system, while eventually give rise to a functioning set of blood and immune cells, providing a lifelong cure,” said Miklos.

But in about half of such transplant procedures, patients ultimately develop chronic graft-versus-host disease. In one-quarter of all these transplants that involve male recipients and female donors, the risk is even higher.

That’s an intentional tradeoff. While female-to-male bone-marrow transplants put the recipient at 80 percent higher risk of either acute or chronic GVHD than sex-matched transplants, they also reduce the male recipient’s risk of a cancer that accounts for 10 percent of all cancers.

Cancer cells are, at heart, unstable and thus prone to mutations or differentiation into other cell types. But any cells that it perceives as “foreign,” including healthy cells bearing surface features the immune system hasn’t be- come accustomed to over the course of its long-term exposure to the body’s various tissues. So, the occupying army of immune cells from the donor all too often mounts a vicious, enduring, all-fronts attack on the recipient’s healthy tissues.

The standard treatment for cGVHD is to administer steroids, which can glob- ally suppress the entire immune system. This therapy has its drawbacks: notably, a greatly increased vulnerability to infections disease, weight gain, osteoporosis, muscle weakness and severe mood swings. Plus, it doesn’t always work or, often, becomes a lifelong requirement.

The early warning indicator Miklos’ team found is a particularly configured kind of B lymphocyte, one of many cell types that comprise the immune system and are routinely infused in a bone marrow transplant.

Recently, B cells have not been commonly suspected to induce cGVHD, because the job they’re most well-known for is producing antibodies, an array of secreted proteins similar to arrows with design tips. These archetypal “very varying shapes” — by some estimates, as many as a quadrillion (the number one followed by 15 zeroes) in a single per- son’s immune system — give antibodies a collective capacity to bind to virtually every other protein that may do a for- eign cell’s surface. Antibodies can grab onto an infecting pathogen, for example, immobilizing it and flagging it for an all-out assault and likely destruction by a heavyweight squad of aggressive im- mune cells.

Even when not engaged in antibody production, every B cell has surface re- ceptors whose shapes closely resemble the “design tips” of the antibodies the cell or its progeny will ultimately produce and secret, should it become active. It was this shared feature that permitted the first-ever association of a set of B cells with the onset of cGVHD, Miklos said.

Essentially all human cells package their genetic materials as 23 chromo- some pairs, some composed of one mater- ially derived and one paternally derived kind. And the proteins encoded by these chromo- somes are closely similar. One pair, how- ever — the one that determines our sex — consists of two chromosomes that, in a woman, are similarly close (two copies of the X version) but, in a man, are as different as a pair. So, migrating stem cells harbor- ing dormant bacteria might reactivate the disease in the lung. Interestingly, I and other physicians treating patients with tuberculosis for a persistent pulmonary disease — which results in lung inflam- mation — have seen a strong correlation between COPD and tubercular relapse. It is possible that the tuberculosis relapse in COPD might involve the stem-cell mechanisms that underlie reactivation of a dormant tu- berculosis infection.

In the future the scientists plan to fo- cus on investigating the cellular mecha- nisms used by the tuberculosis bacteria to infect and persist in the mesenchymal stem cells, and how reactivation occurs through the stem-cell niche. They’re also interested in the possibility that tuberculosis might not be the only microbial bad actor that can establish itself in the stem cells’ properties as a perfect hiding place.

This could possibly be a more gen- eral paradigm,” said Felcher. “Other in- fection agents might use stem cells in a similar manner. We’d like to further characterize whether and how these stem cells provide a protective niche for other infectious agents.”

The research was funded by the Bill & Melinda Gates Foundation, the Cana- dian Cancer Society, the KaviKrishna Foundation, the Laurentian Foundation, the National Institutes of Health and the Department of Defense. The work was also supported by the medical school’s Department of Medicine.
our immune systems have never before seen might stem from our constant exposure to ubiquitous, mostly harmless microorganisms, from our gut and lymph nodes to our skin, our doorknobs, our telephones and our iPod earbuds.

CD4 cells are members of the immune club known as T cells. CD4 cells hang out in our circulatory system on the lookout for micro-organisms that have found their way to our blood, to give our immune system a head start. In order to be able to recognize and then coordinate a response to a particular pathogen without initiating a Madrid-overreaction to anything and everything, CD4 cells possess a diverse array of genes that allows them to generate the billions of differing epitope-targeting capabilities represented in aggregate by T cells. He found that T cell antigen receptors (TcRs), or to 1967, it was, and it is, believed, only that epitope. Contact with that epitope can cause a CD4 cell to replicate, to divide rapidly and perform the immunological equivalent of posting bulletins, passing our bullets and bellowing attack orders through a bulletin to other immune cells. This hyperactivity is vital to the immune response. (It is CD4 cells that are targeted and ultimately destroyed by HIV, the virus responsible for AIDS.)

