

# Evolution of Bioengineering at UCSD

By Shankar Subramaniam

**B**ioengineering is a young albeit important discipline that is still in the process of evolution. Frequently, insightful and prospective students have asked me two important questions: 1) What is the field of bioengineering and where is it going? 2) Given the diversity of bioengineering and expertise in your department, what is the unifying factor? To answer these, let us ask, what do bio and biomedical engineers do? Engineers measure components of systems with existing techniques or develop new technologies, understand the design principles of the system, develop a quantitative model, and study the behavior of the system through the model by introducing perturbations. Thus, they are able to build similar systems that can provide similar and different input-response characteristics and lead to innovation. Bioengineers apply these principles to living systems. The end goal is societal and economic benefit, which goes beyond merely satisfying intellectual curiosity.

The University of California at San Diego (UCSD) has played a very important role from the beginning and continues to pioneer the evolution of the discipline. The UCSD Program in Bioengineering began in 1966 with Dr. Y.C. Fung, Dr. Benjamin Zweifach, and Dr. Marcos Intaglietta joining the then Department of Applied Mechanics and Engineering Science to work on the application of mechanical engineering principles

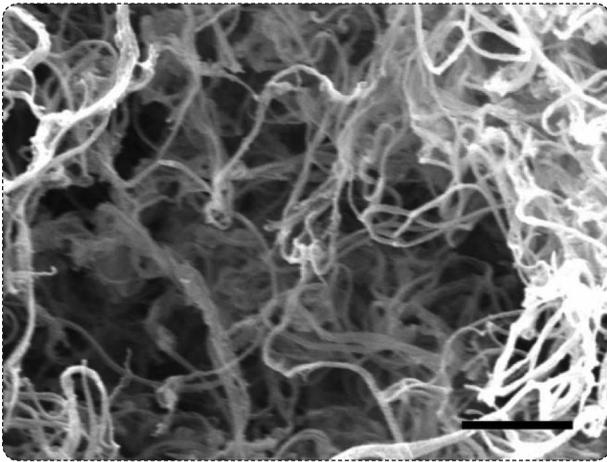


## Opening New Vistas

to physiology. Areas of biomechanics and microcirculation applied to physiology, in general, and vascular physiology, in particular, initiated a new era in bioengineering. Before this, the field of bioengineering referred to biomedical engineering of prosthetic devices in physiology. In addition to exciting applications of engineering principles, UCSD Department of Bioengineering began to extend the notion of engineering models of physiological systems to physiological processes. This led to a conceptual shift in the discipline and contributed to

the areas of tissue and physiological process engineering. In 1988, Dr. Shu Chien and Richard Skalak joined UCSD to begin research and education on cellular and molecular bioengineering, especially, mechanobiology. Dr. Fung and Dr. Skalak initiated the new field of tissue engineering. These two decades of evolution of bioengineering and its growth across the country was spearheaded by the Whitaker Foundation, whose leitmotif was the build-

ing of bio- and biomedical engineering across the country. The leadership and staff of the Whitaker Foundation were messianic in their zeal for the spreading of bioengineering, and the community owes a significant amount to the vision espoused by them. A more comprehensive and broad history of the early development of bio- and biomedical engineering and the role of Whitaker Foundation can be found on the Institute of Engineering in Medicine (IEM) Web site (<http://iem.ucsd.edu>). The UCSD and a selected set of institutions were presented development and leadership awards by the Whitaker Foundation, and



**FIGURE 1** A cardiac-specific scaffold developed by Dr. Christman. The material is a liquid that self-assembles into a porous and fibrous scaffold upon injection into the heart. Scale bar = 1  $\mu$ m. (Photo courtesy of UCSD Jacobs School of Engineering Newmedia.)

the legacy of these awards continues and their impact speaks for the investment. At UCSD, these awards were instrumental in the establishment of the Department of Bioengineering in 1994 with Dr. Chien as the founding chair and the construction of a Bioengineering Hall in 2002.

Concurrent to the developments in bioengineering, the field of radiology continued to evolve at a rapid pace, and the ability to study hard tissues in detail became feasible. At UCSD, the early pioneers of bioengineering realized that the emergence of more modern technology would provide the ability to study the design principles of tissues and engineer them, and the beginnings of tissue engineering, focused on both hard and soft tissues, started to flourish in the 1990s. Departments across the country began to recruit engineers whose research interest lay in soft tissue engineering. Meanwhile, the sequencing of the genome and the technologies for in vitro and in vivo probing of cells and their components in detail began to emerge, and this redefined the ability to engineer across scales from molecule to cellular to tissue to organ in physiology. In the early 2000s, the UCSD Department of Bioengineering proposed that quantitative systems biology is essentially an intellectual quest of bioengineering and should be embraced by the Department of Bioengineering. Given that a number of principles of intracellular and molecular system scale across organisms, the scope of bioengineering expanded to microorganisms and single-cell eukaryotic systems. UCSD's early adoption of this concept led departments across the country to recruit in the field of systems biology and today it is a common place for students interested in systems biology to seek bioengineering programs. This was also augmented by the development of new technologies ranging from genome to live cell imaging by researchers in bioengineering departments. In the mid-2000s, systems biology gradually shifted to mammalian, especially human systems, and systems medicine with molecular and cellular perspectives began to emerge. The ability to study diseases in molecular detail and investigate the effects of disease at the systems level led to deciphering systemic pathways and concepts of off-target effects of

