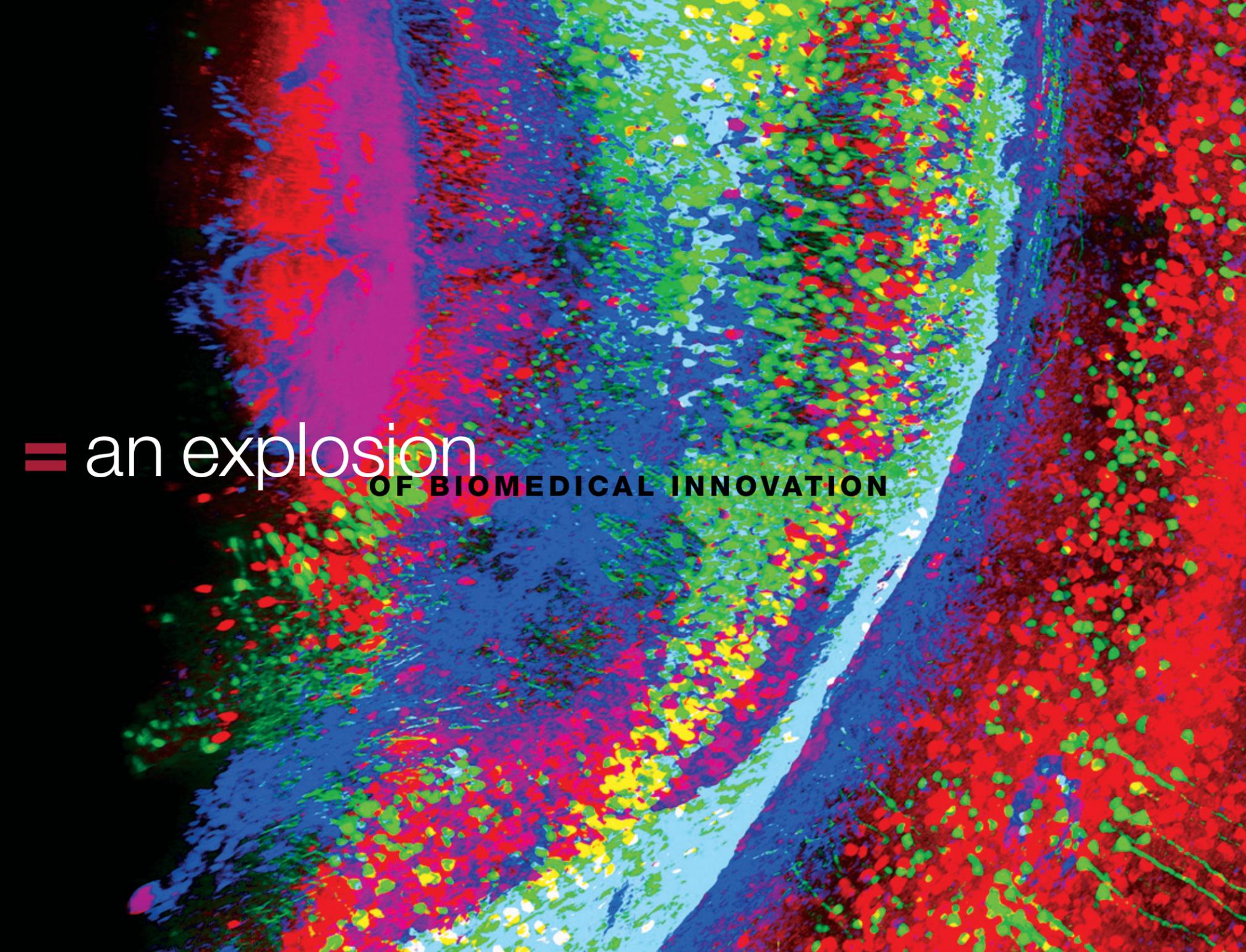




**BIOMEDICAL INNOVATION INITIATIVE**

Campaign for  
 **Stanford  
Medicine** + you =



= an explosion  
OF BIOMEDICAL INNOVATION

# Box? What box?

“We don’t think  
outside the box  
because we never  
see one to begin with.”



— **Lucy Shapiro, PhD**  
Stanford Professor of Developmental Biology and  
2013 National Medal of Science recipient

◀ Image of a transparent mouse hippocampus created with the CLARITY process developed by Karl Deisseroth, MD, PhD (also on cover).



= infinite possibilities

FOR HUMAN HEALTH

**We are in the middle of a biomedical revolution** more profound and far-reaching than the industrial and digital revolutions that made it possible. Over the past two decades, biomedical knowledge has grown exponentially, giving us utterly new insights into how life works. Breathtaking advances in genomics, bioinformatics, imaging, and stem cell medicine are offering up possibilities that were unimaginable just a few years ago. New tools that will allow us to not only heal disease, but to predict it and prevent it, are finally within our reach. This is more than just a revolution in science and health care – it's a revolution in the human condition.

