Professor Tom Webster loves to sweat the really, really small stuff.

IMAGINE THAT!

Better living through engineering.

BY KRIS CAMBRA

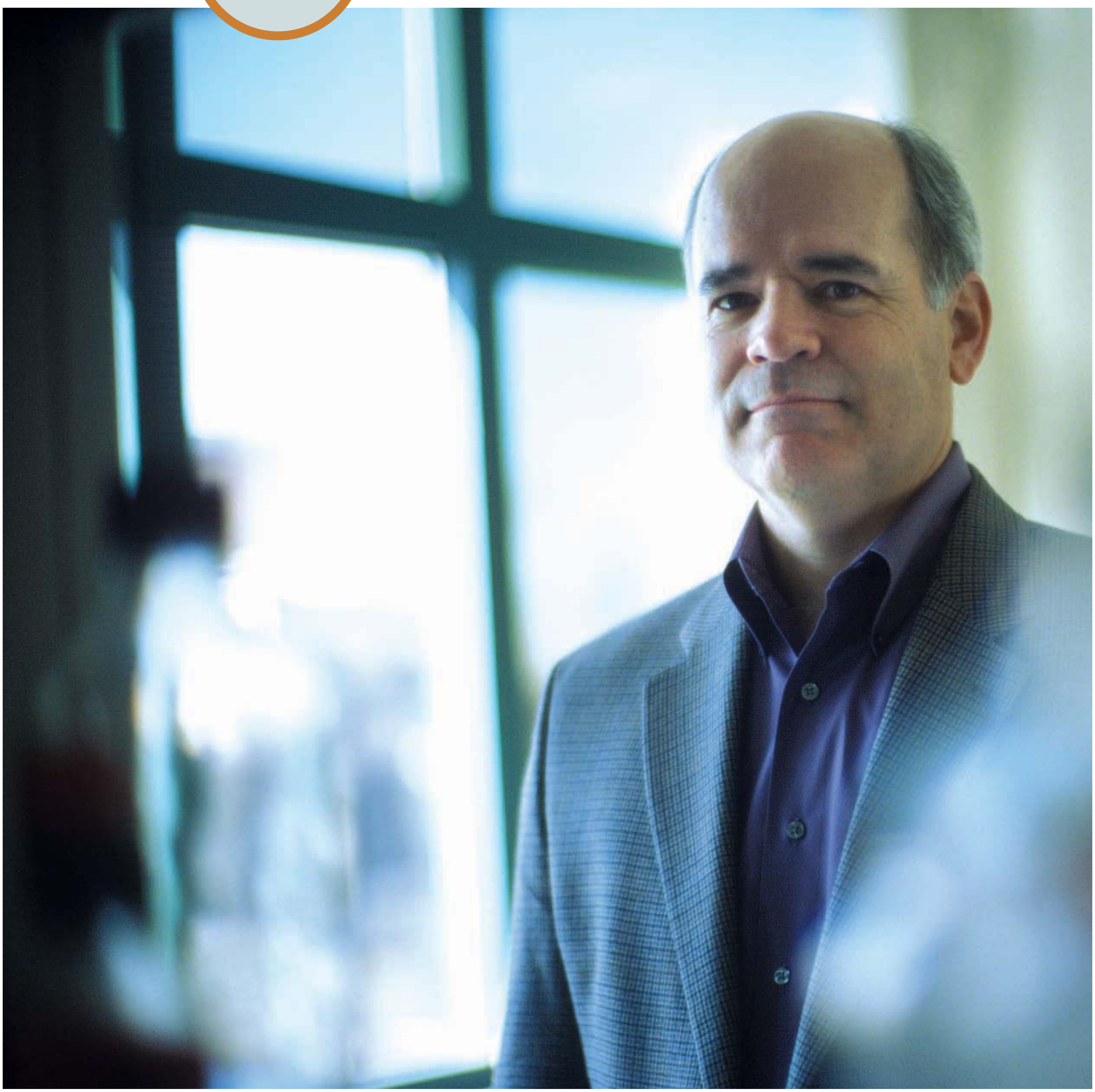
The bright blue gel on Tom Webster's desk looks more like the latest hair product than a nanomaterial with the ability to hold a human bone together. But that's what makes it such a cool trick for kids. Last July, Webster packed up the blue goo and traveled to Portland, OR, where he filmed an episode of "Dragonfly TV" for the PBS affiliate there. The show, which unravels the wonders of science for eight- to twelve-year-olds, demonstrated how nanomaterials are changing our world.

