INSIDE STANFORD MEDICINE

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Anesthesiologist Audrey Shafer discusses how *Frankenstein* raises questions about science and technology that are relevant today.

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Lab bridges virtual reality, operating room

By Nicoletta Lanese

PAUL SAKUMA

Neurosurgery instructor Kumar Abhinav with trainees at the Neurosurgical Simulation and Virtual Reality Center in the Grant Building.

A new anatomy lab in the basement of the Grant building gives Stanford neurosurgery trainees a convenient place to hone their skills.

"Our anatomy labs have all been coordinated at outside facilities, and for people on call, they can't just go 30 minutes away to do a lab," said neurosurgery resident Linda Wei Xu, MD. "It'll be great to have our own lab for day-to-day use."

The off-campus labs focused on theoretical cases. With their own lab on the Stanford campus, residents will be able to practice for specific cases, Xu said.

The lab complements the Neurosurgical Simulation and Virtual Reality Center, which opened in 2016 and allows trainees to explore three-dimensional, digital renditions of brain structures. The new anatomy lab acts as a bridge between the simulation center and operating room.

"In the simulation lab, the residents can put on the goggles, interact with the patient anatomy and learn about the case they're about to do the next day," said Harminder Singh, MD, clinical associate professor of neurosurgery. "Then in the anatomy lab, they do the dissection on real cadaver heads and practice the surgery techniques."

Anand Veeravagu, MD, assistant professor of neurosurgery, said, "It's to give them an opportunity to feel safe, to train outside of the OR, and not feel they ever need to do anything for the first time in the operating room."

Gary Steinberg, MD, PhD, professor and chair of neurosurgery, spearheaded the creation of the simulation and anatomy labs with the help of Singh, Veeravagu and Michel Kliot, MD, clinical professor of neurosurgery. The simulation lab has already become integral to resident education and clinical practice.

'A versatile system'

"It's really a versatile system that translates from patient engagement and intraoperative navigation all the way through to resident and fellow education," said biomedical engineer Malie Collins, the virtual reality program coordinator. Since the simulation lab opened, Collins has constructed over 500 virtual-reality models of complex neurosurgical cases, including aneurysms, tumors and spine deformities. The software, called Surgical Theater, transforms two-dimensional patient data sets, like angiograms, MRIs and CT scans, into 3-D virtual environments.

The lab seems plucked from a video gamer's wildest dreams. Cushy chairs face ultra-high-definition monitors. By donning virtual-reality goggles and using handheld controllers, residents can navigate through an actual patient's neuroanatomy, manipulating it — rotating structures, removing obstructing tissues — as they explore.

The operating system can also travel beyond the simulation lab, wheeled on to operating rooms and clinics. Surgeons can use the system to plan operations and guide their instruments during surgery, like a 3-D GPS system. In the clinic, patients are able to visualize their conditions in a new, totally customized way.

"Even patients that know everything about their disease still benefit, because I guarantee they haven't flown inside their spine or their brain," **See ANATOMY, page 7**

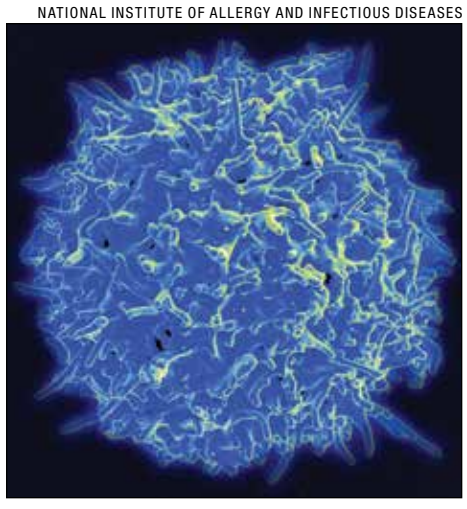
Workaround erases side effects of promising cell-based cancer therapy

By Bruce Goldman

Altering a powerful immune-signaling chemical plus its receptor on immune cells may bring a promising cancer treatment closer to the clinic, according to a study led by investigators at the School of Medicine.

If the advance proves as beneficial in humans as in mice used in the study, which was conducted in collaboration with researchers at the University of California-Los Angeles and UC-San Francisco, then incorporating it into the experimental regimen, called adoptive cell transfer, could speed that treatment's acceptance as a standard anti-cancer practice.

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES



A T-cell image from a scanning electron microscope.

In adoptive cell transfer, immune cells called killer T cells are purified from a patient's blood, endowed with superior tumor-recognition features via genetic engineering, and induced to proliferate. The modified cells are returned to the patient's circulatory system, where they can efficiently and selectively destroy tumors.

But this approach is hampered by the modified T cells' failure to continue to survive, multiply and sustain their targeted rampage for substantial amounts of time after they've been transferred back into the patient. That's because the altered T cells need frequent "booster shots" of a crucial protein called interleukin-2, or IL-2, **See T CELL, page 7**

Researchers identify cells that signal probable relapse of pediatric leukemia

By Erin Digitale

Researchers at the School of Medicine have developed a technique that allowed them to determine at diagnosis whether children with acute lymphoblastic leukemia would relapse following treatment.

Kara Davis

The method, described in a paper published online March 5 in *Nature Medicine,* predicted relapse in the cohort they examined with 85 percent accuracy, a significant improvement from 66 percent accuracy achieved by the current risk-stratification method used at diagnosis. The method examines cancer cells one at a time using mass cytometry, a technique developed by Garry Nolan, PhD, professor of microbiology and immunology and a senior author of the study. Using data on the cells' stage of development and signaling behavior, the scientists figured out how to identify a tiny subset of malignant cells that, if present, predisposed a patient to relapse.

Called the Developmentally Dependent Predictor of Relapse, the technique could help identify which acute lymphoblastic leukemia patients need a different approach to cancer treatment, and may provide good clues about how to find new drugs to target the deadliest cancer cells, the researchers said.

"We really need to personalize treatment to leukemia patients better than we do now," said graduate student Zinaida Good, the study's co-lead author. "There is a lot of room for improvement here. This study makes a contribution to our ability to stratify patients better and not treat everybody the same way."

Postdoctoral scholar Jolanda Sarno, PhD, is the other lead author.

Pediatric acute lymphoblastic leukemia is the most common childhood cancer, diagnosed in about 3,000 American children per year. The study focused on the most frequently found type of the disease, called B- **See LEUKEMIA, page 6**

Using antibody to treat 'bubble boy disease' shows early promise

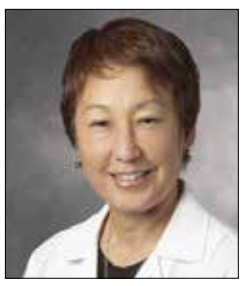
By Christopher Vaughan

Researchers at the School of Medicine said they are encouraged by early results from a clinical trial in which participants are being given an antibody-based treatment rather than chemotherapy or radiation to prepare them for a blood stem cell transplant.

The trial is the first time that the approach has been tested in humans. The researchers noted that these are preliminary results from the first two participants in the trial. Judith Shizuru, MD, PhD, professor of medicine at Stanford, discussed the trial Feb. 27 at the annual meeting of Stanford's Center for Definitive and Curative Medicine.

The phase-1 trial involves participants who have a condition known as severe combined immunodeficiency. SCID, also known as "bubble boy disease," is a genetic disorder that disturbs the normal development of immune cells, leaving people with the condition vulnerable to infections that most people ward off easily.

SCID patients can be given infusions of stem and progenitor blood-forming cells to boost their immune response, but that effect can wear off over time if significant numbers of the healthy stem cells can't replace the diseased stem cells. The only cure for SCID involves a blood stem cell transplant, in which the patient's defective stem cells are wiped out with chemotherapy or radiation so that large numbers of normal blood stem cells from a donor can take their place.



Judith Shizuru

The problem with chemotherapy or radiation is that they can be very damaging. "Physicians often choose not to give chemotherapy or radiation to young children with SCID because there are lifelong effects: neurological impairment, growth delays, infertility, risk of cancer, etc.," Shizuru said.

Administering an antibody

The current trial is testing a different method of removing the defective stem cells. Shizuru and her colleagues — including Rajni Agarwal, MD, associate professor of pediatrics; and Maria Grazia Roncarolo, MD, PhD, professor of medicine and of pediatrics and co-director of the Stanford Institute for Stem Cell Biology and Regenerative Medicine — are giving the participants an antibody to CD117, a cell surface marker found on blood and immune stem cells.

The potential therapy is based on work originating in the laboratory of Irving Weissman, MD, director of the Stanford Institute for Stem Cell Biology and Regenerative Medicine. Assistant professor of pediatrics Agnieszka Czechowicz, MD, PhD, while still a graduate student in Weissman's lab, showed that an antibody could be used to block, in mice, a critical stem cell factor from binding to the receptor CD117. This binding had been previously shown in the Weissman lab to be required to keep blood stem cells alive. The use of the antibody could thereby eliminate most blood stem cells, clearing the way for donor stem cells to take up residence in the bone marrow.