In the early 1980s, Davis, now the Burt and Marion Avery Professor of Immunology at Stanford, unraveled the mystery of how organisms such as ourselves, equipped with 100 billion T cells, can recognize and respond to a nearly infinite variety of pathogens. He found that T cell antigens bearing epitopes in the body's cellular components, such as those seen in the germs we are exposed to, are bound to T cells' antigen receptors, or TcRs. The T cell's DNA triggers massive and-catch-mass of these genetic components during cell division, so each resulting T cell sports its own unique variation of a T cell antigen receptor and, therefore, is geared to recognizing a different epitope.

That variation accounts for our ability to mount an immune response to all the antigens, whether familiar or previously unseen. But it doesn't account for the phenomenon of immune memory. CD4 cells, like other T cells, can be divided into two groups: so-called 'naive' CD4s randomly targeting epitopes because of their TCRs, and 'memory' CD4s that, having had an earlier run-in with one or more pathogens, are already programmed to recognize similar epitopes. The memory CD4s are responsible for the phenomenon of immune memory. CD4 cell targeting a particular epitope was described by Davis in 1996 and since refined in his and others' laboratories permitted the Stanford team to identify a single new viral epitope shared by different viral strains. Using this method, his team exposed immune-cell-rich blood drawn from 26 healthy adults, as well as from two newborns' umbilical cords, to various epitopes from different viral strains. They were able to fish out, from among hundreds of millions of CD4 cells per sample, those responsive to each viral epitope. Nearly all of the 26 adult blood samples contained CD4 cells responsive to HIV; to HSV, the virus that causes shingles; and to cytomegalovirus, a common infectious agent associated with the development of cGVHD, or graft-versus-host disease.

What was surprising was that, on average, about half of the virus-responsive CD4 cells in each adult sample bore unmistakable signs of being in the 'memory' state — a characteristic that indicates that the activating pattern for memory T cells and cardinal determinations of signature biochemical signals, called cytokines, that allow memory cells to do their thing — even though highly sensitive testing showed that these individuals had never been exposed to any of these viruses in real life.

The newborns' blood contained similar frequencies of CD4 cells responsive to the same three viruses. However, all these cells were in the 'naive' rather than the 'memory' state. This could explain, at least in part, why infants are so incredibly susceptible to disease, said the study's first author, Laura Su, MD, an instructor in immunology and rheumatology.

Another surprise: About one-fifth of the adult samples boasted 'cross-reactive' memory CD4 cells responsive to other harmless environmental microorganisms. For example, CD4 cells cross-reacted specifically for their reactivity to HIV turned out to be able to recognize a large number of common environmental microbes, allowing them to target three gut-colonizing bacteria, a soil-dwelling bacterial species and a species of ocean algae. Considering the millions of adaptive immune responses that target all of the microbes a person might encounter, it's a sure bet that this measure of CD4-cell cross-reactivity was an underestimate.

Next, the researchers recruited two adults who hadn't been vaccinated for flu in five or more years, and then vaccinated them. In these volunteers, memory CD4s proliferated and otherwise became activated in response to exposure to certain components of the influenza virus, but also to epitopes of several different bacterial and protozoan parasites. This cross-reactivity could explain why exposure to common bugs in the dirt and in our homes renders us more resistant to dangerous infectious agents.

Which raises another point. "We grow and use experimental lab mice in totally artificial, ultra-clean environments," Davis said. "That's not like the environment that we live in. The CD4 cells from adult mice in the lab environment are almost entirely in the naive state. They may be more representative of newborns than of adult humans.

Petri described the new study as paradigm-shifting. "It was one of those rare, seminal findings that changes the way I think about the immune response," he said.

Davis' study offers hope that some of the immunity conferred by a vaccine extends beyond the specific microbe it targets, Petri said. "This adds support to the impetus to vaccinate infants in the developing world," he said. As many as 30 different pathogens can cause severe or life-threatening infections against all of them — even if those vaccines existed — would require so many separate injections as to be logistically hopeless. Understanding the mechanism by which cross-reactivity occurs might further allow immunologists to develop "wide-spectrum vaccines" that cover a number of infectious organisms.

The study was funded by the National Institutes of Health and the Howard Hughes Medical Institute. Other Stanford co-authors were senior bioinformatics specialist Brian Kidd, PhD; clinical fellow Arnold Han, MD; and biology undergraduate student Jonathan Kortz.

The work also was supported by Stanford's Institute for Immunity, Transplantation and Infection.
Physician honored for work serving medical center alumni

Linda Hawes Clever, MD, was honored last month at a luncheon of the Board of Governors of the Stanford University Medical Center Alumni Association for her many contributions to alumni affairs. Clever, a former university trustee, served as the associate dean of alumni affairs for the medical center from September 2009 through December 2012.

