Lab bridges virtual reality, operating room

By Nicoletta Lanese

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 topics. 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 neurological 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 wild- est 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 blown inside their spine or their brain.”

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.

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-ALL.

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.

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 campaign 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.

Researchers have long sought to eliminate either the need for IL-2 or the toxic side effects that it causes. A number of drugs have been developed to increase the survival of the modified T cells, but they haven’t had much success.

Collaborating with researchers at the University of California at San Francisco, a team of investigators led by Akiko Kawamura, MD, PhD, and Luis Miquel, MD, PhD, successfully coaxed the modified cells to survive longer in mice.

The researchers altered the immune signaling molecule called interleukin-2, which is on the surface of T cells, by surgically exchanging it with a slightly different molecule, called interleukin-2a, which is not naturally present on T cells.

This switch was capable of erasing the toxic side effects caused by IL-2 and allowing the cells to expand for longer periods without needing to be reinforced by IL-2. The engineered cells were also shown to prevent the growth of tumors in mice after multiple injections of cancer cells.

The researchers are now working on developing a similar approach for cancer treatment in humans.

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While the researchers believe this discovery will allow for a simpler application of adoptive cell transfer to cancer treatment, they are still working to translate their findings into the clinic.

They are now testing the idea on patients in a clinical trial and hope to begin human trials using the engineered cells in the near future.

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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 of the first two participants in the trial. Judith Shizuru, MD, PhD, professor of medicine at Stanford, discussed the trial at the annual meeting of Stanford’s Center for Defin- itive and Curative Medicine.

The bubble of life involves participants who have a condition known as severe combined immunodeficiency. SCID, also known as the "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 avoid easily.

SCID patients can be given infusions of blood and progenitors to 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.

The researchers, with chemotherapy or radiation is that they can be very dam- aging, and people 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 Berti, PhD, professor of medicine and of pediatrics and co-director of the Stanford Institute for Stem Cell Biologi- cal and Regenerative Medicine — are giving the participants an antibody called 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 Re- generative Medicine. Assistant- professor of pediatrics Agnieszka Czeczotka, MD, PhD, while still a graduate student in Weissman’s lab, showed that an antibody could be used to block, in mice, a criti- cal cell surface factor needed by 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 very much what was observed in animal studies. Specifically, the antibody appears to be effective in the depletion of geneti- cally defective stem cells.

Given these results, the researchers plan to continue their clinical trial and include infants with the disease, since in- fancy is a time when the negative effects of chemotherapy or radiation can be partic- ularly devastating.

The first cases also suggest that the antibody-based conditioning may be useful in combating other diseases, including cancer, Shizuru said. Autoimmune dis- eases like Type 1 diabetes, multiple sce- lerosis and lupus may have treatments using blood stem cell transplantation, but are not currently treated this way because the dangers of chemotherapy or radia- tion usually outweigh the benefits.

The trial is being supported by a grant from the California Institute for Regen- erate Medicine.

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

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 discovered insights into the genetic underpinnings of amyotrophic lateral sclerosis, a neurodegenerative dis- ease that’s notoriously tricky to parse.

The hope is that finding “just the tip of the iceberg” 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 im- pairs the brain’s ability to communicate with the body, making simple voluntary movement — 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 feature: abnormal protein clumps that build up in the brain.

In ALS, these protein clumps, or aggregates, are thought to be fa- tally 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 likely are driving the pathology in the disease, but no one really knows how they cause neuronal cell death,” said Aaron Gitler, PhD, professor of genetics. He shares senior authorship with Michael Bassik, PhD, assistant pro- fessor of genetics.

Gitler’s and Bassik’s lab used CRISPR-Cas9 gene editing to sort through the entire human ge- nome and pick out the genes that help neurodegeneration develop alongside the toxic protein. Not only did some genes give the researchers a deeper mechanis- tic understanding of the disease itself, a handful seemed 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. 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 ef- forts 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 vari- ous rogue proteins, they gum up neuro- nal function and lead to cell death.

“In a healthy person, you might see 10 to 20 of these DNA repeats,” Haney explained, help the researchers spot genes that were particularly potent protectors. “When you find them, you know that the ab- sence of that gene actually protects the longer toxic, then you know that the ab-

Haney said. “We could imagine that Tmx2 might make a great drug candidate," Haney said. "If you have a small mol- ecule that could somehow impede the function of Tmx2, there might be a ther- apeutic window there.

Right now, Tmx2’s role in the endo- plasmic reticulum isn’t completely clear. But researchers hope to understand how the response to various environmental stress- ors, 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.

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 disrupted when these toxic species kill the cell, and it could point to what path- ways we should look into," Kramer said.

Nine and six out of 24 CRISPR screens like the one in this study have been used to investigate a range of disease pathways. But what’s new about this is the first time using their knowledge, that a genomewide hu- man CRISPR knockout screen has been used to discover clues about a neurode- generative disease. Gitler and Bassik are currently teaming up to use this same approach to understand cancer and ALS and even other neurologi- cal diseases — Huntington’s, Parkinson’s and Alzheimer’s — that involve toxic protein aggregates.

