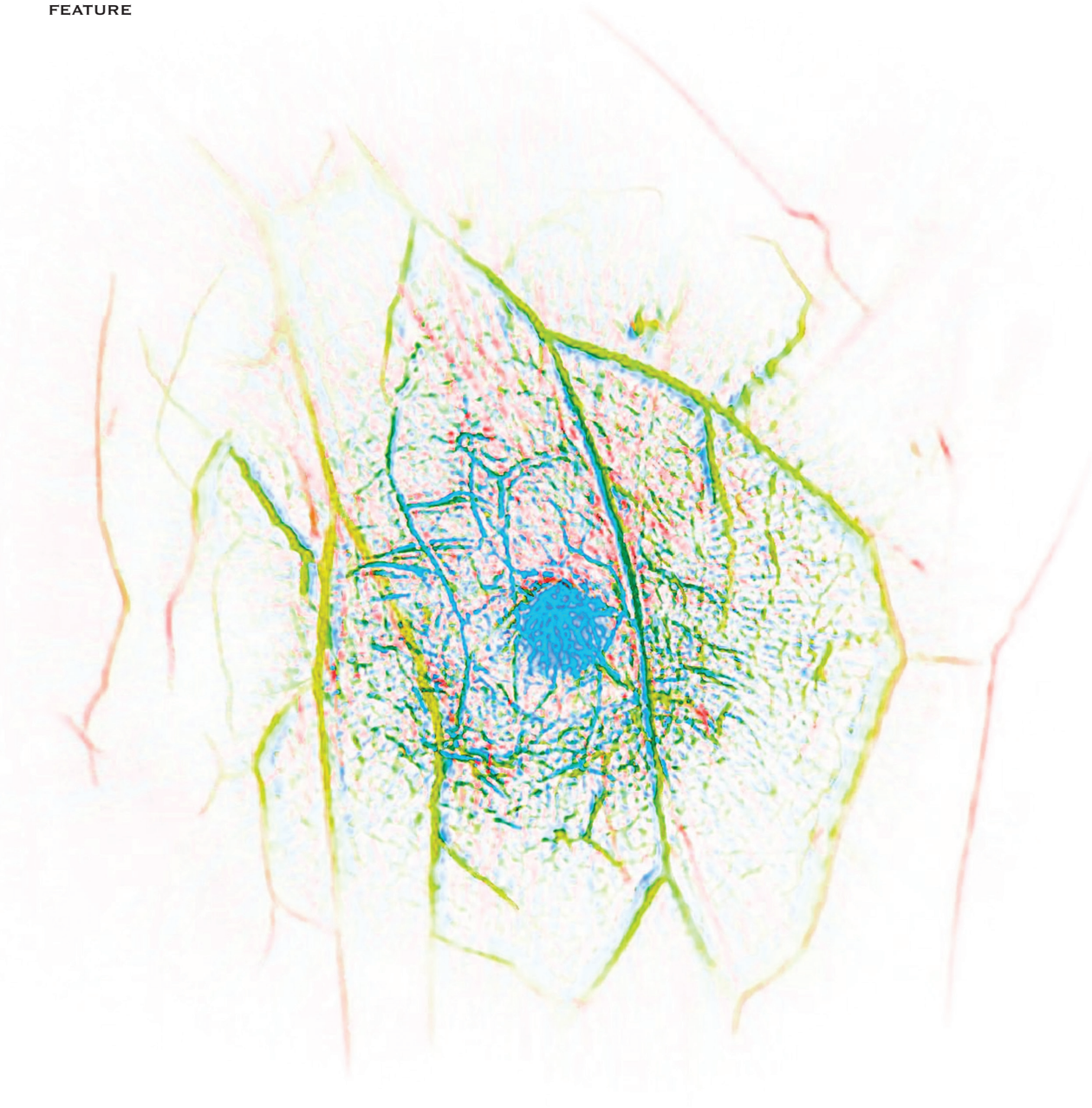

Photoacoustic computed tomography of a healthy human breast acquired *in vivo* within a single-breath hold without using any harmful ionizing radiation or contrast agent. This new technology can image blood vessels as small as a few times the diameter of a human hair, outperforming all other imaging technologies. The initial clinical testing has successfully identified all breast tumors imaged. Color here encodes depth.