The gel could be injected into a fractured bone to help stabilize it while the bone heals. That means a patient could be applying weight to the affected area soon after the injection rather than hobbling around on crutches for weeks. As the fracture heals, the material disappears, leaving no trace.

Webster is just one of a growing group of biomedical engineers who are crossing physical and disciplinary boundaries to invent solutions to medical problems. From the earliest days of the Division of Biology and Medicine, which was founded under the guidance of the late biomedical engineer Pierre M. Galletti, biotechnology has been an area of excellence. But in recent years, on the strength of new collaborations forged by former Dean of the Division of Engineering Gregory Crawford with Alpert Medical School faculty, Brown has blossomed into a powerhouse of academic biomedical engineering, research, and entrepreneurship.

PHOTOGRAPHS BY KAREN PHILIPPI

“nANOTECHNOLOGY IS BEING



USED ALL OVER MEDICINE.

Associate Professor Jeffrey Morgan wants to improve prosthetics by creating a surface that sticks to the skin.

WICKED SMALL STUFF

Though Webster is tackling some complex and common medical problems, he's an associate professor in a materials engineering concentration in the Division of Engineering with a dual appointment in the Department of Orthopaedics. "I'm still very materials science focused but then I have this part of the lab that is biologically, clinically focused," he explains.

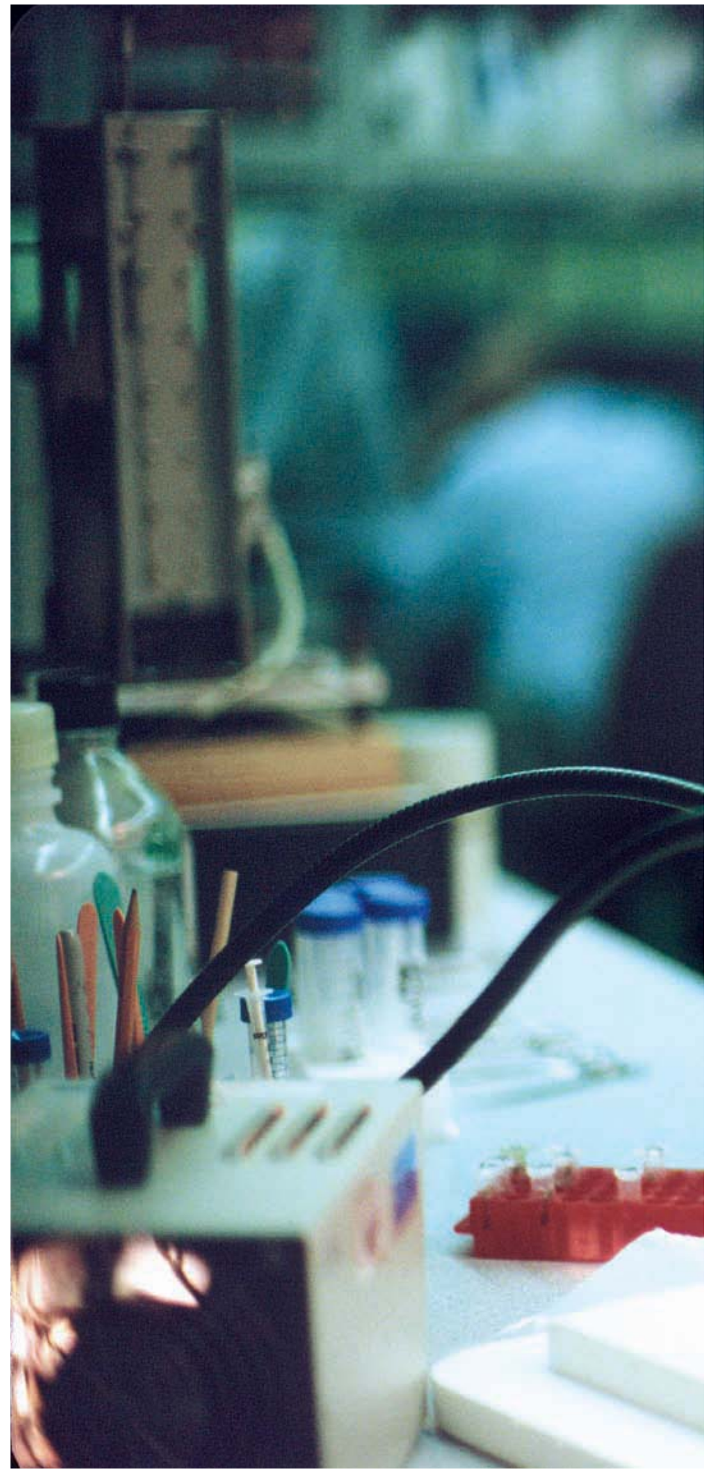
Webster hopes to promote tissue growth with nanotechnology—defined as using nanomaterials, whether they are coatings, particles, or fibers. His lab focuses on six body tissues: bone, cartilage, vascular applications, central nervous system, skin, and the bladder. Nanomaterials that promote bone and cartilage growth could help arthritis sufferers. Vascular applications include modifying the metals used for arterial stents so that they repel clots without the need for drug coatings. In the central nervous system, Webster hopes to use carbon nanotubes to promote nerve cell growth. A member of Brown's Center for Restorative and Regenerative Medicine at the Providence VA Medical Center, he is trying to help orthopedists grow new skin around prosthetic limbs that are connected directly to residual bone. Working with a former colleague at Purdue, a urologist at Riley Children's Hospital in Indianapolis, Webster has developed a nanostructured polymer that would help the bladder keep its original size after part of it is removed due to bladder cancer.