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Patient care has long been about doctors treating patients once disease has already set in, but the emerging focus on precision health will change the landscape. 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 level. It’s like monitoring your child for signs of 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 biologists and engineers play in translating these technologies to the clinic.

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 Hanan Culverhouse asked Gambhir about the ways in which precision health improves care.

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

GAMBHIR: Precision health creates an opportunity for the clinical assistant to become more of an educator, to utilize more detailed and comprehensive health data sets to be better-informed about their patient’s individualized health. When appropriately interpreted and shared, it will 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 on how they treat patients.

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 overall health. Rather than simply follow a standard appointment schedule, patients would only visit their physicians if they feel something is wrong and still have contact with their health care team through a secure health portal. This approach could, when appropriate, reduce the number of patients visiting their physicians or may even stop physical contact altogether.

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. A 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 is “normalized” to each person, rather than only using trends from the population, individual abnormalities will be identified more quickly. 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 without waiting for a diagnosis. Over time, frequencies or trends in biomarkers could 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 for particular health conditions to be identified earlier, when positive clinical outcomes are still possible. 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.

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

GAMBHIR: Wearable technology, including physiological 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 can detect changes in urine volume or a toothbrush that analyses saliva — and other monitoring technologies that run in the background will be necessary. For example, in the kitchen could become two of the most important rooms in the home for a health-monitoring perspective.

Everyone, at and even before birth, could have a unique health-risk profile created. Based on this profile, physicians would be able to diagnose and treat illnesses before they develop in order to prevent health conditions from developing.

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 and health transitioning processes that take place throughout the disease continuum. Effective disease biomarkers are also essential.

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 also 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 require the cooperation and support of venture capitalists, policy specialists and other stakeholders can anticipate un- preccoCd by machin©©. 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 other companies, such as Amazon, Google and Verily, are innovating in the personal 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 care providers will need to adopt the technology and see the benefits for these health-monitoring approaches to be effective.

6 How would you describe the future of precision health with respect to technology and its adoption?

GAMBHIR: 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 quality of the health data they capture. It’s important to note that technology is ahead of our understanding of the underlying biology.

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7 How do you see the public’s education and adoption of precision health?

GAMBHIR: The public is becoming increasingly aware of the latest advances in technology and is starting to engage in conversation about precision health. Prevention is a fact of life and in clinical care.

8 What do you see as some key questions researchers need to ask themselves as they work in the area of precision health?

GAMBHIR: How does the practice of precision health change our understanding of disease states that are treatable, while perhaps not curable? How do you make technology adoption happen when appropriate, reduce the number of patients visit- ing their physicians only when necessary.

9 What new questions does precision health raise for medical research and practice?

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GAMBHIR: 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 care providers will need to adopt the technology and see the benefits for these health-monitoring approaches to be effective.
Families face financial and caregiving on the mother and family. "What's important is the health of the infant, but also deployment or the period of returning deployment," said Jonathan Shaw, MD, clinical assistant professor of medicine at Stanford. "The findings are surprising. Until now, behind-closed-doors deliberations meant nobody knew for sure how the committee of physicians practices its recommen- dations, according to recent research, which Medicare typically adopts. And longstanding criticisms of con- flicts 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 com- mittee members were entirely neutral, only 1.9 percent of the $70 billion Medicare spends annually on health care would be redistributed across all services. "This is not a complete vindication of the AMA committee, we find that committee bias has subtle implications for different medical fields and for Medicare as a whole," said David 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 disadvan- taged by the presence of specialty physicians on the committee, actually benefit from shared interests with other doctors," he said. "And when primary care gets higher-quality information when the commit- tee has connections with specialties."

As a result of the work, the researchers found an increased likelihood that committee members will rec- ommend higher prices for specialties they are connect- ed 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.

Researchers then measured how closely connected a proposed price change was to the specialties represented on the committee and the effect that affili- ation had on the recommendation. 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 a committee bias toward a certain industry group to determine its prices? The evidence, Chan said, suggests an explanation: The lack of impartiality on the committee (or fact by finding that the information members contribute to the price-setting process is of higher quality than input from neutral advisers.

Recent deployment linked to higher risk of premature delivery

Female soldiers who give birth within six months of returning from military deployment face twice the risk of having a premature birth compared to other active-duty ser- vice women, a new study from the School of Medicine has found. The study, which examined 12,877 births from women who served in Iraq and Afghanistan, was published online March 1 in the American Journal of Epidemiology. In total, 6,356 of the women 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 Jon- athan Shaw, MD, clinical assistant professor of medi- cine at Stanford. "Pregnancies that overlapped with deployment or the period of returning home of non-deployed partners were more likely to end in preterm birth, which has impacts not only on the health of the infant, but also on the health of the mother. Premature birth can cause problems for the infant's vision, hearing, breath- ing and digestion, as well as lifelong developmental and learning disabilities. Families face financial and caregiving burden 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 service women in the database for whom at least a year of medical data prior to the birth was available. The study examined only spontaneous and induce deliveries excluding early deliveries that were planned by physicians to preserve the health of the mother or baby. "This database allows us to explore the universal issue of healthy mothers and babies, and also the pragmatic issue of how to best care for women who were service- women who delivered to contribute to military readiness," said Lianne Kurina, PhD, as- sociate professor of medicine at Stanford and senior author of the study.