From Bench to Bedside

New Paths, Sharper Resolution, Inventive Devices

The interwoven, interdisciplinary culture of Caltech has inspired two significant gifts that are elevating and intensifying biological and medical engineering research across campus. Andrew and Peggy Cherng have endowed the medical engineering department in the Division of Engineering and Applied Science, and Tianqiao and Chrissy Chen have endowed the Chen Institute for Neuroscience, which finds its home in the Division of Biology and Biological Engineering. The prescience and generosity of these donors is matched only by the insight and creativity of Caltech's faculty—and here we explore several connections and horizons that mark a new period of research at Caltech that brings together biologists, engineers, chemists, computer scientists, social scientists, and physicists in pursuit of revolutionary advances in health and human welfare.

Involving faculty from across the university's six academic divisions, the Chen Institute for Neuroscience at Caltech will catalyze a campus-wide interdisciplinary community with the shared goal of understanding the fundamental principles that underlie brain function. "Everything that we are as human beings—our ability to see the world and ask questions about our universe—is rooted in the structure and function of our brains," remarked Steve Mayo (PhD '87), the Bren Professor of Biology and Chemistry and the William K. Bowes Jr. Leadership Chair of the Division of Biology and Biological Engineering, upon the establishment of the Tianqiao and Chrissy Chen Institute for Neuroscience. "One of the greatest challenges and opportunities of our time is to be able to unlock that structure and how it relates to function, which will have an enormous impact on the lives of real people."

Similarly, "the endowment of the Andrew and Peggy Cherng Department of Medical Engineering draws upon the expertise of faculty members across all engineering and science disciplines to bring innovative, non-invasive, and smarter medical devices to patients," says Guruswami Ravichandran, Caltech's Otis Booth Leadership Chair in EAS and the John E. Goode, Jr., Professor of Aerospace and Mechanical Engineering.

ENGenious spoke with four Caltech faculty members to learn about the passions and forces that are enhancing their work and driving them forward. Each anticipates that the combination of an unprecedented inventory of intellectual and technological resources, the excellence of Caltech students and postdoctoral scholars, and the academic freedom afforded by the Chen and Cherng infusions will yield exponential growth for their research.

Morteza Gharib, Viviana Gradinaru, and Lihong Wang

Viviana Gradinaru (BS '05), Assistant Professor of Biology and Biological Engineering, Heritage Medical Research Institute Investigator, and Director of the Center for Molecular and Cellular Neuroscience in the Chen Institute for Neuroscience, investigates mechanisms underlying neurodegeneration and develops tools and methods for use in neuroscience. "We live in an unprecedented time, where the speed of basic discoveries has been accelerated," she says. "We are sitting on fundamental knowledge and have a duty to transfer it to benefit human health in terms of sensing diseases, monitoring progression, and eventually coping with the symptoms or even treating the disorders."

Gradinaru's lab exemplifies this approach. "As part of our neuroscience work in trying to understand how deep brain stimulation works, we found that detailed maps of neural paths were lacking," she explains. "Brain circuits are comprised of very fine projections that are severed in the standard process of sectioning tissue into paper-thin slices to gain optical access. To bypass this problem, we worked on a method of tissue clearing by removing the lipids that scatter light within the tissue. The result is a transparent organ that becomes a tool to solve problems that have to do with disease, drug screening, and the effect of therapies on tissue. Thus, the techniques that we developed to figure out challenges in basic neuroscience are now a technology that can help with tissue pathology and screening for medical engineering purposes."