**But the innovation that drives all this is at risk.** National funding for biomedical research is becoming increasingly constrained and conservative. Proven results are often expected up front, and novel approaches are often rejected out of hand, regardless of potential. Scientists spend so much time and energy chasing dwindling resources, they have little left to explore new ideas. Our best and brightest are growing disillusioned. Without the right investments, right now, America will lose the next generation of biomedical innovators. Without their creativity and vision, the momentum of this revolution will falter, and its brightest promises will slip through our fingers.

◀ *Colorized scanning electron micrograph of a human egg and sperm during fertilization.*



**= the power**  
**TO DRIVE INNOVATION FORWARD**

**Stanford is uniquely poised to lead the biomedical revolution** and secure its promise for future generations. Over the last 60 years, our unrivaled atmosphere of interdisciplinary exploration and collaboration has produced many of the innovations that sparked this revolution: MRIs, gene splicing, and stem cell medicine were all born on our campus. Today, that same atmosphere, amplified by the astounding intellectual, technological, and financial capital that surrounds us in Silicon Valley, gives us an unprecedented opportunity. Together, in this place and at this moment, we have the chance to change human health forever.

**The Biomedical Innovation Initiative** is a collection of philanthropic investments in disruptive research, visionary faculty, and promising young scientists. With this targeted, flexible funding, we will drive biomedical innovation forward around the world. Through the generosity of our philanthropic partners, we will power a simple idea, proven time and again on our campus: when you set the best minds free to explore to the limits of their talent and imagination, they will deliver a brighter, better future. Read on, and you'll discover just a few examples of the kinds of innovation your philanthropic vision can fuel.▶

◀ *Colorized confocal light micrograph of capillaries (white) filled with red blood cells (red) feeding a neuron (green).*



**= collaborations**  
**THAT CAN CHANGE THE WORLD**

## Lucy Shapiro | PhD untangles the genetic circuitry that makes life possible.

**LIFE IS A COLLABORATION** between thousands of genes, all working together to produce a functioning organism. Lucy Shapiro, who is the Virginia and D. K. Ludwig Professor of Developmental Biology at Stanford, has spent years studying bacteria to learn how genes orchestrate all the complexities of life. Her quest has resulted not only in new insights into how life works, but strategies to design new antibiotics.

“As time goes by,” Lucy says, “every single available antibiotic is becoming increasingly useless.” Every year at least 23,000 Americans die of drug-resistant bacterial infec-

**“Our two teams were able to explore the physics and chemistry of life side by side, and that revolutionized our understanding of the most abundant organism on the planet.”**

tions, and the approaches currently used to discover new antibiotics are failing. But with their research on the bacterium *Caulobacter crescentus*, Lucy and her colleagues are finding new approaches to this global problem.

Working with her husband, physicist and professor of developmental biology Harley McAdams, PhD, and their combined research teams, Lucy mutated *Caulobacter* cells so that each had a snippet of artificial DNA inserted at a random spot around its single, ring-shaped chromosome. Tagged to be found later, these segments disrupted genetic function wherever they landed. After letting the cells multiply for a few days, they sequenced the DNA of the survivors.

Those genes that tolerated the insertion of artificial DNA weren't essential for viability, while those that didn't tolerate it were essential to life. The essential genes comprised 12 percent of *Caulobacter's* genome, and many were part of a complex genetic circuit that integrates multiple cell functions.

With this technique Lucy, Harley, and their teams can quickly identify which genes are essential for survival in almost any microbial species. They can then target the functions those genes control to create antibiotics that are “resistant to resistance” because they at-