a drug on physiology. Recognizing that this will be the sine qua non of medicine in the coming decades, UCSD formed the IEM, which is the harbinger for entirely new approaches to health care. Also, in the mid-2000s, the field of tissue engineering began to realize that our understanding of the principles of tissue generation are sufficiently detailed so that we can begin to think about the use of stem cells in engineering tissues ex vivo. UCSD was once again at the forefront in recruiting bioengineers who work on engineering the environment and the framework of cells that is essential for engineering tissues ex vivo. The ability to study and implement bioengineering across scales is now a reality. Our department represents these frontiers in bioengineering, and you will see that we broadly categorize our research interests to embrace the three pillars of bio- and biomedical engineering, including multiscale bioengineering; tissue engineering and regenerative medicine; and systems biology and medicine.

Our department has outstanding faculty members in all of these areas, and we continue to recruit excellent faculty and students. Two of our faculty members, Dr. Y.C. Fung and Dr. Shu Chien, are members of all three National Academies and are both recipients of the National Medal of Science, the highest honor awarded to a scientist or engineer in the United States. The department has pioneers in every modern aspect of bioengineering. Our present rivals our past in innovation, and our future is in the safe hands of outstanding young faculty members. I accentuate only a few of our accomplishments next.

## Engineering Principles for Regenerative Medicine

### *Regenerating the Heart*

Biology has made dramatic inroads for understanding stem cell differentiation. However, taking these foundational discoveries to practical applications of tissue regeneration is an engineering problem. The channeling of mechanical and physicochemical forces to drive tissue regeneration and organ formation requires understanding the design principles of tissues and organs and developing strategies to model them in theory and practice. Several young faculty members in our department are pioneers in this area. Over the past decade, Dr. Christman and the members of her group have been exploring the use of injectable materials to prevent heart failure after a myocardial infarction. Previously, no materials had been specifically designed for the heart, and while they were injectable via a syringe in needle, the majority did not have the appropriate gelation kinetics to be delivered to the heart via a catheter, which requires multiple injections over a 30-min to hour-long procedure. Dr. Christman's laboratory developed the first cardiac specific injectable material that is also amenable to minimally invasive catheter delivery. The material is derived from decellularized porcine myocardium and, therefore, provides cardiac-specific cues. It is processed into a liquid, and upon injection into the heart, sets into a porous and fibrous scaffold that replaces the degraded extracellular matrix that occurs postmyocardial infarction and promotes cell infiltration to help repair the heart (Figure 1). In rats, Dr. Christman's group found that the material was biocompatible and increased cardiomyocytes in the infarct area in

addition to improving cardiac function. Dr. Christman says that the material, termed VentiGel, “appears to prevent further cardiac muscle death, and we saw evidence of stem cells coming into the area of the heart that had been damaged.” In collaboration with cardiologists Dr. Anthony DeMaria and Dr. Nabil Dib through the IEM at UCSD, her laboratory has recently tested the material in a porcine model and found dramatic increases in cardiac function out to three months postinjection, particularly in decreasing end-systolic volume, which is known clinically to be the greatest indicator of survival postmyocardial infarction. Dr. Christman cofounded a company that anticipates entering clinical trials with VentiGel in Europe at the end of the year.

### Bioinspired Artificial Extracellular Matrices

Research in Dr. Varghese’s laboratory lies at the interface of stem cells, materials science, and regenerative medicine. Dr. Varghese works on elucidating the influence of physicochemical cues of the microenvironment on stem cell fate and function and understanding how the microenvironment in turn affects tissue homeostasis and pathological conditions. The fundamental understandings gained from these studies are used to develop new strategies to reinstate the function of diseased tissues. Most of Dr. Varghese’s effort is devoted to musculoskeletal diseases, where she employs a wide spectrum of *in vitro* and *in vivo* tools.

Her laboratory has developed a self-healing hydrogel that binds in seconds, as easily as Velcro, and forms a bond strong enough to withstand repeated stretching (Figure 2). The material has numerous potential applications, including medical sutures, targeted drug delivery, industrial sealants, and self-healing plastics.