There is a recognition among Caltech's faculty that progress in human health requires scientists and engineers from a wide spectrum of disciplines to attack complex challenges and cross-pollinate ideas. The Cherng Department of Medical Engineering and the Chen Institute for Neuroscience are both dedicated to this approach. Morteza Gharib, Hans W. Liepmann Professor of Aeronautics and Bioinspired Engineering, puts it this way: "What medical and biological engineering provide are venues for researchers from biology, engineering, and information science to work on areas that can go from the lab to the bedside." For example, Gharib's research on the cardiovascular system is applied to new generations of heart valves and monitoring devices that unify multiple vital indices in a single blood-pressure reading in real time. When combined with the expertise of his colleagues in electrical engineering and materials science who share his interest in miniaturizing devices, there emerges the possibility of new monitoring and imaging accessories that can increase both the quality and accessibility of valuable metrics for patients and clinicians.

Medical problems present profound challenges that are ideal for Caltech biologists, chemists, and engineers to tackle together. Gharib is a case in point. "I am a rocket scientist with a PhD in aerospace, and I'm very interested in fluid dynamics," he explains. "I see life as aquatic, and therefore fluid dynamics plays a big role in it. We are small enough to be a real interdisciplinary institution. This approach provides us a significant cushion in the face of being afraid to fail. I can be bold, to the point of taking on what others consider too risky, because I know I can get there with my colleagues, our students and postdocs, and the Caltech level of excellence and resources."

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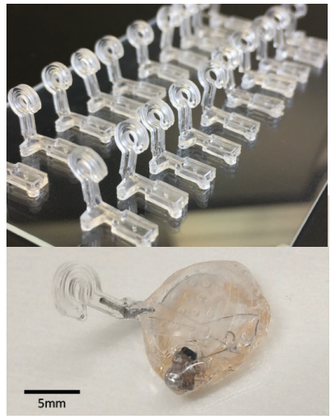
> Morteza Gharib, *Hans W. Liepmann Professor of Aeronautics and Bioinspired Engineering; Director, Graduate Aerospace Laboratories; Director, Center for Autonomous Systems and Technologies*

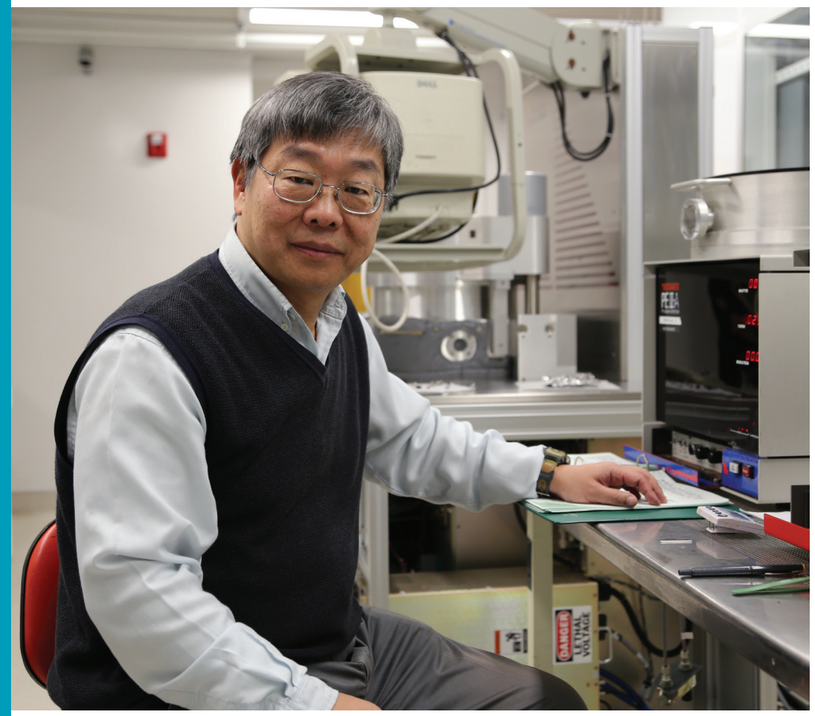
Lihong Wang, Bren Professor of Medical Engineering and Electrical Engineering, adds that Caltech's stature attracts the best students and postdocs, drawing talent from all over the world to help push this kind of leading-edge work forward. "When we combine the strength of our world-class lab members with the number of nearby first-rate medical institutions, we have no shortage of research ideas or clinical collaboration. This combination presents a tremendous opportunity for biological and medical engineering at Caltech."