Early data from the clinical trial show that the antibody's activity in humans is similar to what was observed in mouse studies. Specifically, the antibody appears to be effective in the depletion of genetically defective stem cells.

Nine and six months after the treatment, respectively, the two participants have shown evidence that the donor stem cells have taken root and are producing immune cells, Shizuru said.

Given these results, the researchers plan to continue their clinical trial and include infants with the disease, since infancy is a time when the negative effects of chemotherapy or radiation can be particularly acute.

The first cases also suggest that the antibody-based conditioning may be useful in combating other diseases, including cancer, Shizuru said. Autoimmune diseases like Type 1 diabetes, multiple sclerosis and lupus may be curable through blood stem cell transplantation, but are not currently treated this way because the dangers of chemotherapy or radiation usually outweigh the benefits.

The trial is being supported by a grant from the California Institute for Regenerative Medicine.

Lucile Packard Children's Hospital Stanford and Stanford's departments of Medicine and of Pediatrics also support the work. **ISM**

Potential drug targets for ALS revealed in study using CRISPR

By Hanae Armitage

In a new application of gene-editing technology, researchers at the School of Medicine have gleaned insights into the genetic underpinnings of amyotrophic lateral sclerosis, a neurodegenerative disease that's notoriously tricky to parse.

The team's findings are a step toward demystifying how the disease progresses and could even help lay the groundwork for new therapeutic targets.

ALS, also known as Lou Gehrig's disease, erodes muscle function and impairs the brain's ability to communicate with the body, making simple voluntary muscle movements — such as brushing your teeth, talking or even breathing — exceedingly difficult and, eventually, impossible. ALS falls into a category of neurodegenerative diseases that all share a common "signature" — abnormal protein clumps that build up in the brain.

In ALS, these protein clumps, or aggregates, are thought to be fatally toxic to neurons, ultimately leading to the devastating physical symptoms of the disease. But the process of the cells' demise is still largely a black box.

"These toxic protein aggregates are what's likely driving the pathology in the disease, but no one really knows how they cause neuronal cell death. That's really what we wanted to probe in this study," said Aaron Gitler, PhD, professor of genetics. He shares senior authorship with Michael Bassik, PhD, assistant professor of genetics.

Gitler's and Bassik's labs used CRISPR-Cas9 gene-editing technology to sort through the entire human genome and pick out the genes that helped neurons shore up defenses against the toxic protein. Not only did some genes give the researchers a deeper mechanistic understanding of the disease itself; a handful seem to hold potential as drug targets, too.

A simple but deadly protein

A paper describing the research was published online March 5 in *Nature Genetics*. Graduate students Nicholas Kramer and Michael Haney share lead authorship.

The discovery that mutations in the C9orf72 gene is a relatively common cause of ALS has helped ignite efforts to understand how ALS works at the molecular level. In ALS, the mutated C9orf72 gene contains a huge segment of DNA that repeats itself and, when that part of the gene is erroneously turned into various rogue proteins, they gum up neuronal function and lead to cell death.

Tmx2 may be a modulator of other genes that set off the cell-death process.

"In a healthy person, you might see 10 to 20 of these DNA repeats," Haney said. "But in ALS, they expand to hundreds or even thousands of repeated segments, and that's the template for the production of these toxic proteins."

Gitler and Bassik set out to answer two basic questions: How do the toxic proteins snuff out otherwise healthy neurons? And are there other genes that inherently protect against — or conversely, exacerbate — the effects of the toxic proteins in the brain?

Aaron Gitler

Michael Bassik

Rather than separately interrogate every gene in the human repository, the researchers used a tactic called genomewide screening, which harnesses CRISPR-Cas9 to alter the function of every single human gene simultaneously. In this case, they used the technology to produce "gene knockouts," targeting genes with a kind of molecular scissors that makes precise cuts, leaving them unable to carry out normal function.

The gene knockouts, Kramer explained, help the researchers spot genes that either enhance toxicity or prevent it: If you identify a gene and knock it out, and the ALS protein repeats are no longer toxic, then you know that the absence of that gene actually protects the neuron against degeneration. And perhaps more importantly, it may be a potential drug target.

Tmx2: A sentinel of cell death

After systematically knocking out every gene in the human genome and measuring the toxicity of the ALS proteins in cells, the researchers found that about 200 genes, when knocked out, either helped to protect the cell from the toxic proteins or made it more vulnerable to them. To zero in on a smaller set of genes, Haney and Kramer followed up with two subsequent knockout screens in primary mouse neurons.

They found a handful of knockouts that were particularly potent protectors. One, for example, helped block off critical entrances through which the toxic ALS proteins infiltrate the cell and corrupt it. But there was another knockout in particular that caught the group's attention for its mysterious ability to ward off neural death. The gene normally codes for a protein called Tmx2, which is found in a part of the cell called the endoplasmic reticulum. But when depleted in mouse neurons in a dish, the cells survived nearly 100 percent of the time — quite a jump, considering that the survival rate for normal neurons was 10 percent.

"We could imagine that Tmx2 might make good drug-target candidate," Haney said. "If you have a small molecule that could somehow impede the function of Tmx2, there might be a therapeutic window there."

Right now, Tmx2's role in the endoplasmic reticulum isn't completely clear. But it's thought to be involved in the response to various environmental stressors, particularly those that trigger cell death. According to the study's findings, it may be a modulator of other genes that set off the cell-death process.

"We're still in early phases, but I think figuring out exactly what Tmx2 normally does in a cell is a good place to start — that would hint at what functions are disturbed when these toxic species kill the cell, and it could point to what pathways we should look into," Kramer said.

More broadly, CRISPR screens like the one in this study have been used to investigate a range of disease pathways. But the team said this is the first time, to their knowledge, that a genomewide human CRISPR knockout screen has been used to discover clues about a neurodegenerative disorder. Gitler and Bassik are currently teaming up to use this same approach to understand additional causes of ALS and even other neurological diseases — Huntington's, Parkinson's and Alzheimer's — that involve toxic proteins. "I think it's a really exciting application for CRISPR screens, and this is just the beginning," Bassik said.

Other Stanford authors of the study are graduate students David Morgens, Gregor Bieri and Kimberly Tsui; former postdoctoral scholar Ana Jovicic, PhD; research associ-

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STANFORD MEDICINE

5 QUESTIONS

an occasional feature in which an expert answers five questions on a science or policy topic

Sam Gambhir on progress in precision health

Patient care has long been about doctors treating patients once disease has already set in, but the emerging focus on precision health aims to change that dynamic. The idea is this: Empower individuals to monitor their own health, and let health care providers use the collective data to piece together a high-resolution picture of human health at the individual and population level. The goal is not just to glimpse the finer details of health and disease, but to consistently track and actively apply the collected data to prevent disease or detect it earlier.

Stanford Medicine, under the leadership of Dean Lloyd Minor, MD, began laying the groundwork for precision health in 2015 in an effort to provide targeted, predictive and personalized care. Stanford researchers were also working with the Canary Foundation as early as 2008 to lay out a roadmap of precision health, specifically for early cancer detection.

In a perspective piece published Feb. 28 in Science Translational Medicine*, researchers at the School of Medicine examine some of the key building blocks of precision health, give examples of cases in which it's already happening and highlight the role that monitoring technologies will play in elevating its success as a whole.*

Sam Gambhir, MD, PhD, professor and chair of radiology and director of Stanford's Precision Health and Integrated Diagnostics Center, is the lead author of the article. Recently, writer Hanae Armitage asked Gambhir about the ways in which precision health can improve health care.

1 How does the practice of precision health change standard doctor-patient relationships?

GAMBHIR: Precision health creates an opportunity for the entire health care team, including physicians, to utilize more detailed and comprehensive health data sets to be better-informed about their patient's individualized health. In turn, it allows physicians to more accurately address their patient's health risk profile and tailor monitoring methods and early intervention to that individual. This type of approach will empower doctors to be more focused and directed in how they treat patients.

Sam Gambhir

For patients, increased health monitoring allows them to more proactively engage in their own health — in some cases in real time — and see how it relates to their lifestyle or other health factors. Rather than simply follow a standard appointment schedule, patients would only visit their physician when needed, but they could still have contact with their health care team through a secure health portal. This approach could, when appropriate, reduce the number of patients visiting the clinic and allow physicians to more thoroughly engage with the patients who do come.

2 Explain the concept of "pre-patient care" and how it fits into precision health.

GAMBHIR: Not all health conditions require a regular visit to the doctor. An integrated health portal analyzing data from "smart" devices in the home and on the body could monitor a range of health data — from sleep patterns to biomarkers — and notify your physician if something seems out of the norm. Because health data would be "normalized" to each person, rather than only using trends from the population, individual abnormalities could be detected more frequently. Each individual becomes their own "control."