“She has championed the issues of alumni engagement with a passion and dedication that has truly inspired us as alumni, volunteers and faculty. We are extremely grateful for her service and her contributions,” said Lloyd Minor, MD, dean of the School of Medicine. “Her work over the past three years was transformative, and we are all deeply in her debt as we continue to build on the work she did.”

Clever helped advance the strategic planning process for the association and its goals of engaging and inspiring alumni. She sponsored a number of initiatives that brought together students, faculty and alumni in building a community to support the medical school and its graduates.

“Linda has an unwavering dedication to Stanford University, as well as the School of Medicine,” said Jane Lom- bard, MD, the alumni association president. “She has championed the issues of alumni engagement with a passion and dedication that has truly inspired us as alumni, volunteers and faculty. We are extremely grateful for her service and her contributions.”

Clever, who did both her undergraduate and graduate work at Stanford, served on the university’s Board of Trustees for 14 years. She is a recipient of the Stanford Medal, the Dinkelspiel Award, SUMCAA’s J. E. Wallace Sterling Award for Lifetime Achievement, the Elizabeth Blackwell Medal from the American Medical Women’s Association, and the Stengel Award from the American College of Physicians. An intern with a specialty in occupational medicine, she served as editor of the Western Journal of Medicine. She is a member of the medical center’s adjunct faculty.

The position of associate dean of alumni affairs will not be continued. Instead, its responsibilities will be absorbed by Dan Herschlag, PhD, senior associate dean for graduate education and post-doctoral affairs, and Charles Prober, MD, senior dean for medical education.

Stanford outpatient cancer center in South Bay expected to open in 2014

Stanford Hospital & Clinics has announced plans for a new outpatient cancer center in San Jose at the intersection of Los Gatos Boulevard and State Route 85.

Housed in an existing 70,000-square-foot building at the site, the center is expected to open in 2014 and will offer the latest in cancer care, along with complementary practices, provided by physicians from Stanford and the local medical community.

The new outpatient facility will support the latest advances in cancer treatments, including access to clinical trials and Stanford’s National Cancer Institute-designated cancer center. “As an oncologist, I am excited about the opportunity to significantly expand patient access to Stanford’s cancer care and our nationally recognized quality programs,” said Douglas Blayney, MD, a professor of oncology and medical director of the Stanford Cancer Center.

“When it opens, this new outpatient center will offer patients coordinated medical services which are integrated with those they could receive by traveling to the Stanford campus, all in one convenient South Bay setting,” Blayney said. “The four-story building will be Stanford’s most comprehensive outpatient medical facility outside of Stanford Hospital & Clinics in Palo Alto and the Stanford Medicine Outpatient Center in Redwood City.”

“We are extremely pleased to be able to provide residents of the South Bay region with convenient access to Stanford’s leading-edge, patient-centered care,” said Amir Dan Rubin, president and CEO of Stanford Hospital & Clinics. “Stanford is home to some of the most important innovations in cancer treatment, including the first use of the linear accelerator, which is the basis for today’s radiation therapy, as well as development of the CyberKnife, a robotic radiosurgery tool which provides a whole new way to treat certain kinds of tumors. With more than 300 ongoing clinical trials in cancer and pioneering work under way in genomics to develop targeted therapies, Stanford is helping lead the fight against this challenging disease.”

Lucy Shapiro medals in science

President Barack Obama presented Lucy Shapiro, PhD, the Virginia and D. K. Ludwig Professor at the medical school and director of the Beckman Center for Molecular and Genetic Medicine, with a National Medal of Science on Feb. 1 at the White House. The Stanford developmental biologist was one of 12 recipients of the 2012 medal. Her research helped launch the field of systems biology and has led to the development of novel antibacterial and antifungal drugs.

Joanna Wysocka

Web-based fellowship promotes care for older adults of various ethnic groups

In an effort to promote successful aging and end-of-life care for multicultural older adults, Stanford recently launched the Internet-based Successful Aging program, or iSAGE. The mini-fellowship is funded with a grant from the National Institute on Minority Health Disparities, and it’s being offered for free to both health-care professionals and members of the public.

The self-training program was developed by V.J. Periyakoil, MD, director of palliative care education and training at Stanford, in partnership with the School of Medicine’s Office of Diversity and Leadership.

Hannah Valentaine, MD, senior associate dean for diversity and leadership and a collaborator on the project, said iSAGE addresses the critical need to educate Americans, across racial and ethnic groups, about successful aging. “Americans are aging and becoming more diverse,” she said. “In order to provide the best possible care for multicultural American older adults, we need to activate the lay public and health personnel by increasingly increasing awareness about the principles of successful aging.”

For more information about the program is available online at http://geriatrics.stanford.edu/iSAGE.

To read a Q&A in which Periyakoil discusses the program, visit http://scopeblog.stanford.edu/2013/01/23/stanford-introduces-web-based-mini-fellowship-program-on-successful-aging.