Tackling these tough medical problems requires interface with clinical faculty. "There is really only so much we can do until we talk to clinicians, to people who are in the trenches, who are facing problems with what current materials can provide for them. So we have very close connections with orthopaedic surgeons like Roy Aaron, who give us a lot of clinical input in terms of 'Yes, you're going down the right path' or 'No, that's really not how it is,'" Webster says.

What also helps is Brown's new Institute for Molecular and Nanoscale Innovation (IMNI), founded last year as an umbrella organization to support centers and collaborative research teams in targeted areas of the molecular and nanosciences. IMNI describes itself as "polydisciplinary," boasting fifty-five faculty members from nine departments. Nano, it seems, is no longer small.

"Nanotechnology is being used all over medicine. It's only getting stronger with the establishment of these new centers serving as focal points to bring these [research] groups together," Webster says.

With many applications—in eye implants, in treating cancer, for instance—nanotechnology opened a door to treating and diagnosing diseases differently through the use of hard-core engineering,



like controlling the roughness of a material. That's how these "nanosurfaces" are created.

Webster's work is driven by existing, less-than-perfect outcomes for tissue growth. "We're trying to create a material that's better than what we're implanting today," he says. He recalls learning that hip implants only last ten to fifteen years. "I said, 'That's awful!' [At age thirty-six], if I had to have my hip replaced, I'd have to go through four revision surgeries before I died.

"That was the first piece of information that was critical. You can go through each one of those tissues and see similar statistics. Take a vascular graft, a small diameter artery one less than 6 millimeters: the success rate is 25 percent after five to seven years. It cried out, 'There's got to be something you can do about this.'"

The key, it appears, is on the surface. Our bodies are composed of nanostructures. When the nanomaterials mimic that nanoroughness, new tissue growth is more successful.

"The amazing thing is that no matter what body tissue we're in, whether we're doing this for metals, polymers, or ceramics (the three classifications of materials that you can regrow tissue on), if we make a nanostructured surface, we're seeing better tissue growth on all of those materials for all of those implant applications. We're just intrigued by the promise," Webster says.

THE SKIN WE'RE IN

Webster's colleague, Jeffrey Morgan, is tackling similar issues from a different direction. An associate professor in the Department of Molecular Pharmacology, Physiology and Biotechnology, Morgan is also part of the Center for Restorative and Regenerative Medicine and is co-director of Brown's Center for Biomedical Engineering. Arto Nurmikko, of the Division of Engineering, is the Center's other director.

MORGAN'S LAB INTRODUCED

Last year, Morgan's lab made news around the globe when it introduced the first three-dimensional Petri dish. The surface of the dish is made of agarose, molded to have nooks and crannies that resemble tissue in vivo. Cells self-assemble naturally on the material and form "microtissues."

"The fields of cell biology and cell culture have been moving toward 3-D," Morgan explains. "Tissues grown in typical plastic Petri dishes are great, but they don't mimic all in vivo processes."

Like Webster, he's also been working on improving the skin growth around "osseointegrated" prosthetic limbs. These next-generation prostheses use a titanium rod that actually attaches to the remaining bone. As new bone grows around the rod, it becomes completely attached to the patient's body. The problem is, the area where the prosthesis penetrates the skin is prone to inflammation and infection. These issues affect the entire family of percutaneous devices, which include commonly used dialysis ports and indwelling catheters.