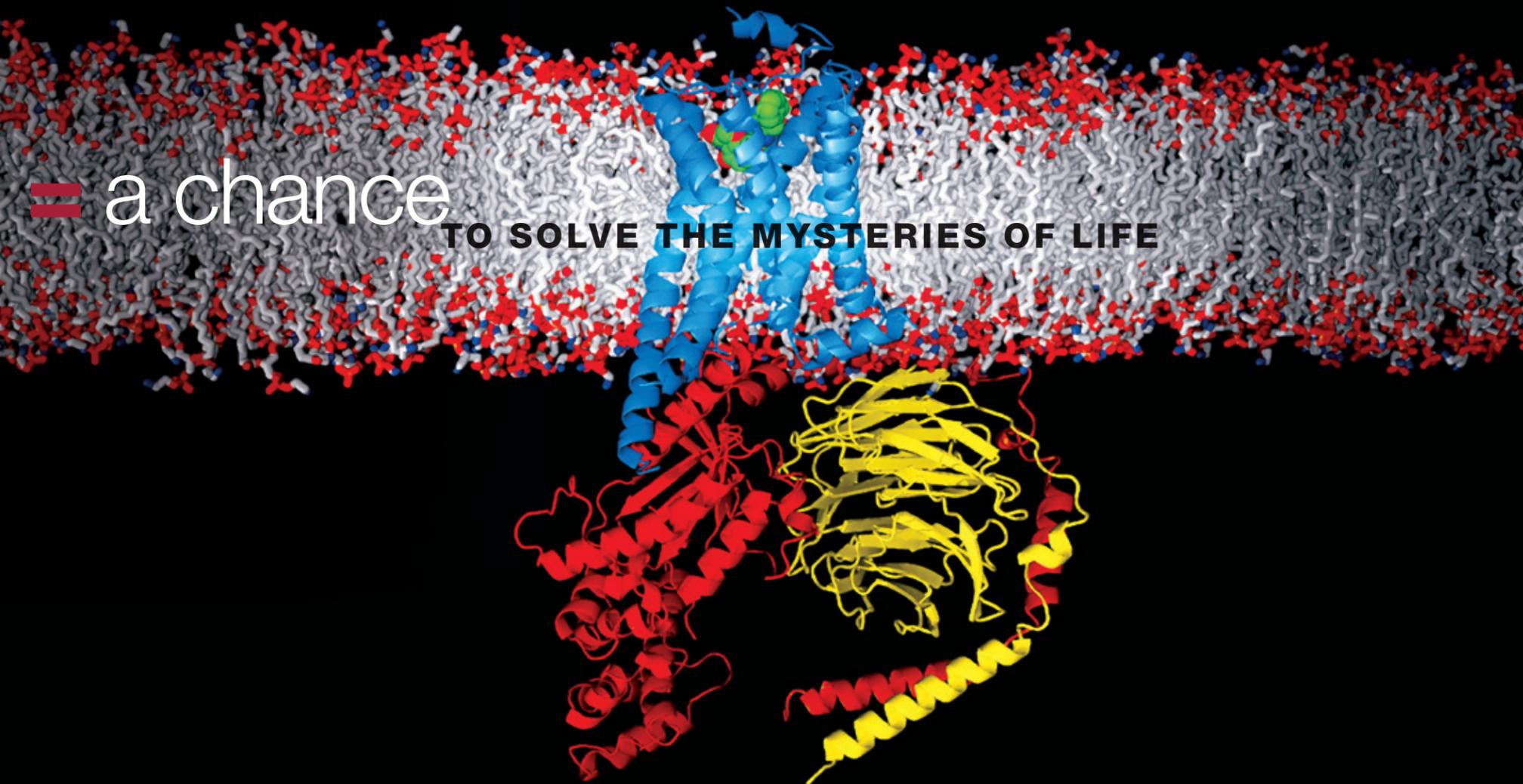


tack multiple vulnerabilities simultaneously. They already have several in clinical trials.

By combining talents and teams, Lucy and Harley have given the world a better understanding of bacteria and a better way to develop desperately needed drugs. “His students have been physicists and engineers, while mine have been biologists and geneticists,” Lucy says. “They work side by side.”

Despite the potential of interdisciplinary collaborations like this, they are often excluded from the narrow purview of many funding agencies. This creates a vital and exciting role for philanthropists – by helping scientists from different fields collaborate, they can be part of a team that changes the world.

◀ *Colorized scanning electron micrograph of a colony of *Caulobacter crescentus* bacteria.*



## Brian Kobilka | MD scrutinizes how cells receive the signals we need to send.

**“A MOLECULAR MASTERPIECE.”** That’s how the Nobel committee described the image that earned Brian Kobilka and his colleagues the 2012 Nobel Prize in Chemistry.

After more than 20 years of herculean effort, Brian, who is the Hélène Irwin Fagan Chair in Cardiology, did what many thought impossible. He and his team took an atomic snapshot of a G-protein coupled receptor, just as it transmitted a signal.

G-protein coupled receptors (GPCRs) are molecular complexes embedded in the outer membranes of cells. Tiny relay stations, they receive chemical signals from outside the

cell and transmit them inside. GPCRs are the largest class of cellular receptors, and nearly half of all drugs target them. But getting that picture wasn’t easy. First, large amounts of the receptor had to be produced via recombinant DNA. Then it had to be purified, locked in its “on” position, and crystallized before being bombarded with X-rays from hundreds of angles. Finally, like re-creating a sculpture from only its shadows, the image had to be extrapolated from all the diffraction patterns the X-rays produced as they hit the crystals.

It wasn’t cheap, either. Just one tiny bottle of the special detergent they needed to purify a week’s worth of receptor cost \$1,000. They ran out of fund-

**“Basic research like this can lead to drugs that benefit us all, but NIH funding for it is limited. We often have very bright people with very good ideas who can’t pursue them.”**

ing twice, and at one point, Brian offered to cut his salary just so they could keep going.

Then, out of the blue, a friend called and asked about their progress. Brian told him they were close, but almost out of money. His friend, who understood the project’s potential, donated \$300,000, no strings attached. Along with several smaller gifts, this relatively modest infusion of unrestricted funds allowed Brian and his team to finally succeed.

As Brian says, this kind of flexible funding means you can “take that extra shot,” when tackling a difficult problem. For Brian, it meant he could look failure in the face and still keep his eyes on the prize.