The physician and health care team could then use the information from the integrated health portal and, with their personal knowledge and experience, create interventions that would promote and improve overall health. Patient monitoring could range from minimal to continuous and could have the potential to empower patients to maintain their health. The goal: keep patients out of the clinic when they don't need to be there and have them visit their physician only when necessary. An active partnership and trust between patient and physician is a must if we're to maximize the benefit of these emerging approaches. This open communication and partnership is facilitated through secure health portals, regular remote health surveillance and early interventions when necessary.

3 What kind of role will technology play in improving the health of individuals as well as large populations?

GAMBHIR: Wearable technology, including implantables; data analytics; and an understanding of the mechanisms and biomarkers associated with the transition from health to disease state will be necessary in improving health care beyond current standards. Furthermore, passive measurements through "smart home" devices — such as a toilet that monitors biomarkers or a toothbrush that analyzes saliva — and other monitoring technologies that run in the background will be a crucial piece. The bathroom and kitchen could become two of the most important rooms in the home from a health-monitoring perspective.

Everyone, at and even before birth, could have a unique health-risk profile created. Based on this profile, physicians would prescribe appropriate wearables or other health monitoring or surveillance methods. Over time, an individual's monitoring needs will likely change, and this adaptation process will allow the types and frequency of health measurements to evolve with the patient through age, health status and other factors.

On a population level, shared health data sets could be useful in improving the predictability of health risk models. While not every data point will be relevant for each person, it would allow those at inherent risk for particular health conditions to be identified earlier, when positive clinical outcomes are still possible. Additionally, health-sensor technologies have already been adapted into cellphones and could be deployed into other settings too, like bathrooms, cars or public transportation.

4 How close are we, technologically speaking, to being able to realistically monitor individual health on a large scale, consistently?

GAMBHIR: The greatest challenge to understanding human disease is accurately and reliably monitoring the transitions that take place throughout the continuum of disease. Effective disease biomarkers are also essential. The technical capability and accuracy of health monitoring systems already exist for many conditions and could be produced at scale, but these devices are only as useful as the predictability of the biomarkers they measure. It's important to note that technology is ahead of our understanding of the underlying biology.

We're already able to monitor human health in a number of ways; however, it's critically important to identify the most informative and useful data. In addition to Stanford, many companies, such as Apple, Amazon, Google and Verily, are innovating in the human health arena.

Beyond development, validation and scalability, another important challenge is widespread adoption. User engagement will be critical to eventual success of these strategies: Real people and health providers will need to see value in using these devices in order for these health-monitoring approaches to be effective.

5 What do you and your colleagues see as some key ways to persuade large populations to not only participate in precision health efforts but to be active collaborators?

GAMBHIR: For precision health efforts to be successful, we as a society will need to work together. These efforts are bigger than any one group can tackle alone, and they require large numbers of participants over very long time horizons. That said, while there's great potential for individualized monitoring, each individual participant also benefits the overall population. In this way, active participation, whether as a study participant or investigator, can give back to the community by helping everyone stay healthy for as long as possible.

We have created and are involved in multiple large efforts. This includes the new Precision Health and Integrated Diagnostics Center at Stanford, and Project Baseline, which is a collaboration between Duke, Stanford, Google and Verily that launched in mid-2017 and was designed over a three-year period by more than 70 investigators. These efforts encourage investigators and participants from our community and beyond to get involved in precision health practices.

Furthermore, it's crucial to emphasize to participants that early detection and intervention are the best ways to improve health outcomes. Too often, disease is detected too late for treatments to be effective. This paradigm shift toward precision health seeks to keep society healthy for as long as possible, and catch disease before it strikes. **ISM**

ALS

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ate Julien Couthouis, PhD; research technicians Amy Li and James Ousey; research assistant Rosanna Ma; postdoctoral scholar Nicholas Hertz, PhD; and, Marc Tessier-Lavigne, PhD, professor of biology and president of Stanford University.

Gitler and Bassik are both members of Stanford Bio-X and the Stanford Neurosciences Institute. Bassik is also a member of the Stanford Cancer Institute and Stanford ChEM-H.

Researchers at the University of Southern California also contributed to this work.

The study was funded by the National Institutes of Health, the Genome Research Institute, the Robert Packard Center for ALS Research at Johns Hopkins, Target ALS, the Stanford Brain Rejuvenation Project of the Stanford Neurosciences Institute, the Muscular Dystrophy Association and U.S. Department of Defense.

Stanford's Department of Genetics also supported the work. **ISM**

Symposium set for April 17 to grapple with balance between human and artificial intelligence in medicine

By Amy Jeter Hansen

It's tempting to frame artificial intelligence in medicine as "us vs. them" — with "them" being the machines.

But Stanford's Abraham Verghese, MD, professor of medicine and the Linda R. Meier and Joan F. Lane Provostial Professor, believes there should be a more nuanced conversation around what technology can do for doctors and how the medical community and other stakeholders can anticipate unexpected changes brought by artificial intelligence.

"The way here is not to think technology versus human," Verghese said, "but to ask how they come together where the sum can be greater than the parts for an equitable, inclusive, human and humane care and practice in medicine."

To this end, the Presence Center is hosting a daylong symposium April 17 for physicians, researchers, technologists, venture capitalists, policy specialists and others interested in discussing issues surrounding humans and machines in medicine. The event will feature talks from speakers with diverse perspectives, including Verghese; Lloyd Minor, MD, dean of the School of Medicine; Robert Califf, MD, a former commissioner of the Food and Drug Administration; Eric Topol, MD, founder of the Scripps Translational Science Institute; and Fei-Fei Li, PhD, director of the Stanford Artificial Intelligence Lab.

Lawrence Tierney, MD, professor of clinical medicine at the University of California-San Francisco, will unpack a diagnostic puzzle in real time to illustrate what human experts can do and spur discussion about whether this expertise can be replicated by machines.

It's important to have a realistic picture of what computers can accomplish, said Jonathan Chen, MD, PhD, assistant professor of biomedical informatics research and co-chair of the symposium's planning committee. "With machine learning/AI situated at the peak of inflated expectations, we can soften a subsequent crash into a 'trough of disillusionment' by fostering a stronger appreciation of the technology's capabilities and limitations," Chen said.

Additionally, the speakers will explore such questions as: What role can technology play in disseminating expertise? How does one balance the drive for innovation against immediate patient safety? And should people worry about AI systems taking their jobs?

"The debacle with the electronic medical records and a decade of physician dissatisfaction has shown us that physicians must be at the helm, helping shape the AI solutions to hopefully ensure the intended impact on humans is also considered," Verghese said.

More information about the event, including registration pricing, can be found at https://med.stanford.edu/presence/initiatives/hiai-symposium.html. **ISM**

What conventional wisdom gets wrong about Medicare reimbursement

By Krysten Crawford

An advisory committee for Medicare is biased in favor of physician specialties, but this bias may in fact improve the quality of the price-setting recommendations it makes, researchers say.

David Chan, MD, PhD, assistant professor of medicine at the School of Medicine, and his colleague, Michael Dickstein, PhD, an assistant professor of economics at New York University, gained access to more than 4,000 fee proposals that were reviewed over a 21-year span by the committee, which is part of the American Medical Association. Their independent analysis is in a working paper released Feb. 26 by the National Bureau of Economic Research.

The findings are surprising. Until now, behind-closed-doors deliberations meant nobody knew for sure how the committee of physicians reaches its recommendations for health care service prices, which Medicare typically adopts. And longstanding criticisms of conflicts of interest have been largely based on anecdotal evidence and the assumption that tasking doctors with setting their own prices must be the equivalent of the fox guarding the henhouse.

But according to the empirical research, even if committee members were entirely neutral, only 1.9 percent of the $70 billion Medicare spends annually on health care would be redistributed across all services.

"Though the analysis is not a complete vindication of the AMA committee, we find that committee bias has subtle implications for different medical fields and for Medicare," said Chan, who is also a faculty fellow at the Stanford Institute for Economic Policy Research.

Benefits of bias

"Primary care doctors, once thought to be disadvantaged by the presence of specialty physicians on the committee, actually benefit from shared interests with other types of physicians," he said. "And overall, Medicare gets higher-quality information when the committee has connections with specialties."

In their research, Chan and Dickstein set out to uncover whether committee members exhibit bias in their recommendations and, if they do, how much it affects overall prices.

Since 1992, Medicare has tasked the AMA committee, formally known as the Relative Value Scale Update Committee, or RUC, with calculating the time and effort component which, together with service costs, accounts for 96 percent of the Medicare reimbursement rate. Most private insurers also establish their payment rates based on Medicare pricing.