### Making Muscle

Stem cells derived from fat have a surprising way of replacing damaged cells: while developing on a myogenic firm substrate (approximately 10 kPa), they undergo a remarkable transformation toward becoming mature muscle cells. The new cells remain intact and fused together even when transferred to a stiff, bonelike surface, which has USCD Department of Bioengineering Prof. Adam Engler and colleagues intrigued. These cells, they suggest, could hint at new therapeutic possibilities for muscular dystrophy (MD). In diseases like MD or a heart attack, “muscle begins to die and undergoes its normal wounding processes,” said Engler. “This damaged tissue is fundamentally different from a mechanical perspective” than healthy tissue (Figure 3).

Transplanted stem cells might be able to replace and repair diseased muscle, but up to this point, the transplants haven’t been successful in MD patients, he noted. These cells tend to clump into hard nodules as they struggle to adapt to their new environment of thickened and damaged tissue. Engler, postdoctoral scholar Yu Suk Choi, and the rest of the team think that their fat-derived stem cells might have a better chance for this kind of therapy, since the cells seem to thrive on a stiff and unyielding surface that mimics the damaged tissue found in people with MD. Cells from the fat lineage were 40–50 times better than their bone marrow counterparts at displaying the proper genes involved in becoming muscle. These genes are also more likely to turn on in the correct sequence in the fat-derived cells, Engler said.



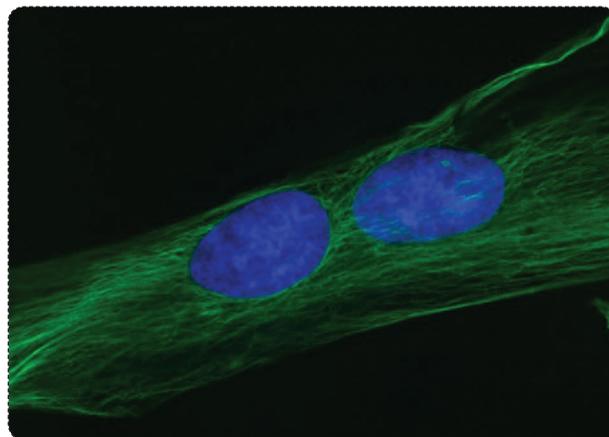
**FIGURE 2** Self-healing hydrogels developed by Dr. Varghese’s group. (Photo courtesy of Dr. Shyni Varghes.)

Most surprisingly, muscle cells grown from the fat stem cells fused together, forming myotubes to a degree never previously observed. Myotubes are a critical step in muscle development, and it’s a step forward that Engler and colleagues hadn’t seen before in the lab. The fused cells stayed fused when they were transferred to a very stiff surface. “These programmed cells are mature enough so that they don’t respond the environmental cues” in the new environment that might cause them to split apart, Engler says. Engler and colleagues will now test how these new fused cells perform in mice with a version of MD.

### Shocking the Sceptic Shock

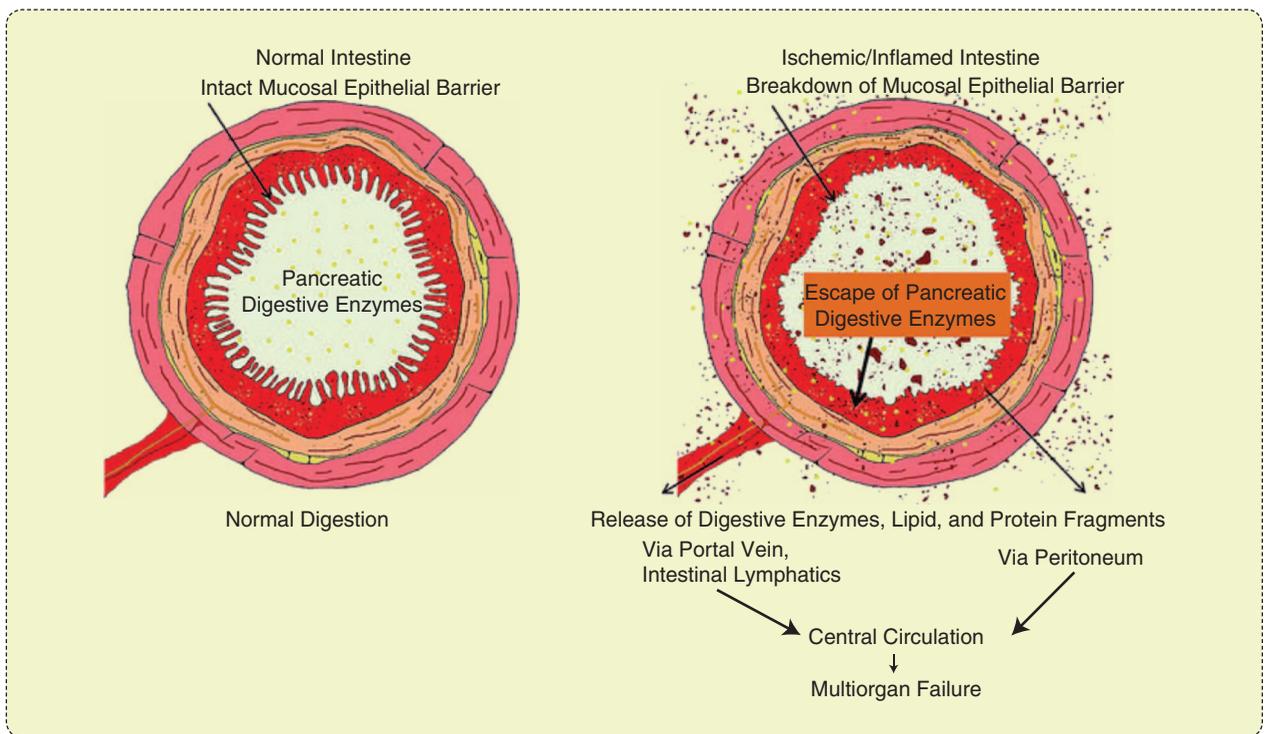
A 200-patient Phase 2 clinical pilot study was initiated in May 2012 to test the efficacy and safety of a new use and method of administering an enzyme inhibitor for critically ill patients developed by UCSD Department of Bioengineering Prof. Geert Schmidt-Schoenbein. Conditions expected to qualify for the study include new-onset sepsis and septic shock, postoperative complications, and new-onset gastrointestinal bleeding.