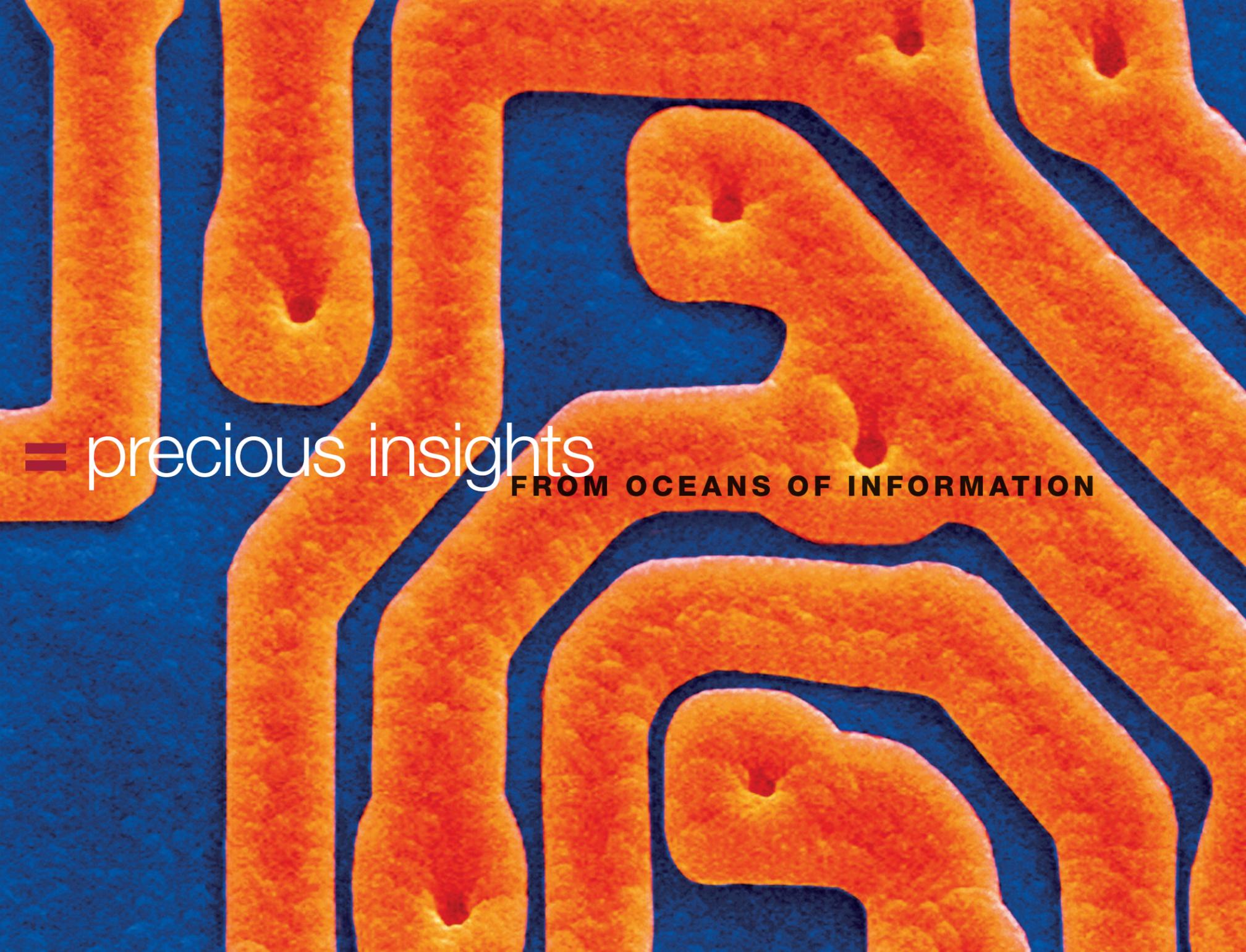
ing twice, and at one point, Brian offered to cut his salary just so they could keep going.

Then, out of the blue, a friend called and asked about their progress. Brian told him they were close, but almost out of money. His friend, who understood the project’s potential, donated \$300,000, no strings attached. Along with several smaller gifts, this relatively modest infusion of unrestricted funds allowed Brian and his team to finally succeed.

As Brian says, this kind of flexible funding means you can “take that extra shot,” when tackling a difficult problem. For Brian, it meant he could look failure in the face and still keep his eyes on the prize.



◀ The image created by Brian and his team of a  $\beta_2$  adrenergic receptor (blue) with its coupled G-proteins (red and yellow) in action.



**=** precious insights  
FROM OCEANS OF INFORMATION

## Atul Butte | MD, PhD explores huge datasets to find life-saving patterns.

**A DIGITAL TREASURE HUNTER**, Atul Butte spends his days diving into oceans of data in search of new ways to improve health and save lives. Teasing out hidden patterns and correlations, he is on an endless quest for fresh insights.