Considering risk factors

In their analysis, the scientists con- sidered many factors thought to poten- tially affect the risk of premature birth. They compared women with zero, one, two or more lifetime de- ployments; looked at the timing of deployment in re- lation to the time of con- ceiving or terming; and examined whether having a current or past diagnosis of conditions such as PTSD or diabetes relating to the risk of preterm delivery. Half of the women studied had been deployed at least once in their lifetime.

The overall rate of premature birth, 6.1 percent, was lower than that within the general U.S. population, surprising given that soldiers have low rates of known prematurity risk factors, such as obesity and advanced maternal age. The team that 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 preterm birth. Recently re- turned 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. Women who had been di- agnosed with post-traumatic stress disorder were no more likely than other women to deliver preterm, although only 4 percent of women in the study had a past or current PTSD diagnosis. (Prior research by Shaw and 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 un- intended pregnancy in the military and emerging evidence that the most reliable forms of contraception (long-acting reversible contraceptives) are underutilized in the Army," 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. "It's reassuring that 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 prematu- re baby," Shaw said. But soldiers should know about the risks of becoming preg- nant around the time they are deployed, he said. "It wouldn't be good to have a baby. It's pretty stressful time; consider returning home and settling in for a few months before trying to have a baby." The research was supported by the National Institutes of Health (grants DP5OD019903, L30AG051189 and P30AG21080). Chan is also supported by the National Institute on Aging. The research was supported by the National Institutes of Health (grant DP5OD019903). Chan is also supported by the National Institute on Aging. The research was supported by the National Institutes of Health (grants DP5OD019903, L30AG051189 and P30AG21080). Chan is also supported by the National Institute on Aging. The research was supported by the National Institutes of Health (grants DP5OD019903, L30AG051189 and P30AG21080). Chan is also supported by the National Institute on Aging. The research was supported by the National Institutes of Health (grants DP5OD019903, L30AG051189 and P30AG21080). Chan is also supported by the National Institute on Aging.
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 intersecting 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 and “so-called year without a summer.” Byron, Percy Bysshe Shelley and Dr. Godwin at the time (then called natural philosopher) wrote the first novel to forefront science fiction 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 reviled by the sight of the “monster,” whom he describes as hideous. This rejection of the monster leads to a cascade of calamities.

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. It is a means to discover and test new ideas, and an impetus for paradigm shifts. Science is equated with progress and with advancements 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 institutional review board approval processes 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 amazing 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 technological advances. We do not even need to speculate on the potential repercussions of, for example, the creation of a laboratordy-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 generic engineering, tissue engineering, transplantation, transfusion, artificial intelligence, robotics, bioelectronics, virtual reality, cryogenics, synthetic biology and neural networks. These fields are fascinating, worthy areas of exploration.

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 consequences of advances in medicine, bioengineering 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 sapiens 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.

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.
Doctors contemplating the best therapy for lung cancer patients may soon be able to predict the efficacy of a widely used 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 lung cancer cells, in tumor tissue that absorbs the tracer, as well as the nearby bone that does not.

Using mass cytometry, the researchers tested bone marrow samples from 60 ALL patients at the time of their diagnosis. Each patient had three to 15 years of marrow samples taken from 60 ALL patients at the time of their diagnosis. They plan to validate their method in a larger number of patients and to evaluate it as a potential treatment-monitoring tool.

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

"For those who show low signals, they're likely not going to respond, so you need to look into other treatment options," Gambhir pointed out that the tracer, 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 it's like taking a biopsy of the entire body, and that gives us a more complete picture of the mutation status of the primary tumor, which allows you much better information to treat the cancer," Gambhir said.

"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.

"It is with broad strokes that's true, there's a flaw to that approach: If the therapy isn't effective, the tumor will not continue to grow, but continue to become more and more complexly mutated.

"In the time you wait for tumors to shrink, those tumors continued to evolve, and that makes it more difficult to treat with the same tools that we think we had before."

That's where a relatively quick scan could come in very handy: patients whose tumors are active when a PET scan is taken, but whose therapy is only 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 mutation that could act as a growth factor, which overexpressed spurs cell division. The F-MPG tracer floats throughout the body and is taken up by many tumors, right onto any mutated epidermal growth factor receptors. 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 in the tracer in a patient's lung cancer, that's predictive of someone who is going to do well on the specific growth factor therapy," Gambhir said.

"We have to keep looking for different ways to interrogate the underlying biology of the tumor."
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 anatomy 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, was donated to Stanford by an anonymous donor who was inspired by his son's experience in the anatomy lab. "I was impressed with the way 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 demonstrating rare procedures and new techniques."

"The real benefit is that, you can have the 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."
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. 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 genomic 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 whose gene accounts 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 their care. The genetic counselors 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.

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 the 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 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 through the underlying genetic cause. I am certain of that.”

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