Schmid-Schönbein and his colleagues at the UCSD Jacobs School of Engineering discovered that, under conditions of shock, the epithelial cell barrier that lines the small intestine becomes permeable, causing the potent digestive enzymes to be



**FIGURE 3** Two fat-derived stem cells display a continuous cytoskeleton, indicating that they have fused together. A bone marrow-derived stem cell fails to fuse under similar conditions in the laboratory.

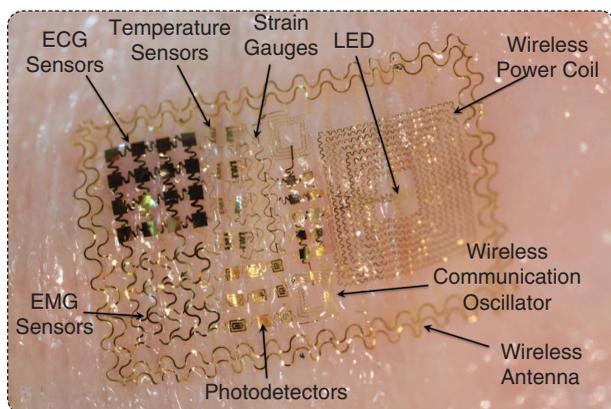
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**FIGURE 4** Autodigestion in acute shock. (Image courtesy of Dr. Geert Schmidt-Schoenbein.)

carried into the bloodstream and lymphatic system where they digest and destroy healthy tissue, a process he named *autodigestion* (Figure 4). The treatment involves blocking the enzymes with an enzyme inhibitor.

In 2005, the team's protocol was licensed a development-stage, critical care start-up company called Inflammagen Therapeutics under an agreement developed by UCSD's Technology Transfer Office. Inflammagen Therapeutics developed the Inflammagen Shok-Pak, a drug/delivery platform that delivers the enzyme inhibitor through a nasogastric tube directly into the stomach and lumen of the intestine, preventing shock and multiorgan failure. Schmid-Schönbein serves as a scientific advisor to Inflammagenbut and is not an employee of the company. Instead, he has chosen to focus on continuing to conduct fundamental research on autodigestion at UCSD.



**FIGURE 5** The demonstration platform for an epidermal electronics system with multimodal sensing and wireless transmission capability. (Photo courtesy of the University of Illinois.)