"We're trying to solve this problem by trying to make better coatings that bring about better adhesion of skin to the device and coatings that release antibacterial compounds," Morgan says.

Another potential solution is finding flexible materials that have

Biomedical engineering graduate student Kimberly Waller studies the leg of a transgenic mouse that lacks the genes to produce lubricin, a mechanism in synovial fluid that prevents cartilage wear and improves joint lubrication.

THE WORLD'S FIRST 3-D PETRI DISH.

biomechanics that are similar to skin. "We think one of the problems is the devices are very hard, the skin is fairly soft, and any place those two meet will lead to stress concentrations that will lead to breakage of any seal that will form." Biomedical engineering graduate student Brian Holt has been working with Morgan on this aspect. Holt has measured the viscoelasticity of the skin and is now finding polymers that match these viscoelastic properties.

Holt is a PhD candidate in the program, which was approved in 2002 and enrolled its first students in 2003. In five short years, Morgan says, the program has become increasingly more visible and attracts high-quality students. An undergraduate concentration is also offered, and students take advantage of opportunities to do research, publish papers, and go to conferences.

"Biomedical engineering is multidisciplinary and collaborative. It's very common for students to have a couple of mentors—co-mentorship happens," Morgan points out. Holt, for example, is co-mentored by Morgan, an expert on skin, Assistant Professor of Engineering Anubhav Tripathi, an expert in viscoelastic measurements, and Professor of Medical Science Edith Mathiowitz, an expert in polymer chemistry.

TO MARKET, TO MARKET

It's not just campus-based faculty who are on the biomedical engineering bandwagon. Clinicians, particularly in the departments of Orthopaedics and Emergency Medicine, are hot to find bioengineered solutions to the problems they face with their patients every day.

Enter Gregory Jay, MD, PhD, engineer and emergency physician. He says he has the right vantage point for bringing the research to the bedside.

"The needs [we] are addressing are smaller, like orphan needs, but you can build small research engines that improve the care of patients," Jay says.

His chief project involves joint lubrication. In 2007, he and his team showed that lubricin, a protein found in the cartilage of joints, protects against early wear and higher friction in the joint. A knockout mouse which lacks the protein, developed by Dr. Matthew Warman '78, currently at Children's Hospital Boston, has proven these findings. "This is contrary to what was previously believed, as many have thought, that hyaluronic acid was the principal lubricant in synovial fluid. We are now developing structures for the joint to prevent adhesions and damage," Jay explains.

BIOENGINEERING LENDS ITSELF TO TRANSLATIONAL RESEARCH, BUT HOW DO YOU GET THE TECHNOLOGY TO THE BEDSIDE?

This is pre-clinical research that could be used to prevent arthritis after joint trauma, cruciate ligament tears, or blunt trauma. In 2004, Jay helped form a biotech company spun out of Rhode Island Hospital that is developing an injection treatment for inflamed joints that contains lubricin.

Biomedical engineering lends itself naturally to translational research. The question for all fields is: How do you get the technology to the bedside? That's a question most MDs leave to the MBAs to figure out.

But Jay advocates for more researcher control and more institutional support, possibly from Brown's Clinical Translational Science Award, to help bring ideas to the bedside.

"When you look at the timeline to go from bench to bedside, there is a void," he says. "You have an idea, you create an animal model, there's the intellectual property piece, filing for a patent, finding grant support. Then it becomes more applied. Should I spin off a company? The answer to that is complicated, maybe yes or maybe no."

Help is also available through Small Business Technology Transfer (STTR) grants from the National Institutes of Health. Federal agencies with extramural research and development budgets over $100 million are required to set aside 2.5 percent of their budget annually for grants to small companies to conduct innovative research or research and development that has potential for commercialization and public benefit. Since the programs were mandated in 2000, $12 billion has been distributed to small businesses which share technology development with academic institutions.

Still, many faculty are uneasy about using business mechanisms to advance research. Jay advises, "If you create a conflict but always put patients first, and manage it aggressively, you should be in keeping with the desired elements of translational research as set forth by NIH."

Another spinoff company is Corum Medical, founded in 2006 by Alan R. Kivnik in association with Brown's Gregory Crawford and John McMurdy of the Division of Engineering, Jay, and Selim Suner '86 MSc'87 MD'92, of the Department of Emergency Medicine. Their product, Lumen*I*, uses biophotonics to measure hemoglobin by aiming a light at the eye. The light meter reads the patient's conjunctiva, and translates this precise color analysis into a reading of blood hemoglobin measured in grams per deciliter, making it a rapid and non-invasive test for anemia.