"We are earning our name based on the successful approaches we already have in place that solve really difficult problems and incorporate new technology," says Yu-Chong Tai, Anna L. Rosen Professor of Electrical Engineering and Mechanical Engineering and the Executive Officer of the Cherng Department of Medical Engineering. "Chronic diseases are costly; Caltech engineers can help by making the future of medical technology smaller, cheaper, and better."

Trained in electrical and mechanical engineering, Tai is a self-described electromechanical engineer who makes small gadgets that target the four major causes of blindness: cataracts, glaucoma, macular disease, and diabetic retinopathy. He is also working on catheter-tip-sized diagnostic devices that can probe the heart to analyze plaque. Continuing to push boundaries, he is aiming to develop "non-invasive diagnostics and sensors that draw on electrical engineering and electromagnetism to develop approaches for assessing edema and both ischemic and hemorrhagic strokes. I am also interested



Implantable devices for the treatment of diabetic retinopathy: passive oxytransporters (top) developed by graduate students Nick Scianmarello and Colin Cook (2016) and an active oxygenator (bottom) developed by Nick Scianmarello (2017).



Yu-Chong Tai

in developing drug delivery systems that are wireless and smart." Tai notes that the young researchers he mentors are a critical part of these efforts: "We continue to recruit students and postdocs who are interested in artificial intelligence as it could apply to medicine. I think their influence on devices will change the way we do medicine."

Even the labs themselves, with their impressive infrastructure, contribute to Caltech's frontier status. "There were items that were only on my wish list that are now doable thanks to the setup of Lihong's lab," says Gradinaru. "I can now see the route that is established as blood flows through the brain. Currently we do this postmortem. If we can know how and where blood enters the living brain, then we can get a handle on region specificity, which could be very meaningful to noninvasive delivery of brain therapies." Add to that easy interdisciplinary collaboration, and what you get is potentially global reach. According to Gradinaru, "We're also going to see a huge influence on hardware and software as a result of solving our data problems in medical engineering and engaging our colleagues in data processing."

Caltech's creative interplay of disciplines also reflects the democratization of medicine. Caltech doesn't have a medical school, so it forms partnerships with medical institutions in the region for access to physicians and patients. Gradinaru points to the Caltech–City of Hope collaboration, in particular: "We brought the quantitative engineering excellence of Caltech. They brought the real-world medical applications and the great physicians and scientists of City of Hope. Jointly, we can better influence clinical practice for patients' benefit."

These collaborations are part of Caltech's overall strategy of incorporating the broadest possible range of technical approaches to improving health. "Our mission to improve human health allows for full inclusion. You might not necessarily need to change any biology to do that. Mining behavioral data and developing effective feedback systems can go a long way in guiding patient behavior to a healthier outcome," Gradinaru explains.

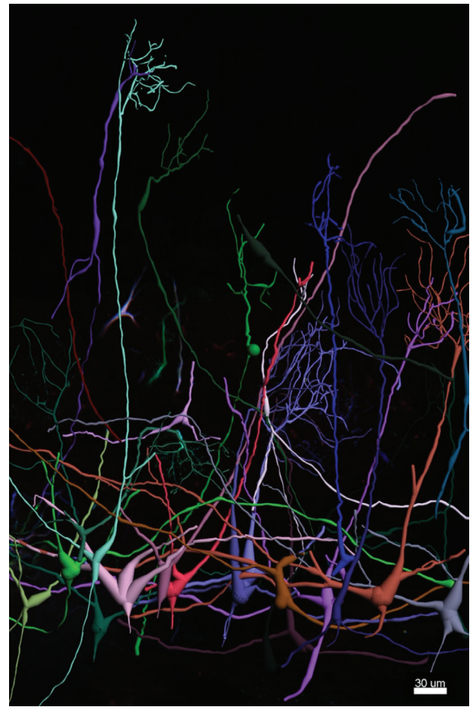
One of the researchers' overarching aims is to make medical technology more affordable and accessible. "Some machines range in cost from 30 to 50 thousand dollars, but all the physician wants to measure is actually something simple, to see if they even need to escalate diagnostics," says Gharib, by way of example. There is a great need for devices that can inexpensively triage patients and do pre-screening. Gharib's research has shown that the flow coming out of the heart can be measured with a $10 device he has prototyped, rather than a $30,000 device currently used in hospitals. This is the kind of progress that Caltech aims to deliver: "It means working smarter, not harder, with our resources, both on the patient side and the delivery side."