### Flexible Bioelectronics and Tatoos

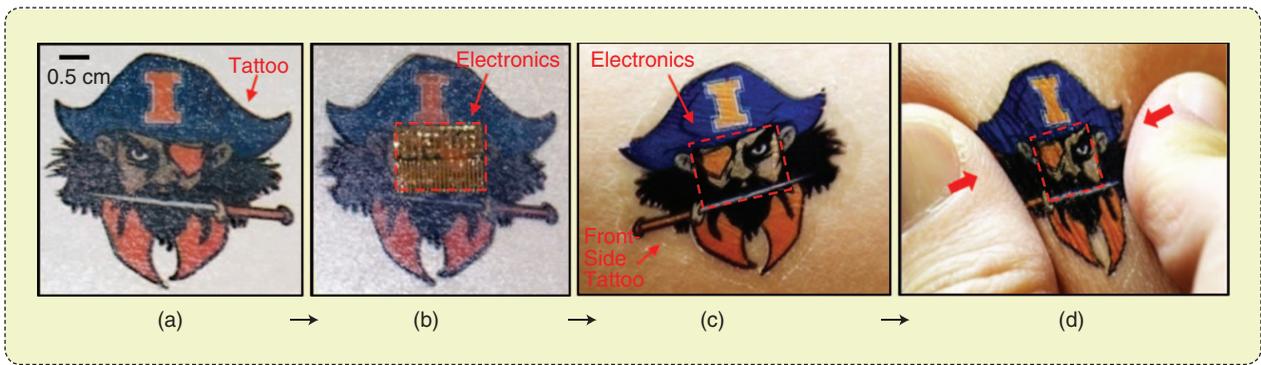
Dr. Coleman was originally trained as an electrical engineer and then did postdoctoral research in neuroscience, and his early faculty career was in the electronic and computer engineering department as well as the neuroscience program at the University of Illinois. That's where he began to work on projects at the intersection of neuroscience and engineering. He addressed research problems at the intersection of neuroscience and engineering, e.g., to build brain—machine interfaces. To make these systems more unobtrusive, he codeveloped a class of flexible skin-mounted electronics (Figure 5) that can be embedded in a temporary tattoo (Figure 6). In collaboration with John Rogers at the University of Illinois, Coleman builds these tattoo sensors that can sense and wirelessly transmit multiple modalities (electrical, temperature, mechanical, and optical).

### Adaptive Evolution in the Laboratory

"We now can observe evolution in laboratory experiments, define its dynamics, and determine the genetic changes underlying new phenotypes," says Dr. Palsson, a professor in our department who is a pioneer in microbial systems biology. Palsson and his laboratory have developed genome-scale models of microbes that have revolutionized our understanding of microbial function and are paving the way for a variety of basic and applied research programs from engineering drugs from microbes to making bio-fuels. Palsson's laboratory built the first complete model of an *E. coli* organism (Figure 7).

### Cancer Metabolism

Research from a new bioengineering faculty member, Dr. Christian Metallo, demonstrates that our cells metabolize nutrients in a different manner than has long been thought. Cells growing



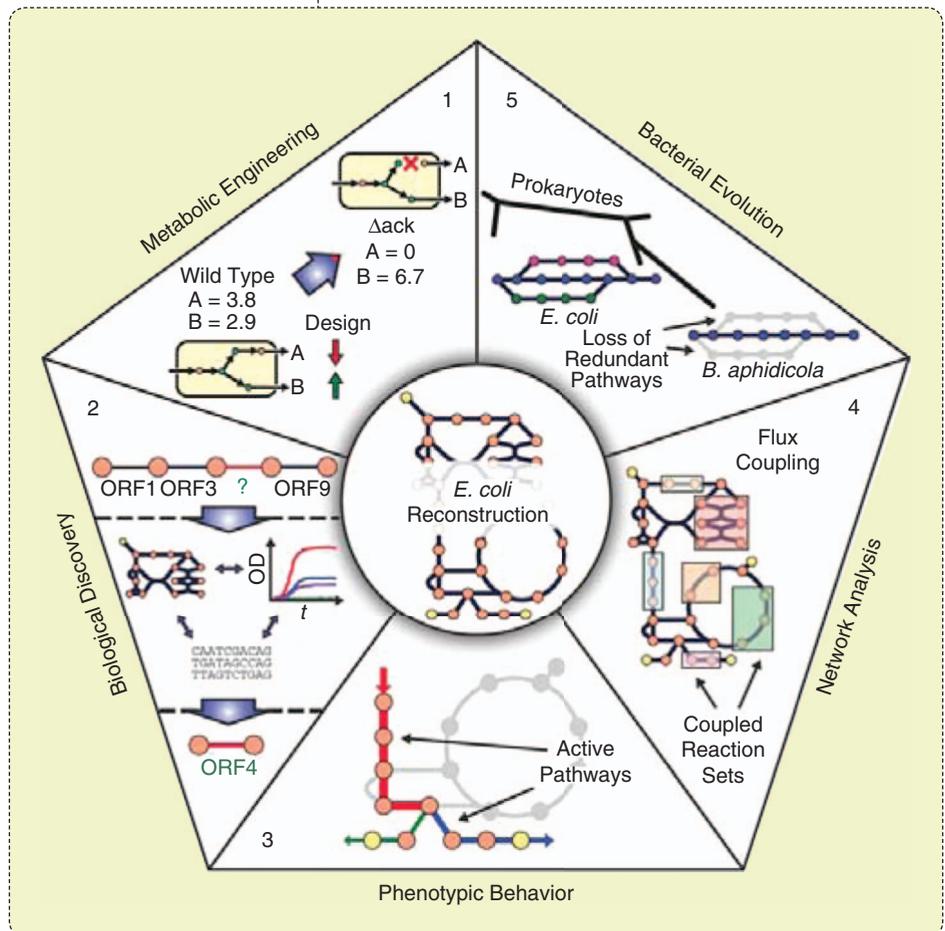
**FIGURE 6** Epidermal electronic systems can be embedded in a temporary tattoo that laminates onto and deforms with the skin [1]. (a) Backside of tattoo, (b) after transfer, (c) after integration onto skin, and (d) after deformation. (Photo courtesy of Dr. Todd Coleman, adapted from *Science*.)