A tsunami of medical data is crashing all around us. Since the advent of electronic medical records, virtually every patient leaves a detailed data trail. These days, everything gets saved. Prescriptions, test results, imaging studies, DNA sequences, clinical trials data, and more all end up in vast databases, contributing to a flood of information that's growing by a

Atul calls his approach "data-driven systems medicine," and it's yielding valuable results fast. By comparing data from thousands of cancer patients with data on hundreds of FDA-approved drugs, he and his team found that desipramine, an antidepressant that's been in use for years, has a surprising side effect. It kills certain lung and neuroendocrine tumors. They tested the effect and began phase II clinical trials in less than a tenth of the time and for a fraction of the cost it takes the pharmaceutical industry to start trials on a new drug. And that's just one example of many.

**"Hiding in these seas of data is knowledge that could change a patient's life – or the entire world. There's priceless stuff out there. With a little funding, we can find it."**

zettabyte ( $10^{21}$  bytes or a billion terabytes) every year.

Making sense of all this data and putting it to work for patients is no small task. That's where a visionary like Atul, supported by Stanford's world-class programs in computer science and quantitative analysis, has an edge. With a multidisciplinary crew of collaborators, Atul searches these seas of information for what he calls "biomedical moments."

These moments are tipping points – crucial times when things can either go well or wrong for patients – and precious insights often hide in the data surrounding them. "We want to know what will keep patients on the right track to a good outcome," Atul says, "and these moments tell us where to look."

A wildly productive bunch, Atul and his team average a new publication every 16 days. They can move at this blistering pace because they don't have to start with long, expensive laboratory experiments to gather the data they need to test their ideas. It's already out there, much of it in public databases, just waiting for someone to ask the right questions of it. That makes this a particularly promising area for philanthropy – modest investments here can quickly return significant results.

"I think of it as thawing frozen discoveries," says Atul, who was named a 2013 Champion for Change by President Obama. "They're out there, waiting. All we have to do is find them."



◀ *Colorized scanning electron micrograph of a computer processor.*



**= a new awareness**  
**OF WHAT IT MEANS TO BE HEALTHY**

## Mark Davis | PhD illuminates the “black box” of the human immune system.

**WHY DO KIDS EAT DIRT?** Mark Davis may know why. The human immune system is an incredibly complex learning machine. It “remembers” all the pathogens you encounter so it can fight them off in the future. Mark suspects the urge to make (and eat) mud pies might have evolved to train our immune systems to meet the challenges of life in a messy world.

Despite the central role it plays in our health, human immunity is so complex that most of its inner workings are still a mystery. Plus, much of our understanding is based on a mouse model, and while laboratory mice have served us well

At the Stanford Human Immune Monitoring Center (HIMC), Mark and his team can take more than 50,000 different measurements from a single blood sample – more than a hundred times the information that shows up in a typical blood panel. By casting such a broad net, they can analyze immunity in exquisite detail, and not just on an individual level. Working with big data experts like Atul Butte, they’re comparing millions of data points from thousands of patients and healthy people to establish a baseline picture of a normal immune system. From there, real understanding

**“Flexible funding gives us the freedom to innovate. One idea we’re pursuing is an easy-to-use blood test patients can use to see how their immune systems are doing.”**

in our efforts to understand the basic principles of immunity, they aren’t very much like us. Bred to be genetically similar, they live their entire lives in sterile, controlled environments.

That’s a far cry from how we were raised, no matter how spotless our parents kept the house. We’re exposed to thousands of germs every day of our lives. We’re also genetically diverse. Which begs the question: how much can we really learn about human immunity from mice?

Mark thinks we should look to ourselves for answers. He calls his approach “immunity taught by humans,” and with technology developed here at Stanford, he and his team are digging into human immunity like no one ever has before.

of how human immunity works – in all its wondrous complexity – will finally be within reach.

It’s an audacious endeavor, and Mark credits philanthropy for getting it off the ground. With just \$2 million raised solely from donors, he and his colleagues founded the HIMC in 2007. Since then, it’s generated more than \$70 million in grant funding, and is now used by researchers and clinicians across Stanford. Mark is also the Burt and Marion Avery Family Professor of Immunology, and the income from this endowment has given his group the freedom to explore new ideas. “I give most of it to my grad students,” he says, “so they can work on really exciting stuff.”



◀ *Colorized scanning electron micrograph of human blood with red blood cells (red), T-lymphocytes (yellow), and platelets (brown).*



**= unexpected ways**  
**OF LOOKING AT DISEASE**

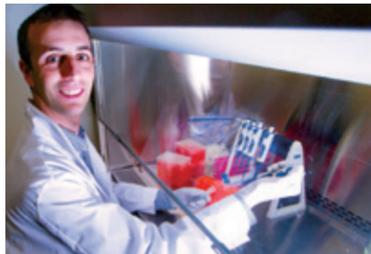
## Adam de la Zerda | PhD lights up tumors with lasers, sound, and nanoparticles.