David Chan

The lopsided composition of the committee — specialists significantly outnumber primary care physicians — has fueled suspicions that prices for complex procedures are rising quickly because doctors on the committee are inclined to increase the cost of the procedures that either fall under or are closely related to their practice areas.

After reviewing internal deliberations on 4,423 fee proposals from 1992 to 2013, the researchers found an increased likelihood that committee members will recommend higher prices for specialties they are connected with. For example, a spinal surgeon on the committee is likely to agree with a price increase for a hand surgery procedure because both share revenue from orthopedic procedures.

The researchers then measured how closely connected a proposed price change was to the specialties represented on the committee and the effect that affiliation had on the recommended reimbursement. They found that the more connected the overall committee was to specialties representing a procedure, the more likely it was to go along with a suggested rate increase.

So why would Medicare rely on a biased industry group to determine its prices? The evidence, Chan said, suggests an explanation: The lack of impartiality on the committee is offset by the finding that the information members contribute to the price-setting process is of higher quality than input from neutral advisers.

"There is this trade-off between bias and the quality of information," Chan explained. "An unbiased but very imprecise price may be worse than a biased price that is closer to the truth."

Positive for primary care doctors

Contrary to common perception, the researchers also suggest that primary care doctors are not always harmed by these biases. They found that services performed by primary care doctors and specialists often overlap, which means that Medicare pricing policies affect them in similar ways more often than people think. For example, primary care physicians who are internists and family medicine doctors perform some procedures that cardiologists and radiologists do. So, if the price of an electrocardiogram goes up, primary care doctors stand to gain financially from the procedure as much as cardiologists and cardiothoracic surgeons do.

And because primary care specialties already benefit from affiliations with other specialties, doubling the number of internists on the committee and quadrupling the number of family medicine practitioners would increase their specialty revenues by less than 1 percent, the researchers found.

Further, the analysis showed that such shared interests — and the closer connection between committee members and the specialties communicating the costs of a procedure — helped boost the overall quality of information behind committee decisions.

"There are very likely several features in Medicare's pricing structure that disadvantage primary care," Chan said. "But our research suggests that the arrangement of the RUC is not one of them."

The research was supported by the National Institutes of Health (grants DP5OD019903, L30AG051189 and P30AG012810).

Stanford's Department of Medicine also supported the work. ISM

Recent deployment linked to higher risk of premature delivery

By Erin Digitale

Female soldiers who give birth within six months of returning from military deployment face twice the risk of having a preterm baby as other active-duty servicewomen, a new study from the School of Medicine has found.

The study, which examined 12,877 births to American soldiers from 2011-14, was published online March 1 in the *American Journal of Epidemiology*. In total, 6.1 percent of births studied were premature, meaning the baby was born three or more weeks early. But among women who had recently returned from deployment, 11.7 percent of deliveries were premature. Women giving birth soon after deployment were, on average, younger than other military mothers, and with lower education and lower pay, the study found.

"What's important is the timing of deployment," said lead author Jonathan Shaw, MD, clinical assistant professor of medicine at Stanford. "Pregnancies that overlapped with deployment or the period of returning home were much more likely to end in preterm birth, which has impacts not only on the health of the infant, but also on the mother and family."

"What's important is the timing of deployment."

Premature birth can cause problems for the infant's vision, hearing, breathing and digestion, as well as lifelong developmental and learning disabilities. Families face financial and caregiving burdens associated with meeting the child's needs.

Shaw and his colleagues used the Stanford Military Data Repository, which contains de-identified medical and administrative data on United States Army soldiers. They identified pregnant servicewomen in the database for whom at least a year of medical data prior to the birth was available. The study examined only spontaneous premature birth, excluding early deliveries that were planned by physicians to preserve the health of the mother or infant.

"This database allows us to explore the universal issue of healthy mothers and babies, and also the pragmatic issue of how scientific insights can support our servicewomen and contribute to military readiness," said Lianne Kurina, PhD, associate professor of medicine at Stanford and senior author of the study.

Considering risk factors

In their analysis, the scientists considered many factors thought to potentially affect the risk of premature birth. They compared women with zero, one, two and three or more lifetime deployments; looked at the timing of deployment in relation to the timing of birth; and examined whether having a current or past diagnosis of post-traumatic stress disorder influenced the risk of preterm delivery. Half of the women studied had been deployed at least once.

The overall rate of premature birth, 6.1 percent, was lower than that within the general U.S. population, which was unsurprising given that soldiers have low rates of known prematurity risk factors, such as obesity and advanced maternal age.

The team found that having recently returned from deployment was strongly associated with a higher risk of preterm delivery, regardless of how many times the mother had been previously deployed. Women who gave birth within six months of returning home were twice as likely as mothers who had never been deployed to have a premature delivery, while women who gave birth seven or more months after returning from deployment faced no increase in prematurity risk. Among those who had recently returned, more lifetime deployments were linked to an increased risk of premature delivery: Recently returned soldiers were 1.6 times more likely, 2.7 times more likely and 3.8 times more likely than never-deployed women to deliver early if they had a lifetime total of one, two, or three or more deployments, respectively.

Jonathan Shaw

Women who had been diagnosed with post-traumatic stress disorder were no more likely than other women to deliver prematurely, although only 4 percent of women in the study had a past or current PTSD diagnosis. (Prior research by Shaw and his colleagues found a correlation between post-traumatic stress disorder and premature delivery in mothers who are military veterans.)

Pregnancy planning

Of the women who gave birth within six months of returning from deployment, 74 percent were deployed in the period seven to 10 months before giving birth, suggesting that conception occurred during deployment in many cases. Pregnancy during deployment is considered a medical emergency, requiring immediate evacuation from the combat theater.

"The concerns raised by these findings are heightened in the context of prior research documenting high rates of unintended pregnancy in the military and emerging evidence that the most reliable forms of contraception (long-acting reversible contraceptives) are underutilized in the Army, especially around the time of deployment," the authors wrote in the study's discussion.

"This study shows that the time around deployment is a period during which we should empower our soldiers to prevent unintended pregnancies," Shaw said. In addition, these findings could be used to help counsel soldiers who plan to have children during their years of military service.

"It's reassuring that deployment itself is not a risk factor for having a premature baby," Shaw said. But soldiers should know about the risks of becoming pregnant around the time they are deployed, he added. "We could tell them, 'It's a pretty stressful time; consider returning home and settling in for a few months before you add to your family.'"

Other Stanford authors of the paper are postdoctoral scholar D. Alan Nelson, PhD; Kate Shaw, MD, clinical associate professor of obstetrics and gynecology; and Ciaran Phibbs, PhD, associate professor of pediatrics.

Jonathan Shaw is a member of Stanford's Child Health Research Institute.

The research was supported by the Stanford Clinical and Translational Science Award to Spectrum from the National Institutes of Health. All data used in the study were provided under a cooperative agreement with the United States Army Medical Command.

Stanford's Department of Medicine also supported the work. ISM

VANTAGE POINT

one in an occasional series of essays written by faculty and staff

Ethical issues in *Frankenstein* resonate today

By Audrey Shafer

"Clear!" At some point during medical education and practice, every physician has heard or given this command. One person — such as a closely supervised medical student — pushes a button to deliver an electric shock and the patient's body jerks. The code team, in complex choreography, works to restore both the patient's cardiac rhythm and a pulse strong enough to perfuse vital organs.

After a successful defibrillation effort, team members do not have time to dwell on the line crossed from death to life. It is even difficult to focus on the ultimate goal: to enable the patient to leave the hospital intact, perhaps to grasp a grandchild's — or grandparent's — hand while crossing the street to the park.

Despite these dramatic hospital scenes, many scientists, doctors and patients balk at any mention of the words Frankenstein and medicine in the same breath. Because, unlike the Victor Frankenstein of Mary Shelley's novel, the reanimators at a hospital code have not toiled alone in a garret; assembled body parts from slaughterhouses, dissecting rooms and charnel houses; or created an entirely new being. Nonetheless, in this bicentennial commemorative year of the book's publication, it is not only germane, but important to consider the impact of this story, including our reactions to it, on the state of scientific research today.

Shelley's *Frankenstein* has captured the imaginations of generations, even for those who have never read the tale written by a brilliant 18-year-old woman while on holiday with Lord Byron, Percy Bysshe Shelley and Dr. John Polidori amid extensive storms induced by volcanic ash during the so-called year without a summer. Mary Shelley (her name was Mary Wollstonecraft Godwin at the time) was intrigued by stories of science such as galvanism, which she would have heard through her father's scientist (then called natural philosopher) friends.