Wang sees great potential in such application of new engineering approaches in medicine. "Traditional medicine is really not that quantitative," he says. "With technology, it is becoming more quantitative and therefore more effective. We can hasten the efficacy by injecting the lessons of physics, chemistry, biology, and quantitative science to solve medical problems more fundamentally." In Wang's research, this data-based approach has expanded the range of what doctors can observe happening in the body, from the smallest systems to the largest. "Right now, we are the only lab in the world that provides multiscale *in-vivo* imaging from organelles all the way to whole-body organisms using the same contrast mechanism," says Wang.

Integrated science and first-rate research are hallmark strengths of Caltech, but the exceptional funding from Tianqiao and Chrissy Chen and Andrew and Peggy Cherng provides the essential, stabilizing force that has enabled Caltech to carve out this important niche. "In order to thrive, we need collaborative ecosystems with clear missions," Gradinaru says. "Rather than each lab doing this on the side as peripheral outcomes of our research, what the Chen and Cherng gifts have done is allow us to be explicit. We can identify, assess, target, and work together deliberately to move along faster and smarter. These gifts are catalysts of exponential growth for research already happening across campus."

Gharib believes this to be something these donors recognized instinctively. "They saw that this faculty, these excellent students and postdocs, all they needed was a venue and a start," he says. "Once this free flow of research is started, progress happens—and our students today, and future Caltech students for a long time to come, will be solving medical problems as a result of this momentum."

These gifts are particularly timely, given the current anxiety about continued government funding. Wang stresses that maintaining the Caltech standard, especially with respect to problems that involve such complex systems, is dependent on consistent, significant support. "Our main challenge is having enough resources, which include people, time, and money," he says. "We are all singularities here. We all stand out in our own fields. If we are limited by resources, the synergies weaken and the system starts to underperform. We are not an average institution; we cannot be limited to average resources. The outstanding quality of each individual is maximized by the abundant support of research here. To keep that model alive, we need support."



Neuron morphology in mitral cells of an adult mouse olfactory bulb, shown reconstructed using vector-assisted spectral tracing (VAST), developed in the Gradinaru lab. Neurons are labeled with multiple colors to facilitate morphology tracing.

Gradinaru offers a personal framing of the necessity and impact of funding these efforts. She recalls a trip with her young sons to see the dentist, who told them, "Take good care of these molars, because they're permanent, and you're going to live to be 110." She was struck by the comment. "It hit me. Lifespan has been increasing because of medical advancements, and along the way, this created new needs and opportunities for medical and biological engineering. We're soon going to need better molars." It's the kind of reflection that makes the big picture that much clearer. "One thing is for sure: contributions to the Andrew and Peggy Cherng Department of Medical Engineering and to the Chen Institute for Neuroscience are contributions to our loved ones and ourselves. We are all recipients of these gifts, and we should all participate." ENG

Morteza Gharib is the Hans W. Liepmann Professor of Aeronautics and Bioinspired Engineering, Director of the Graduate Aerospace Laboratories, and Director of the Center for Autonomous Systems and Technologies. Viviana Gradinaru is Assistant Professor of Biology and Biological Engineering, a Heritage Medical Research Institute Investigator, and Director of the Center for Molecular and Cellular Neuroscience. Yu-Chong Tai is the Anna L. Rosen Professor of Electrical Engineering and Mechanical Engineering, the Andrew and Peggy Cherng Medical Engineering Leadership Chair, and the Executive Officer for Medical Engineering. Lihong Wang is the Bren Professor of Medical Engineering and Electrical Engineering.

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