**ONE MILLION CANCER CELLS.** Once a tumor grows beyond this size (about a millimeter), it gets aggressive. It starts attracting blood vessels, growing faster, and spreading to other parts of the body. Unfortunately, MRIs and CT scans are limited to a resolution of several millimeters, or about 10 million cells, which means clinicians can only “see” tumors that have grown past this critical threshold.

But not for long. Adam de la Zerda and his team have figured out a way to detect tumors a tenth that size. Called photoacoustic molecular imaging, it works like this: first, gold

It’s a quantum leap forward. With the precision guidance of antibodies and 10 times the resolution of the current standard, Adam’s method promises to revolutionize oncology.

When he first came to Stanford, Adam wanted to pursue a PhD in electrical engineering. But soon after he arrived, a close friend died of cancer. Deeply affected, he decided to devote his skills to helping patients. Encouraged by advisors, he shadowed Stanford physicians for inspiration. It struck as he watched a breast cancer surgery: he would build more accurate imaging tools.



**“The first question most graduate students are asked when they want to join a lab is ‘Are you funded?’ That’s the wrong question. It should be ‘What really excites you?’”**

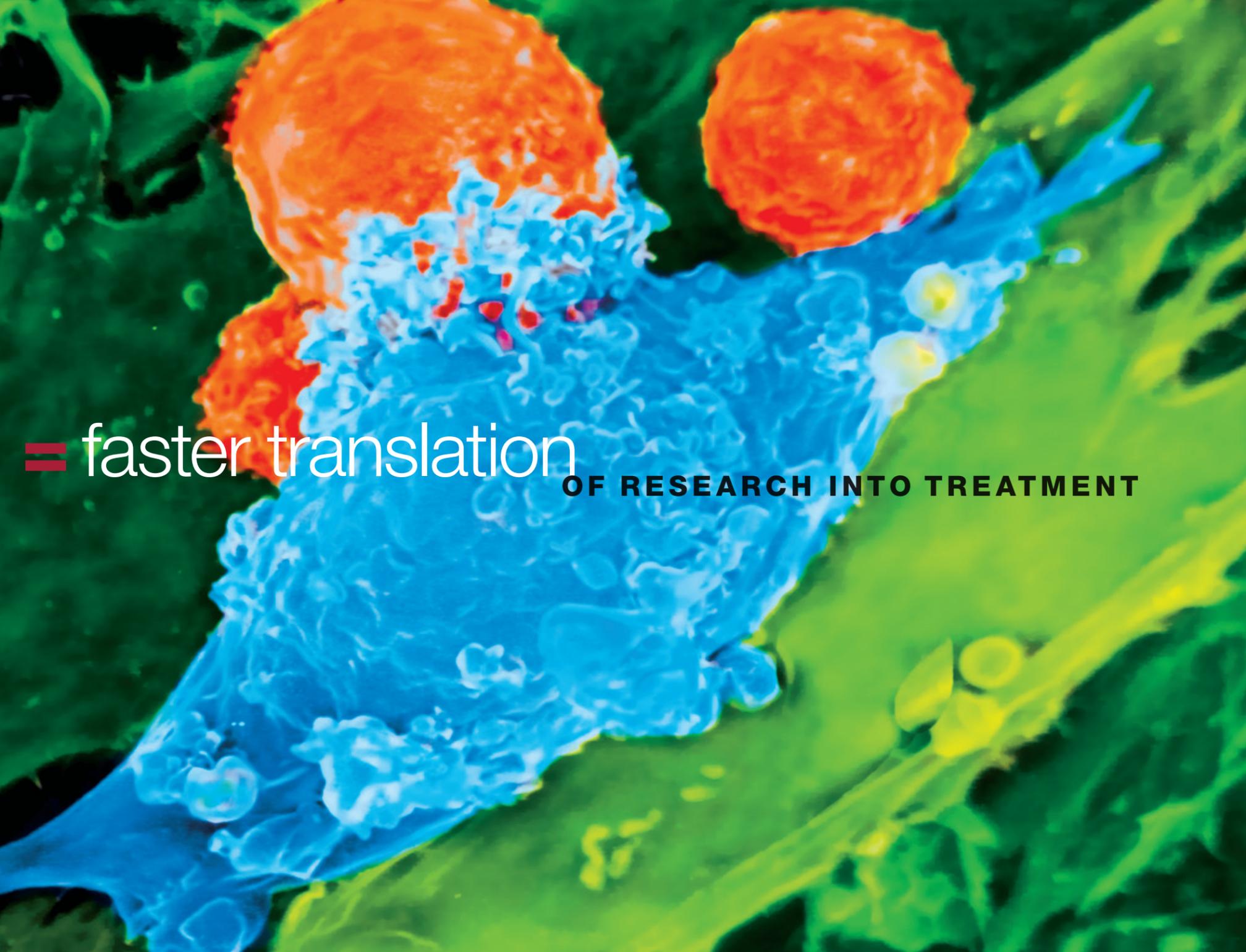
nanoparticles are coated with antibodies keyed to bind to specific molecules (called biomarkers) produced by a patient’s tumor. Then these coated nanoparticles are injected into the bloodstream. As they encounter cells displaying the biomarkers, these tiny antibody-covered nuggets glom on, sticking to tumor cells like magnets while passing normal cells by.