With *Frankenstein*, Shelley wrote the first novel to forefront science as a means to create life, and as such, she wrote the first major work in the science fiction genre. Frankenstein, a flawed, obsessed student, feverishly reads extensive tomes and refines his experiments. After he succeeds in his labors, Frankenstein rejects his creation: He is revulsed by the sight of the "monster," whom he describes as hideous. This rejection of the monster leads to a cascade of calamities. The subtitle of the book, *The Modern Prometheus*, primes the reader for the theme of the dire consequences of "playing God."

A framework for examining morality and ethics

Frankenstein is not only the first creation story to use scientific experimentation as its method, but it also presents a framework for narratively examining the morality and ethics of the experiment and experimenter. While artistic derivations, such as films and performances, and literary references have germinated from the book for the past 200 years, the current explosion of references to *Frankenstein* in relation to ethics, science and technology deserves scrutiny.

"Science is, by its very nature, an exploration of new frontiers."

Science is, by its very nature, an exploration of new frontiers, a means to discover and test new ideas, and an impetus for paradigm shifts. Science is equated with progress and with advances in knowledge and understanding of our world and ourselves. Although a basic tenet of science is to question, there is an underlying belief, embedded in words like "advances" and "progress," that science will better our lives.

Safeguards, protocols and institution approvals by committees educated in the horrible and numerous examples of unethical experiments done in the name of science are used to prevent a lone wolf like Victor Frankenstein from undertaking his garret experiments. Indeed, it is amusing to think of a mock Institutional Review Board approval process for a proposal he might put forward.

But these protections can go only so far. It is impossible to predict all of the consequences of our current and future scientific and technologic advances. We do not even need to speculate on the potential repercussions of, for example, the creation of a laboratory-designed self-replicating species, as we can look to unintended consequences of therapies such as the drug thalidomide, and controversies over certain gene therapies. This tension, this acknowledgment that unintended consequences occur, is unsettling.

Science and technology have led to impressive improvements in health and health care. People I love are alive today because of cancer treatments unknown decades ago. We are incredibly grateful to the medical scientists who envisioned these drugs and who did the experiments to prove their effectiveness.

As an anesthesiologist, I care for patients at vulnerable times in their lives; I use science and technology to render them unconscious — and to enable them to emerge from an anesthetized state.

But, as the frontiers are pushed further and further, the unintended consequences of how science and technology are used could affect who we are as humans, the viability of our planet and how society evolves. In terms of health, medicine and bioengineering, Frankenstein resonates far beyond defibrillation. These resonances include genetic engineering, tissue engineering, transplantation, transfusion, artificial intelligence, robotics, bioelectronics, virtual reality, cryonics, synthetic biology and neural networks. These fields are fascinating, worthy areas of exploration.

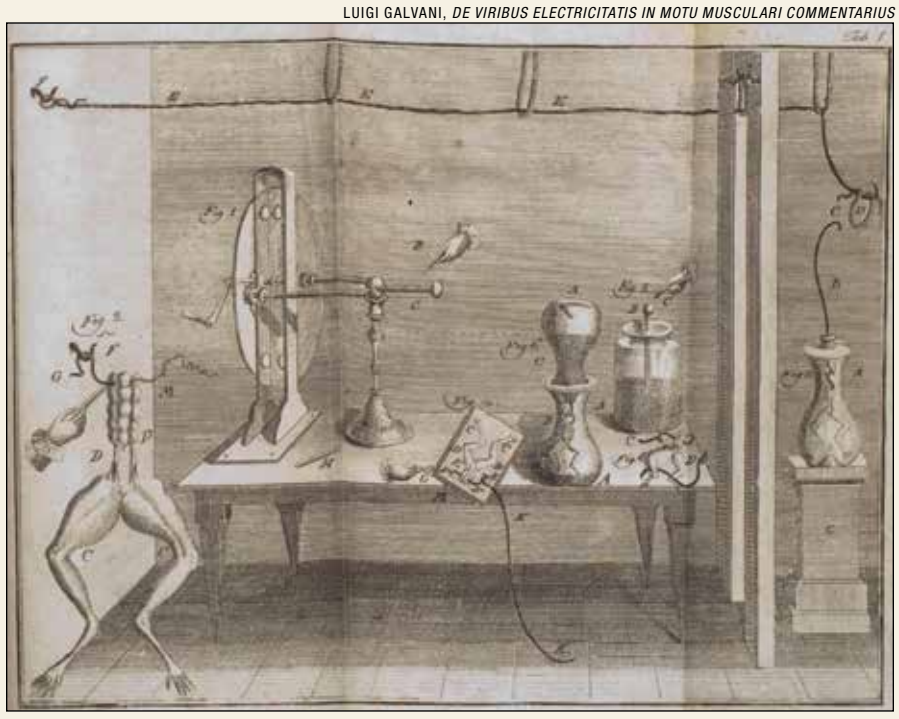
We, as physicians, health care providers, scientists and people who deeply value what life and health mean, cannot shy away from discussions of the potential implications of science, technology and the social contexts which give new capabilities and interventions even greater complexity. Not much is clear, but that makes the discussion more imperative.

Even the call "Clear!" and the ritual removal of physical contact with a patient just about to receive a shock is not so "clear," as researchers scrutinize whether interruptions to chest compressions are necessary for occupational safety — that is, it may be deemed safe in the future for shocks and manual compressions to occur simultaneously.

We need to discuss the big questions surrounding what is human, and the implications of those questions. What do we think about the possibility of sentient nonhumans, enhanced beyond our limits, more sapient than Homo sapiens? Who or what will our great-grandchildren be competing against to gain entrance to medical school?

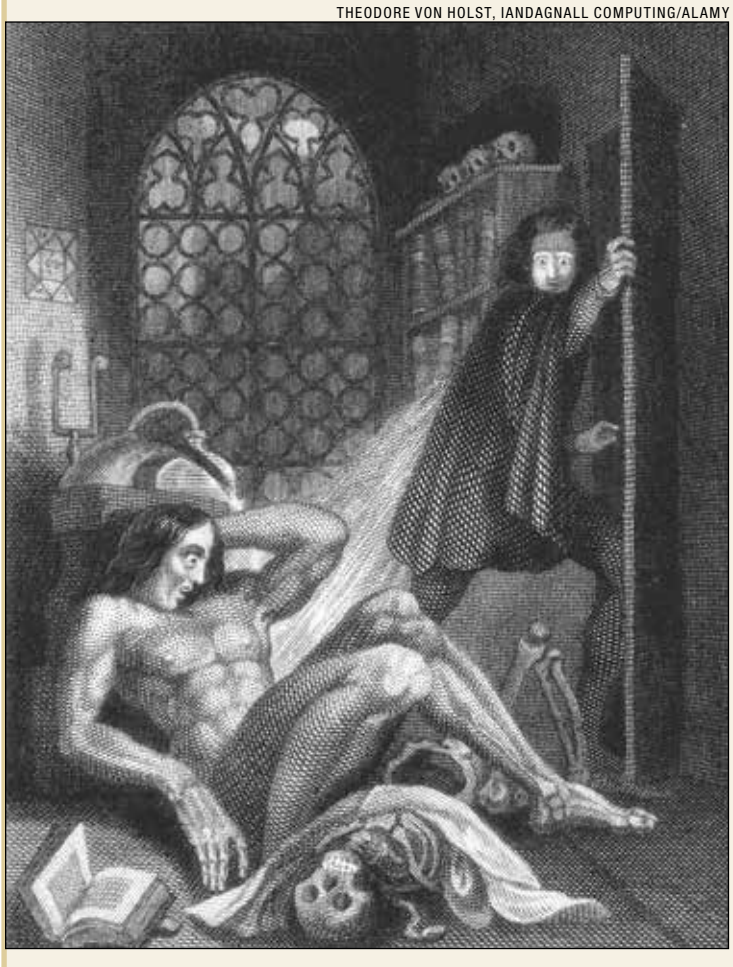
Studying and discussing works of art and imagination such as *Frankenstein*, and exchanging ideas and perspectives with those whose expertise lies outside the clinic and laboratory, such as artists, humanists and social scientists, can contribute not just to an awareness of our histories and cultures, but also can help us probe, examine and discover our understanding of what it means to be human. That much is clear. ISM

LUIGI GALVANI, *DE VIRIBUS ELECTRICITATIS IN MOTU MUSCULARI COMMENTARIUS*



The theory of galvanism — the idea that electricity could reanimate dead tissue — is named after researcher Luigi Galvani, who published an illustrated report on what he called animal electricity.

THEODORE VON HOLST, IANDAGNALL COMPUTING/ALAMY



RICHARD ROTHWELL, GL ARCHIVE/ALAMY

(Left) An illustration from the 1831 edition of *Frankenstein* shows the monster coming to life. (Right) Mary Shelley, the novel's author, was influenced by scientific theories of the time.

Study: Imaging agent helps predict success of lung cancer therapy

By Hanae Armitage

Doctors contemplating the best therapy for lung cancer patients may soon be able to predict the efficacy of a widely used lung cancer drug based on an imaging agent and a simple scan, according to the findings of a new clinical trial co-led by researchers at the School of Medicine.