under conditions similar to those inside tumors prefer to convert amino acids to lipids rather than carbohydrates. The findings change our fundamental understanding of how cells metabolize glucose and glutamine to grow, which was thought to have been settled for more than 50 years. The discovery also means doctors could have a new targets for therapeutic drugs designed to stop cancer cell growth.

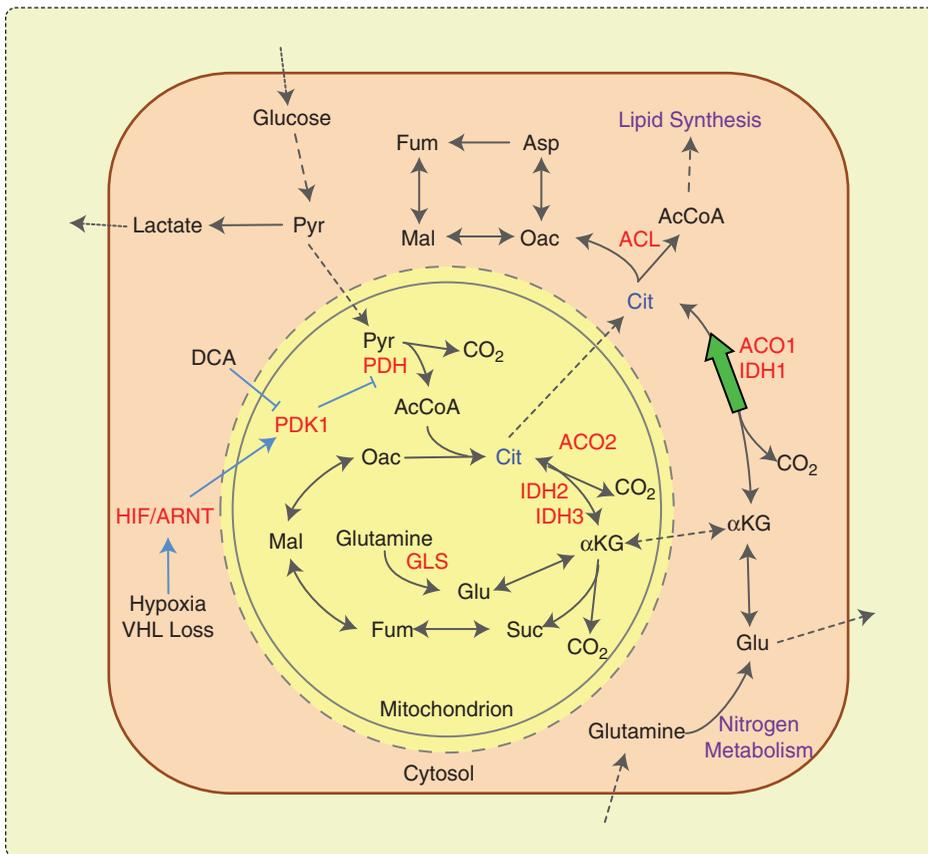
Metallo joined the Department of Bioengineering this summer after completing a postdoctoral fellowship on the metabolism of cancer cells. “We’re exploring how metabolism controls how our cells function,” said Metallo. “Dysfunctional metabolism is a very important driver of disease, but we often don’t understand the details of what’s going inside the cells and how we can fix the problems that arise when our cells and body are sick. The metabolic pathways we are studying are used by virtually all the cells in our body, so these results actually impact our understanding of metabolism in many different tissues and diseases.”

Metallo and collaborators at the Massachusetts Institute of Technology (MIT) and Massachusetts General Hospital also demonstrated that this metabolic pathway (Figure 8) uses reactions that go in the opposite direction of the well-studied Krebs cycle, which is how cells typically breath or respire. In this tumorlike environment, part of this cycle actually goes in the reverse, and cells use glutamine to make their cell membranes instead of glucose. However, kidney cells contain-

ing a mutated copy of a gene that commonly causes renal cancer always used this metabolic pathway, so enzymes which promote flux through this pathway may be new targets against this form of cancer. Interestingly, even normal cells placed in these low oxygen environments behaved in this manner, so these findings change our understanding of metabolism in many of the cells in our bodies. “What we’re starting to realize is that most diseases, from cancer to diabetes to neurodegenerative disorders, all have a metabolic component to them,” said Metallo. “What we need to do is understand how a cell or a person or an animal’s metabolism



**FIGURE 7** Palsson’s laboratory built the first complete model of an *E. coli* organism. (Image courtesy of Dr. Karsten Zengle.)