Next, the area is illuminated with laser pulses while an ultrasound is conducted. The laser light is absorbed by the gold cores of the nanoparticles, causing them to heat up and expand. This pushes on the tissues around the tumor, and the resulting tiny shock waves produce ultrasound signals from which a 3-D image of the tumor can be computed.

Thanks to a Bio-X fellowship funded by philanthropy, Adam had the freedom to drastically alter his focus and join the lab of Sam Gambhir, MD, PhD, chair of radiology and director of Stanford’s molecular imaging program. With Sam as his mentor and guide, he took off in a bold new direction that ultimately led him to develop photoacoustic molecular imaging.

That initial investment in Adam paid off immensely. Now he has his own lab and is collaborating with industry and Silicon Valley to make this technology widely available. He’s also pursuing new ideas. “From 10 million cells to one million,” he muses. “Not bad. But I want to get it down to just one cell.”

◀ *Colorized scanning electron micrograph from one of Adam’s publications showing laser-heated nanoparticles on a tumor.*



**= faster translation**  
**OF RESEARCH INTO TREATMENT**

## Ravi Majeti | MD, PhD [rips away cancer's disguise so the body can eat it.](#)

**“DON'T EAT ME!”** That's what CD47, a protein on the surface of baby blood cells, broadcasts to the immune system as these cells make their maiden voyage from bone marrow to spleen. Without this chemical signal, many normal cells like these could be mistaken for invaders and gobbled up by macrophages, the body's roving cellular garbage disposals.

Researchers at Stanford's Institute for Stem Cell Biology and Regenerative Medicine found that leukemia cells also express a lot of CD47. So Ravi Majeti and his team, with the leadership of the Institute's director Irv Weissman, MD, set

When they replicated Ravi's methods, they had similar successes against more than 20 types of cancer, including breast, ovary, liver, colon, prostate, bladder, and brain. The antibody shrank or even eliminated these tumors and prevented them from spreading.

And just this spring, Irv's labs showed silencing CD47 on cancer cells doesn't just announce their presence to hungry macrophages; it gets killer T-cells to attack them, too. Since T-cells “remember,” this work could make cancer vaccines to prevent recurrence possible.



**“The minute we saw the cancer-killing potential of anti-CD47 treatments, we knew we had to get them to patients fast. This grant gave us the fuel to move at warp speed.”**

out to discover if CD47 was the chemical disguise leukemia cells used to escape detection by the immune system.

Could they get macrophages to go after leukemia cells by silencing CD47's don't-eat-me signal? To find out, they injected mice with aggressive human leukemia cells. Then they treated the mice with an antibody Ravi, Irv, and their colleagues developed that blocks CD47's signal.

It worked. The majority of the mice were cured, and under the microscope, Ravi and his team could actually see macrophages feasting on malignant cells.

Meanwhile, others in Irv's labs started searching for CD47 in solid tumors and found it almost everywhere they looked.

Ravi and his team were the first to reveal the key role that CD47 plays in cancer and the first to realize the huge therapeutic potential of silencing it. Thanks to a \$20 million grant from the California Institute for Regenerative Medicine received at an absolutely critical time, they are about to start clinical trials of anti-CD47 treatments, just seven years after their initial findings. While that may seem like a long time, it's just a third of 20-plus years it typically takes to translate discoveries into treatments in a commercial setting.

Ravi credits Irv's encouragement and Stanford's culture. “We were able to take this all the way from discovery to treatment in record time. We simply couldn't have done it anywhere else.”

◀ *Colorized scanning electron micrograph of a macrophage (blue) consuming leukemia cells (red).*

A colorized scanning electron micrograph showing three red blood cells on a razor blade. The cells are bright orange-red and have a biconcave disc shape. The razor blade surface is a textured, light blue-grey color. The background is a dark teal with fine, vertical, light-colored scratches.

**cutting edge**  
**BIOMEDICAL INNOVATION**

## The Stanford Biomedical Innovation Initiative

### Faculty Innovation Funds

These competitive awards fuel pure innovation – the high-risk, high-reward research ideas that forge new realms of discovery and spark biomedical breakthroughs. Put to work immediately, these expendable funds are available to faculty at all stages of their careers, in all specialty areas, and across the spectrum from basic science through clinical application. Donors will have opportunities to connect with researchers and their work.

### Endowed Chairs and Scholars

Endowed funds give recipients the freedom to pursue their most creative and promising work – an advantage a surprising number of our outstanding faculty currently lack. They also give Stanford the power to recruit the best talent and plan forward with vision. Through this initiative, we will create 20 new endowed chairs to support established faculty for the length of their tenure. Ten new endowed scholar positions will support more junior faculty in term appointments, providing critical funding earlier in their careers. Donors may name these endowments and direct them to their areas of interest.