The researchers developed a PET scan-compatible imaging agent engineered to seek out a specific mutation found in nonsmall cell lung cancer (which accounts for about 80 percent of lung cancers), bind to it and emit a radioactive signal that flags its presence. In addition to exposing the molecular roots of tumors, the imaging agent reveals potential weak spots in the cancer where specific therapeutic drugs can be administered to counteract the pro-tumor mutation.

"Some people wonder, 'Can't you just prescribe the drug and wait to see if the tumor shrinks? If it shrinks, then you know it's working,'" said Sanjiv "Sam" Gambhir, MD, PhD, professor and chair of radiology.

While in broad strokes that's true, there's a flaw to that approach: If the therapy isn't effective, the tumors will not only continue to grow, but continue to become more molecularly complex. "In the time you waited to see if the tumors shrank, those tumors continued to evolve, and that makes it more difficult to treat with the next round of therapy," Gambhir said.

That's where a relatively quick scan could come in very handy; patients whose tumor sites don't emit the tracer's signal while undergoing a PET scan likely don't harbor the mutation, and can be spared the treatment.

A paper describing the findings of the trial was published March 7 in *Science Translational Medicine.* The senior authors of the paper are Gambhir, who also holds the Virginia and D. K. Ludwig Professorship in Cancer Research; Zhen Cheng, PhD, associate professor of radiology at Stanford; and Baozhong Shen, MD, PhD, director of the Molecular Imaging Research Center at Harbin Medical University in China. The lead author is Xilin Sun, MD, former trainee in the Molecular Imaging Program at Stanford and now an associate professor of radiology at Harbin.

'Like a full-body biopsy'

As with many cancer-imaging agents, the new tracer, called F-MPG, works with a PET scan, a common imaging technique used to spot signs of disease while using radioactive tracers. While there's no shortage of PET scan tracers, Gambhir likens the development of these imaging agent to the development of drugs.

"There are hundreds of drugs, just like there are hundreds of imaging agents; we have to keep building new ones for different purposes," he said. "We have to keep looking for different ways to interrogate the underlying biology of the tumor, and the new method we've developed goes after actually measuring mutations in the tumor."

"We have to keep looking for different ways to interrogate the underlying biology of the tumor."

Most PET scans use a tracer that can only tell if a tumor is active in terms of its metabolism. In this case, F-MPG can tell doctors whether the tumor cells are present and whether they contain a mutated version of a protein called epidermal growth factor, which when overexpressed spurs cell division. The F-MPG tracer floats throughout the body, glomming onto any mutated epidermal growth factor proteins. Once latched on, it emits blips of detectable energy in the form of gamma rays, revealing the location and mutational details of the culprit protein.

"If the PET scan shows a high signal from the tracer in a patient's lung cancer, that's predictive of someone who is going to respond well to the specific epidermal growth factor therapy," Gambhir said.

STEVE FISCH

Sam Gambhir and his colleagues found that an imaging agent could help predict which lung cancer patients would likely benefit from a drug.

"For those who show low signals, they're likely not going to respond, so you need to look into other treatment options."

Gambhir points out that biopsies, or a sample of the tumor, can also tell doctors what mutations are present. But tumors are so complex that a single biopsy may not accurately capture the spectrum of mutations present in the mass, and it's even less likely to characterize the mutations present in multiple tumors including those that have spread throughout the body.

"One way to think about this imaging technique is like it's taking a biopsy of the entire body, and that gives a much more complete picture of the mutational status of the primary tumor, which allows you much better information to treat the cancer," Gambhir said.

Guided by the glow

At Harbin Medical University, members of the research team conducted a 75-participant clinical trial with the tracer, monitoring which tumors lit up (or had a high signal) on a PET scan and which had a low signal. Among the participants whose tumors appeared with the help of the tracer — meaning their tumor cells had the epidermal growth factor mutation — more than 80 percent saw a positive response from the targeted drug: Either their tumors shrank or tumor growth slowed. In contrast, only 6 percent of participants who lacked PET scan evidence of the mutation benefited from the drug.

Gambhir noted that the clinical trial was the first time this tracer had been used in humans. The next stage of the research, he said, is to recruit more participants for an even larger trial and, barring unexpected complications, eventually use the tracer's data to guide treatment plans for lung cancer patients. Currently, the tracer is only approved for use in China, so the studies will continue at Harbin.

"We'd like to continue to build our collaboration with the terrific group at Harbin, and work toward a clinical trial network in China for testing many different tracers," he said.

The team's work is an example of Stanford Medicine's focus on precision health, the goal of which is to anticipate and prevent disease in the healthy and precisely diagnose and treat disease in the ill.

Cheng and Gambhir are both members of Stanford Bio-X and the Stanford Cancer Institute. Gambhir also is a member of the Stanford Cardiovascular Institute and the Stanford Neurosciences Institute.

Researchers at Fudan University in Shanghai also contributed to the work.

The study was funded by the National Basic Research Program of China, the National Natural Science Foundation of China, Heilongjiang Province Foundation for Returned Overseas Chinese Scholars and the Key Laboratory of Molecular Imaging Foundation.

Stanford's Department of Radiology also supported the work. ISM

Leukemia

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cell precursor ALL, which occurs when certain white blood cells take a wrong turn during development and become malignant. Although the majority of cases are cured with existing chemotherapy drugs, 10-20 percent of patients relapse. Among those who relapse, about 40-80 percent die of their disease within five years.

"Acute lymphoblastic leukemia is a very well-characterized cancer that has a robust risk prediction measure already, but the final risk of relapse is usually not known until a few months into treatment, and there are still patients who get missed," said Kara Davis, DO, assistant professor of pediatric hematology and oncology and the other senior author of the study. "And, with existing prediction tools, when we do identify someone as high-risk for relapse, we don't know what it is about their leukemia that raises their risk."

A few really bad apples

Prior research strongly suggested that cancer relapse may be driven by a few treatment-resistant cells that are present from the beginning of the disease. "We wondered, can we identify those cells at the time the patient first presents to clinic, and can we treat patients with a specific therapy to target them?" Davis said.

Using mass cytometry, the researchers tested bone marrow samples taken from 60 ALL patients at the time of their diagnosis. Each patient had three to 15 years of follow-up medical records available for analysis, including information on whether they had relapsed.

To identify the problematic cells from among the millions of cells in each sample, the researchers had to figure out how to organize the data. "Every patient has vastly different features to their cancer, and we had to ask, 'Is there any common thread between them?'" Davis said.

The solution, the team found, was to compare leukemic cells to their most similar normal cells along the trajectory of healthy B-cell development. Of 15 developmental cell stages examined, malignant cells arising from just two adjacent stages in B-cell maturation — the pro-B2 and pre-B1 stages — were the bad actors: If these particular types of malignant cells had certain signaling behavior at diagnosis, patients were almost certain to relapse after standard chemotherapy.

"Stem cell biology is evolving, and we've learned a lot about how normal development takes place," Good said. "Now we can use that to understand cancer better."

Combining methods gets better results

When the new method for predicting relapse was combined with existing methods based on patients' early response to treatment, the results were better than those obtained by either method alone.

"We do not understand the mechanisms by which malignant cells from the pro-B2 and pre-B1 stages of development resist treatment," Davis said, adding that the team has begun looking for existing drugs to target them.

"We really need to personalize treatment to leukemia patients better than we do now."

They plan to validate their method in a larger number of patients and to evaluate whether the same general approach could predict relapse in other forms of cancer. Further, since the method provides information about treatment-resistant cells, patients found to be at high risk for relapse could benefit from treatments specific to those cells.

"We think that being more precise in risk prediction could benefit patients at both low and high risk for relapse," Davis said.

The study is an example of Stanford Medicine's focus on precision health, the goal of which is to anticipate and prevent disease in the healthy and precisely diagnose and treat disease in the ill.

Other Stanford authors of the paper are lab manager Astraea Jager; research scientist Nikolay Samusik, PhD; Nima Aghaeepour, PhD, instructor in anesthesiology, perioperative and pain medicine; postdoctoral scholar Erin Simonds, PhD; clinical research coordinator Leah White; Norman Lacayo, MD, associate professor of pediatrics; Wendy Fantl, PhD, assistant professor of obstetrics and gynecology; Robert Tibshirani, PhD, professor of biomedical data science and of statistics; and Sean Bendall, PhD, assistant professor of pathology.

Davis, Fantl, Tibshirani, Bendall and Nolan are members of Stanford Bio-X; Davis, Lacayo, Tibshirani and Nolan are members of the Stanford Child Health Research Institute; and Lacayo, Fantl, Tibshirani, Bendall and Nolan are members of the Stanford Cancer Institute. Good and Nolan are members of the Parker Institute for Cancer Immunotherapy.