**FIGURE 8** A graphic representation of central metabolism is shown. Metallo and colleagues feed metabolic tracers labeled with isotopes to cancer cells. This approach allows them to visualize how cells metabolize their nutrients when growing under stressful conditions. (Image courtesy of Dr. Christian Metallo, adapted from *Nature*.)

is dysfunctional. That will provide us with an arsenal of new drug targets that we can use to combat disease when things go wrong.”

### Glowing, Blinking Bacteria Reveal How Cells Synchronize Biological Clocks

Biologists have long known that organisms from bacteria to humans use the 24-h cycle of light and darkness to set their biological clocks. But exactly how these clocks are synchronized at the molecular level to perform the interactions within a population of cells that depend on the precise timing of circadian rhythms is less well understood.

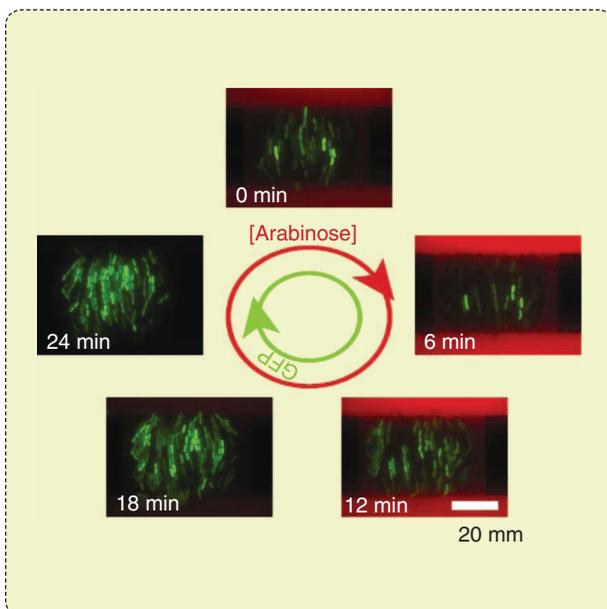
To better understand that process, Dr. Jeff Hasty in the Department of Bioengineering created a model biological system consisting of glowing, blinking *E. coli* bacteria. This simple circadian system allowed Hasty and his team to study in detail how a population of cells synchronizes their

biological clocks and enabled the researchers for the first time to describe this process mathematically.

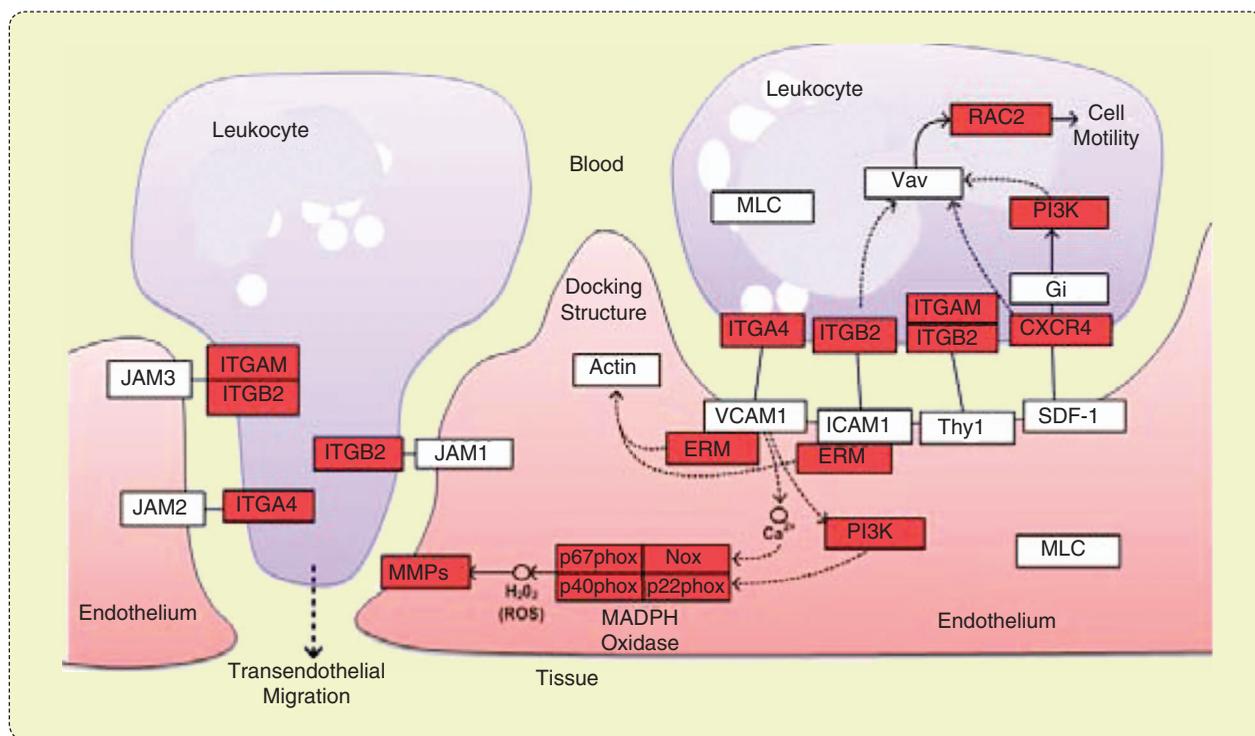
“The cells in our bodies are entrained, or synchronized, by light and would drift out of phase if not for sunlight,” said Hasty. “But understanding the phenomenon of entrainment has been difficult because it’s difficult to make measurements. The dynamics of the process involve many components and it’s tricky to precisely characterize how it works. Synthetic biology provides an excellent tool for reducing the complexity of such systems in order to quantitatively understand them from the ground up. It’s reductionism at its finest.”