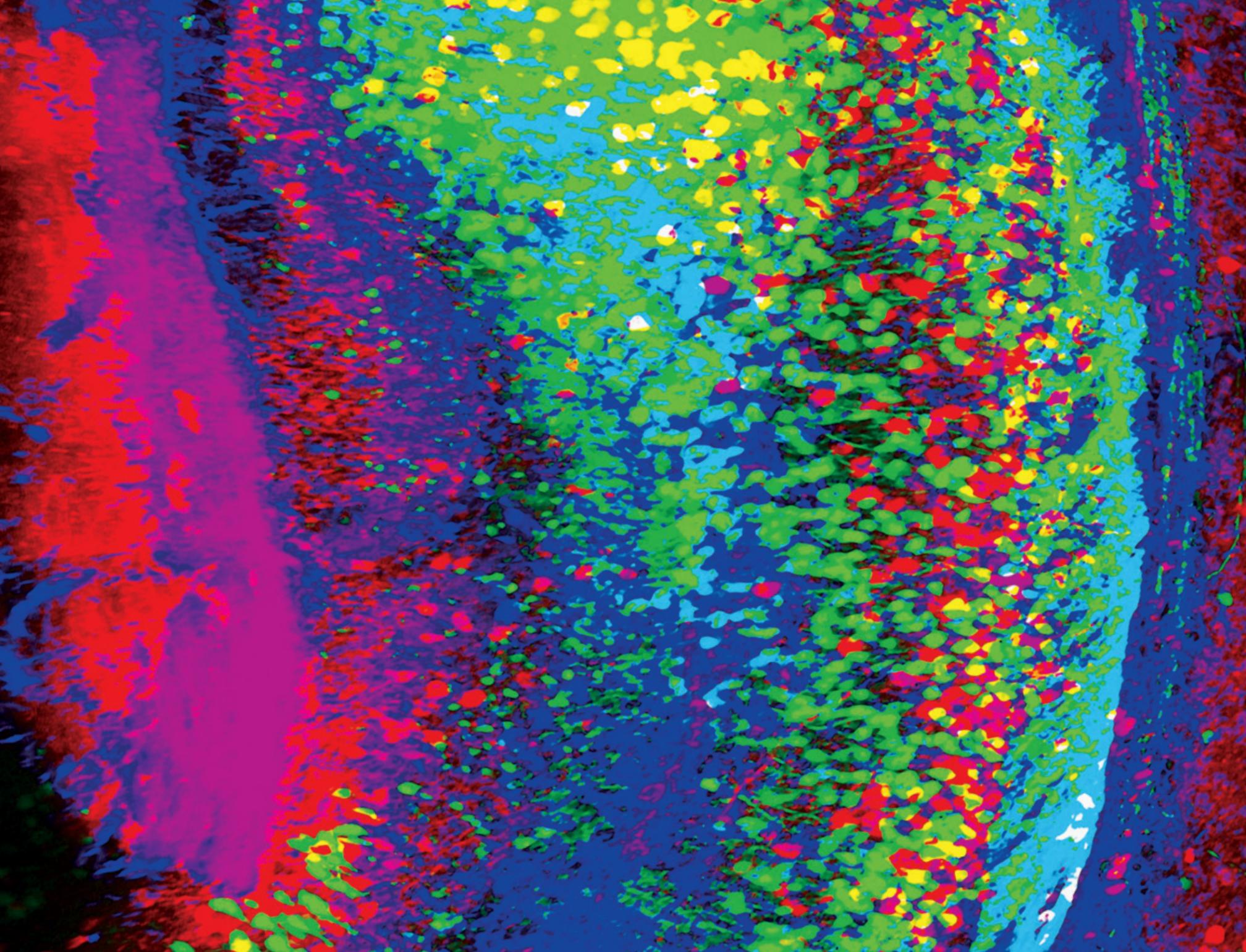
### Graduate Student Support

These expendable funds attract the best graduate students from around the world by fully covering their first four years of training. Relieving financial pressures that can stifle creativity, this support allows aspiring scientists to choose their research directions freely and concentrate on the training they need to become the scientific leaders of tomorrow. Donors will have opportunities to get to know these students and witness the progress of their careers.

### Post-doctoral and Fellowship Support

Like Faculty Innovation Funds, these competitive awards set post-doctoral students and fellows free to pursue their most promising and innovative research ideas. They allow these young researchers to work side by side with senior faculty and take advantage of Stanford's unique strengths across the disciplines to explore engineering, business, biodesign, and other areas to augment their scientific training. Donors will have opportunities to interact with these young scientists and learn about their work.

◀ *Colorized scanning electron micrograph of red blood cells on a razor blade.*



**WE ARE ALL PART OF THE EQUATION**



[medcampaign@stanford.edu](mailto:medcampaign@stanford.edu)