Researchers from the University of Milano-Bicocca in Monza, Italy, also contributed to the study.

The research was funded by the American Society for Hematology/European Hematology Association, the National Institutes of Health; the M. Tettamanti Foundation; the Benedetta è la vita ONLUS Foundation; the Damon Runyon Cancer Research Foundation; the Food and Drug Administration; the NWCRA Entertainment Industry Foundation; the Bill and Melinda Gates Foundation; the NetApp St. Baldrick's Foundation; and CureSearch for Children's Cancer.

Bendall and Nolan are paid consultants for Fluidigm, the manufacturer that produced some of the reagents and instrumentation used in this study.

Stanford's Department of Pediatrics also supported the work. ISM

Anatomy

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Collins said.

The virtual-reality system headset is a powerful visualization tool for surgeons and patients alike, but it cannot offer residents hands-on training. That's where the anatomy lab comes in.

"The room looks a little less impressive than the simulation center, but it's where all the dirty work gets done," Veeravagu said.

The lab is equipped with shiny new tools, including high-speed drills, high-tech navigation systems and dissection instruments. "We are trying to recreate the OR environment in the cadaver lab so residents can have that same experience," Singh said. A new microscope commands particular presence in the corner of the room. Standing taller than a man, it allows residents to project 3-D models directly onto their cadavers.

The lab's donated equipment, worth more than $1.5 million, took about 18 months to procure, and now the lab is ready to go. Residents have unlimited access to the lab to study anatomy, practice surgical procedures and plan operations. The lab will also host workshops demonstrating rare procedures and new techniques. Beyond benefiting residents, these workshops could be instructive to Stanford surgeons and draw practitioners from outside Stanford.

Lab a prototype

The anatomy lab was christened with one such workshop back in June. Residents gathered around the dissection stations to learn a new technique for treating carpal tunnel syndrome. The minimally invasive procedure uses high-powered ultrasound and requires an incision only the size of a pinprick. In the coming months, the lab will host workshops in minimally invasive spine and skull surgeries.

Though the lab is open for business, it is only a prototype. The Grant Building is scheduled for demolition in the next few years, and the neurosurgical anatomy and simulation labs will be relocated to a more permanent location.

The Department of Neurosurgery hopes to build the next dissection lab from the ground up. "Our current space is not made for a cadaver dissection lab — we basically converted it for lack of space," Singh said. "The room has to be built in a certain way so you can explore the lab's full capability."

"The cadavers provide an education for the entire range of trainees we have."

Ideally, the future lab would have space for three additional stations, so six dissections could take place at once. The tables would be built into the walls and the room shielded for X-rays. The walls would be lined with freezers for long-term cadaver storage and LCD screens for endoscopic procedures, in which surgeons use instruments to look inside the body. The department also hopes to add to its microscope collection.

In the meantime, neurosurgery trainees are excited to take advantage of the current lab.

"The cadavers provide an education for the entire range of trainees we have, even medical students," Veeravagu said. "Just getting to specific parts of the brain is very challenging and requires repetitive exercise, and that's what the cadavers allow folks to do."

"The real benefit is that, when you have a case come up, you now have a resource where you have a chance to practice before you do it," Xu said.

Trainees' work in the simulation center promises to make their time in the anatomy lab even more fruitful. Residents will visualize their case inside a 3-D model, perfect their procedural approach on a cadaver and bring that proficiency to the operating room, Veeravagu said.

"It's a seamless way to build confidence and training in what they're doing," he said.

Medtronic, Stryker, Haag-Streit USA and Mizuho donated equipment to the lab. **ISM**

PAUL SAKUMA

Abhinav leads a training session for residents in the new neurosurgical anatomy laboratory.

T cell

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just as natural T cells do.

"IL-2 is a master regulator of the immune system and, in particular, the principal T-cell growth factor," said Christopher Garcia, PhD, professor of molecular and cellular physiology and of structural biology, and a Howard Hughes Medical Institute investigator. "It's responsible for T cells' development, expansion and activation."

Garcia is the senior author of the multidisciplinary study, published March 2 in *Science*. The lead author is former postdoctoral scholar Jonathan Sockolosky, PhD.

HOWARD HUGHES MEDICAL INSTITUTE

Christopher Garcia and his colleagues hope to boost the efficacy and curb the side effects of a treatment in which T cells are taken from a cancer patient, modified and returned to the patient to destroy tumors.

Secreted in response to threats

Produced naturally by various types of immune cells, IL-2 is secreted in response to various threats. When it binds to receptors on T cells' surfaces, including receptors on the T cells secreting it, it spurs them to action. Deprived of this booster substance, once-active T cells become inhibited, exhausted and, ultimately, burnt out.

This applies to the modified T cells infused into cancer patients, said Garcia. "These bioengineered T cells need IL-2 to survive, to work and to expand in number, just as our natural ones do," he said.

That's fine while the T cells are outside the patient's body. But strategies to boost the efficacy of adoptive cell transfer approaches by following up T cell infusion with intravenous IL-2 administrations have had major limitations. The reason is that the side effects provoked by substantial doses of the powerful protein — especially pulmonary edema — are so severe as to outweigh the advantages of the treatment.

The problem is that receptors for IL-2 are found not only on T cells but other immune cells that are better left inactive during cancer therapy — for instance, so-called regulatory T cells whose job is to mute the immune response after the immune system has been mobilized against a tumor or invading pathogen. Failure of the immune system to stand down can spell constant tissue-damaging inflammation and autoimmune disease. Many other types of cells in the body, such as lung cells, also harbor IL-2 receptors, Garcia said, and IL-2 can induce damaging inflammation to the tissues containing those cells.

But Garcia and his research group have found a workaround that should allow adoptive cell transfer to proceed without burnout — and without IL-2's devastating side effects.

Tweaking IL-2

"We engineered a slightly tweaked version of one of IL-2's constituent subunits so that a receptor containing this subunit can no longer bind to IL-2," he said. "And we generated a slightly altered IL-2 molecule that can't bind to its normal receptor." But the modified protein and modified receptor bind with high affinity to one another. Garcia credited Sockolosky for the meticulous matchmaking that paired up this auspicious odd couple.

Using laboratory methods to snap the modified receptors onto T cells from mice, Garcia's group showed in a series of experiments that these T cells responded to modified IL-2 exactly as natural T cells would be expected to respond to ordinary IL-2. But unmodified T cells didn't respond to the modified IL-2 at all.

"New and better ways of delivering IL-2 are a critical unmet need."

Next, Garcia's team and colleagues turned to the laboratories of two of the study's co-authors, UCSF immunologist Jeffrey Bluestone, PhD, and UCLA cancer specialist Antoni Ribas, MD. There, further disease-based experiments were conducted, including some with mice in which a well-characterized type of melanoma had been induced. Mice burdened by this highly aggressive tumor ordinarily die quickly. Adoptive cell therapy — the infusion of the mice's own T cells after they'd been bioengineered to target that specific tumor type — followed by regular IL-2 infusions was able to arrest growth in these melanomas, but the IL-2 caused a plethora of nasty side effects mirroring those of its administration in humans: weight loss, restricted mobility, hypothermia, enlarged spleen and lymph glands, and probable death. (Mice in the study were euthanized if they became sick to the point of likely death.)

However, when T cells similarly bioengineered to attack the tumors, as well as outfitted with modified receptors responsive only to the tweaked version of IL-2, were infused into the mice and bolstered with regular doses of tweaked IL-2, they also shrunk the tumors — but without side effects. These mice's survival was significantly improved in comparison with either untreated mice or those receiving adoptive cell transfer absent IL-2.

"Adoptive cell therapy is on the cusp of becoming a revolutionary new approach to cancer treatment," said Garcia. "It's undergoing explosive growth — it's a multibillion-dollar biotechnology industry already, and it's going to become as routine as bone marrow transplants are now. But all of the approaches in development today need IL-2, so new and better ways of delivering IL-2 are a critical unmet need. Our approach is also applicable to other important immune substances and cell types."

Garcia said his group has now generated human odd-couple IL-2/receptor pairs that, like their mouse counterparts, bind only to one another. He is looking for collaborators in academia or industry to launch a clinical trial based on the new technology. And, he said, he believes the same approach, employed to stimulate regulatory T cells rather than killer T cells, should in principle be effective in combatting autoimmune disease. Bluestone and another study co-author, postdoctoral scholar Eleonora Trotta, PhD, are working on that approach at UCSF, Garcia noted.

Stanford's Office of Technology Licensing has a patent pending on intellectual property associated with this work.

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

Other Stanford co-authors are postdoctoral scholars Lora Picton, PhD, and Akanksha Chhabra PhD; PhD; basic life science research scientist Leon Su, PhD; life science research professional Alan Le; medical student Benson George; and professor of medicine Judith Shizuru, MD.