"The World Health Organization has called anemia the world's biggest health concern," Jay says. "This is an inexpensive technology that can be used in a fully outfitted patient care facility or in a developing country."

Jay has concentrated more on minimally invasive medical device development because the Emergency Department needs screening devices to detect medical conditions quickly and accurately. Like emergency medicine, he's all about fast.

“YOU CAN’T BE A BIOENGINEERING GRAD STUDENT AND NOT HAVE CONTACT WITH PATIENTS.”

A number of faculty have filed patents or licensed their discoveries, like Jeffrey Morgan’s 3-D Petri dish, for which the University has a patent pending. Though direct licensing in some cases does work, “investigator-driven start-ups is the way to go,” Jay advises. “That way investigators remain in control. When you license, you lose control and there are few guarantees that promising discoveries will make it to the bedside.”

MONEY TALKS

Brown’s biomedical engineering efforts have been bolstered over the years by some major external grants. A Whitaker Foundation grant to Michael Lysaght in the Department of Molecular Pharmacology, Physiology and Biotechnology, in 2001, made it possible to hire four new faculty and launch the Center for Biomedical Engineering. Lysaght was instrumental in shepherding the growth of bioengineering at Brown early in this decade. The addition of the National Institute of Biomedical Imaging and Bioengineering (NIBIB) to the NIH has also helped.

Last year, Associate Professor of Medical Science Diane Hoffman-Kim and Professor of Engineering Tayhas Palmore scored $1.27 million from NIBIB to create a biomaterial platform for growing nerve cells in complex environments. They’ll use that to understand how nerve cells navigate guidance cues after injury. Ultimately, the work will provide new information on how to promote nerve cell regeneration. Hoffman-Kim is an optics engineer and neurobiologist by training, while Palmore is an electrochemist. As biomedical engineers, they’ve had to learn to speak one another’s language.

“It’s been a lot of fun and very interesting to immerse our groups in the day-to-day realities of true interdisciplinary work,” Hoffman-Kim says. “Students with very different training backgrounds have come together with open-minded perspectives to address challenging questions about how nerves grow. The two groups push each other in good ways, and leave no assumptions unquestioned!”

The W. M. Keck Foundation recently invested $1.8 million in a new imaging system being engineered by a multidisciplinary group led by Elizabeth Brainerd, in the Department of Ecology and Evolutionary Biology. Composed of bioengineer Joseph Crisco, computer scientist David Laidlaw, orthopedic experts Braden Fleming and Douglas Moore, and biologists Stephen Gatesy, Thomas Roberts, and Sharon Swartz, the team will create a high-resolution, high-speed system that will produce three-dimensional x-rays (see *Brown Medicine*, Spring 2007). The new system, dubbed CTX, will combine the 3-D capability of CT scanners and the real-time movement tracking of cinefluoroscopy. Researchers will be able to track 3-D skeletal movements with 0.1 millimeter accuracy and see the equivalent of 1,000 CT images per second.

MORE TO COME

Selim Suner, one of four Emergency Medicine faculty members with backgrounds in engineering and a co-developer of the Lumen*I* product, credits the explosion in biomedical engineering collaborations to a landmark day-long symposium Greg Crawford (now dean of the College of Science at Notre Dame University) and Greg Jay assembled in 2005 to facilitate interactions among the faculty.

“That provided pivotal momentum in that so many ongoing projects came out of that conference,” Suner says.

His own work with students and residents bridges the divide, providing opportunities for interaction with patients. “You can’t be a bioengineering grad student and not have contact with patients.”

Webster echoes that need. “We actively seek and want that. The students in my lab like to feel that they are addressing a real clinical problem, and unless they are talking to clinicians, I don’t think they get that sense. We try to include clinicians on PhD committees, papers, and conference presentations as much as possible.”

Close and practically seamless collaboration between the engineers and the docs is what makes Brown’s biomedical engineering a rarity, and quite successful.

It’s why Webster came east from Purdue University in 2006. “At Purdue, we did have a medical school and a formal connection. But the problem is distance. It sounds trivial with technology today, but the medical school at Purdue was an hour away and that might as well have been a plane ride. It separated the clinicians from the engineers. Unless you’re on the same campus they’re not really coming together like in Brown’s model,” he says.

What would be ideal, according to Greg Jay, is a translational research building that would go even further, “allowing physicians and engineers to work near each other, be in the same building. That would really seed collaborations.”