To study the process of entrainment at the genetic level, Hasty and his team of researchers at UCSD’s Biocircuits Institute combined techniques from synthetic biology, microfluidic technology, and computational modeling to build a microfluidic chip with a series of chambers containing populations of *E. coli* bacteria. Within each bacterium, the genetic machinery responsible for the biological clock oscillations was tied to green fluorescent protein, which caused the bacteria to periodically fluoresce.

To simulate day and night cycles, the researchers modified the bacteria to glow and blink whenever arabinose—a chemical that triggered the oscillatory clock mechanisms of the bacteria—was flushed through the microfluidic chip (Figure 9). In this way, the scientists were able to simulate periodic day–night cycles over



**FIGURE 9** Periodic pulses of arabinose (in red) act like day and night cycles to simulate how the blinking bacteria synchronize their biological clocks. On the left, a simulation of bacteria in constant darkness reveals how the blinking bacteria are unable to synchronize their biological clocks. The in-phase and out-of-phase oscillations of the biological clocks are shown by the two graphs at the bottom.



**FIGURE 10** An example of an inflammation-immune system pathway that is altered in the pathological state. In this pathway, the genes highlighted in red are significantly upregulated in the insulin-resistant patients and partially restored in responders to treatment. (Image courtesy of Subramaniam and Hsiao, adapted from *Nature Immunology* 2012.)

a period of minutes instead of days to better understand how a population of cells synchronizes its biological clocks.

Hasty said that a similar microfluidic system, in principle, could be constructed with mammalian cells to study how human cells synchronize with light and darkness. Such genetic model systems would have important future applications because scientists have discovered that problems with the biological clock can result in many common medical problems ranging from diabetes to sleep disorders.

### Systems Medicine—The Next Challenge

The advent of genomic technologies and other methods for in vivo assays in living organisms of normal and pathological are paving the way for systems-level analysis of diseases and quantitative engineering approaches to disease prognosis and diagnosis. Researchers in the bioengineering department bring systems engineering principles to major diseases such as cancer, insulin resistance, and skeletal muscle disorders. Recently, my collaborators in the School of Medicine and I have offered the sharpest-yet picture of how core biochemical pathways in skeletal muscle cells and fat cells are altered in people who suffer from insulin resistance—a primary defect in type 2 diabetes and obesity. Taking a systems biology approach, the bioengineers and medical researchers also determined how a common class of drugs for treating insulin resistance—thiazolidinediones (TZDs)—alter these same core pathways. This led the team to uncover previously unknown effects of TZDs and insights that could lead to improved drug therapies for insulin resistance. Some of the questions we addressed in my new study are as follows: When you are insulin resistant, your metabolism suffers. If you take a TZD for your insulin resistance, will the drug

fix the dysfunction in muscle and fat tissues? Will these changes be functionally related to drug efficacy? My team discovered distinct pathway alterations that correlated with improved insulin sensitivity after TZD treatment. In fat tissue, for example, TZDs reduced inflammation and enhanced branched chain amino acid metabolism pathways in subjects who responded to drug treatment, i.e., became more insulin sensitive. My group and I identified major inflammatory and immune regulation pathways (Figure 10) that are impaired in insulin resistance that is not addressed by standard treatments. The ability to differentiate between responders and nonresponders to drugs can only be done at a systems level, and this is the quest of quantitative systems pharmacology.

These are only a few of the leading-edge research projects that are carried out by researchers in UCSD Department of Bioengineering. The newly hired faculty members at UCSD continue to inspire new vistas of research in bioengineering, and the decade ahead holds a significant promise for both advanced research and training of the next generation of leaders at the interface of engineering and medicine.

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### Reference

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