The study was funded by the National Institutes of Health, HHMI, the Stanford Cancer Institute and the Parker Institute for Cancer Immunotherapy.

Stanford's departments of Molecular and Cellular Physiology and of Structural Biology also supported the work. **ISM**

Stanford Medicine launches exome-sequencing program for patients

By Grace Hammerstrom

Ten years is a long time in the life of a child, and it's an eternity in the world of genomic sequencing.

Within hours of her birth in 2003, Tessa Nye began having seizures. At the time, little was known about the cause of her severe form of epilepsy despite years of trial-and-error testing. Her birth came just a few months after the completion of the Human Genome Project, the first sequence of all 3 billion base pairs of human DNA. But broad genetic testing was not yet available to patients.

The Nye family spent years chasing a diagnosis for their daughter, who experienced hundreds of seizures a day, but doctors found no genetic cause for her disorder. The couple went on to have two healthy daughters, and their fears of a genetic basis for their firstborn's disease dissipated. When Kim delivered her fourth child, Colton, that sense of security was shattered. Within 12 hours of his birth, Colton, a seemingly healthy baby boy, suffered a seizure.

But Colton was born in 2013, in an era when genetic sequencing had become available to patients. Gregory Enns, MD, a pediatric geneticist at Lucile Packard Children's Hospital Stanford, ordered whole-exome sequencing for Colton within days of his birth. He had ordered the same test for Tessa when it became clinically available in 2012. The test examines only the genes that code for proteins; those genes account for approximately 1 to 2 percent of the genome.

With two complete sets of genetic data to compare — Tessa's and Colton's — as well as the genetic data of both parents, Kim and Zach, the family's doctors at Packard Children's were able to identify a single-gene mutation that is the source of both children's seizures.

'A total boon'

"That is the power of whole-exome sequencing," said Louanne Hudgins, MD, co-medical director of the Clinical Genomics Program, which will launch this spring at Stanford Health Care and Stanford Children's Health. "It allows us to make accurate diagnoses in 25 to 30 percent of cases. This has been a total boon to what we do clinically. And it has been a total boon for gene discovery."

The Clinical Genomics Program, which began as a pilot program a few years ago, will offer whole-exome sequencing and analysis to patients with undiagnosed genetic diseases. The whole-exome sequencing will be conducted on-site in a Stanford laboratory.

Stanford Health Care and Stanford Children's Health are two of a handful of hospitals nationwide to offer the entire sequencing process in-house. This improves coordination between the doctor requesting the test and the team performing the genetic analysis, helping pinpoint more precise diagnoses for patients, said Hudgins, professor of pediatrics at the School of Medicine. The clinic will include genetic counselors to help families understand the implications of the results, as well as financial consultants to help patients navigate insurance coverage for the test. The program will take referrals from physicians at both the adult and children's hospitals.

In addition to conducting the initial sequencing, every year specialists in the program will reanalyze results from patients whose whole-exome sequencing did not uncover a genetic cause for their disease. New gene mutations are continually being identified: In Tessa's case, for instance, whole-exome sequencing initially came back normal. Only after comparing it with her brother's and her parents' exomes was the mutation discovered. "With yearly reanalysis, we can continue to make diagnoses for years," Hudgins said.

COURTESY OF THE NYE FAMILY

Colton and Tessa Nye with their parents, Kim and Zach. Sophisticated genetic testing helped explain why the two siblings experienced frequent seizures.

Whole-exome sequencing does not look at all 3 billion base pairs of the human genome, but focuses instead on the approximately 21,000 protein-coding genes that have been found to be more causative of human disease. From those, the Stanford-built computational pipeline narrows the results to 100 gene variants; each of these must be interpreted through 20 to 40 hours of manual analysis. This labor-intensive process is improved greatly when the lab scientist analyzing the results can work with the clinician who is familiar with patients' symptoms and disease, said Hudgins. To improve that collaboration, referring physicians will attend weekly meetings to review active cases.

'The essence of precision health'

"Sequencing the genomes of patients and families represents the state of the art in genetic testing for patients today," said Euan Ashley, DPhil, FRCP, co-medical director of the Clinical Genomics Program and professor of cardiovascular medicine at Stanford. "It is the essence of precision health: understanding disease at a deeper level so that we can treat it more precisely. You are essentially looking at someone's DNA and figuring out exactly what is wrong with them."

For the Nye family, whole exome sequencing gave them the answer they had sought for years. "As a parent, it was very meaningful to get a diagnosis," said Kim Nye. "We spent a full 10 years trying to figure out what was going on with our daughter. It's heartbreaking to see your child's health totally fail and have nobody be able to tell you why."

Ultimately, the goal will be to use this information to understand the underlying molecular basis for disease and help develop targeted therapies, Hudgins said.

"We haven't found our miracle cure yet, but whole-exome sequencing has absolutely had an impact on suggesting new treatment options," said Kim Nye. "At some point, there will be a breakthrough based on the underlying genetic cause. I am certain of that." ISM

OF NOTE

reports on significant honors and awards for faculty, staff and students

AGNIESZKA CZECHOWICZ, MD, PhD, was appointed assistant professor of pediatrics, effective Jan. 1. Her research focuses on understanding how blood-forming stem cells interact with their microenvironment and on developing new therapies to improve bone marrow transplantation.

KARLENE CIMPRICH, PhD, professor of chemical and systems biology; **JAMES FORD**, MD, professor of medicine and of genetics; and **AARON STRAIGHT**, PhD, associate professor of biochemistry, received $2.1 million from the V Foundation for Cancer Research. Their project examines how three-stranded DNA-RNA hybrids known as R-loops, associated with BRCA mutations, contribute to genomic instability and whether they can be developed as biomarkers to enable cancer detection.

JOE FORRESTER, MD, administrative chief resident in general surgery, has received the Best Mini-Podium Award from the Pacific Coast Surgical Association for his presentation "Gene-directed surgery for hereditary diffuse gastric cancer: Effect on survival," which was delivered at the organization's annual meeting in February.

SHERI KRAMS, PhD, was promoted to professor (research) of surgery, effective Feb. 1. In addition, she was awarded a $1.8 million, three-year grant from the National Institute of Allergy and Infectious Diseases to analyze samples from more than 1,000 children who have received organ transplants. The goal is to identify new immune-mediated biomarkers that are predictive of outcomes. Her research interests include mechanisms of rejection and tolerance in solid organ transplantation and the role of microRNAs and natural killer cells in viral and immune reactions to nonself human antibodies.

KYLE LOH, PhD, was appointed assistant professor of developmental biology, effective Feb. 1. His research group at the Institute for Stem Cell Biology & Regenerative Medicine has created a road map that describes how embryonic stem cells can develop into a spectrum of over 20 different human cell types, enabling the generation of uniform populations of human liver progenitors, bone progenitors and heart progenitors.

OLIVIA MARTINEZ, PhD, professor of surgery, was awarded a $1.9 million, three-year grant from the National Institute of Allergy and Infectious Diseases. Her project aims to increase the understanding of, and suggest potential improvements in diagnosis and treatment for, Epstein-Barr virus infections in children who have received organ transplants.

KULDEV SINGH, MD, professor of ophthalmology, received the subspecialty award from the American Glaucoma Society, which included delivering a lecture at the American Academy of Ophthalmology's annual meeting. At the November event, his lecture, "The glaucoma renaissance," highlighted translational glaucoma research.

UPINDER SINGH, MD, was promoted to professor of medicine, effective Aug. 1, 2017. Her research examines the determinants of virulence that the parasite *Entamoeba histolytica* uses to cause invasive colonic and hepatic disease. She also studies the epidemiology of *Entamoeba* infections, with the goal of identifying an entamebic molecular signature that correlates with the microbes' invasive potential.

CELINA YONG, MD, was appointed assistant professor of medicine, effective Dec. 1. Her research interests include socioeconomic, gender, racial and geographic disparities in quality of care and outcomes among cardiovascular disease patients. She also focuses on using low-cost, high-tech tools to improve the quality of cardiovascular care delivery. ISM

Agnieszka Czechowicz

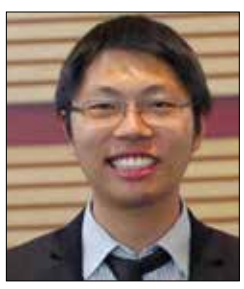
Karlene Cimprich

James Ford

Aaron Straight

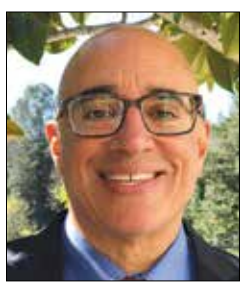
Joe Forrester

Sheri Krams



Kyle Loh

Olivia Martinez



Kuldev Singh

Upinder Singh

Celina Yong