Better Nature

At Harvard, researchers absorb the lessons of the natural world, from the human immune system to an insect-trapping plant, then tweak them to create bold, new technologies for health.

BY GREGORY MONE

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Donald Ingber, founding director of the Wyss Institute for Biologically Inspired Engineering, has made a career of bridging disciplines.
Inside the Boston headquarters of Harvard University’s Wyss Institute for Biologically Inspired Engineering, an exuberant Don Ingber weaves through a maze of chlorine-scented laboratories, glass-walled offices, and darkened rooms. In less than five minutes, Ingber, the institute’s 56-year-old director, has pointed out a mattress that could prevent life-threatening sleep apnea in newborns; simulated lungs, intestines, and hearts made of silicone rubber using microchip manufacturing technology; and a machine that forces mutations in bacteria, directing their evolution so they can produce low-cost biofuels and drugs. More than once, he stops to revel in the scope of the research. “There’s so much,” he says. “It’s just ridiculous.”

The 4-year-old institute consists of six core research areas focused on a wide range of technologies, from cancer vaccines to robotic bees that will pollinate plants. Most of the institute’s 18 core faculty members split their time between other academic departments and the Wyss, where they share multidisciplinary lab space that forces roboticists and biologists, chemists and computer scientists, clinicians and engineers to put their heads together and see their projects through.

What most distinguishes the Wyss is that its scientists treat the natural world as their inspirational springboard. It isn’t just a matter of parroting nature’s methods, but of absorbing lessons from nature and then tweaking them to create something entirely new. Wyss chemist Joanna Aizenberg, for example, borrowed the concept for a new nonstick material from the slick surface of the insect-trapping pitcher plant. But Aizenberg didn’t just copy the plant’s technique—she improved upon it, then spun out prototypes for use in the real world (see “Super Sliders,” page 6).

A New Sensibility

Some scientists are content to publish their ideas in journals and then move on to the next experiment. But for Wyss researchers, translation has always been the major point. In 2005, when Harvard convened a committee to envision the future of bioengineering, Ingber (along with Harvard bioengineer David Mooney) was chosen to lead the charge. Ingber was no stranger to discipline-hopping. His first major scientific insight had its roots in a sculpture class he took while a junior at Yale University. The professor showed the class an abstract sculpture made of wooden dowels and elastic strings. It was built according to the principles of an architectural concept known as tensegrity, in which an object’s structural stability arises from the tension among its parts.

Ingber watched as the instructor pushed down on the sculpture, flattening it out. The energy he exerted was stored in the structure, and as he let go, the sculpture popped back to its normal upright form. A few days earlier, Ingber, a biochemistry major, had seen something similar happen to cells in the cancer research lab where he worked: Cells would adhere to the bottom of culture dishes, flattening underneath and then popping back to a more rounded shape when released. Ingber became convinced that tensegrity applied to cells as well. When he theorized that pushing or squeezing them might affect their function, “people thought I was crazy,” Ingber says. But in the
The Wyss Institute’s suite of machining tools includes 3-D printers (one of which is shown at far right) that make three-dimensional objects based on computer-generated drawings. This wide view is a composite of seven photos.

decades since, his work has proven otherwise. He has demonstrated, for example, that exerting a mechanical force on a cell can activate cell signaling.

At the first committee meeting in Cambridge, Massachusetts, Ingber found himself surrounded by other scientists breaking boundaries—physicists publishing in biology journals, biologists in physics publications. The group resolved to form a research center that not only tolerated but also encouraged the same kind of interdisciplinary sensibility, and whose ideas would be inspired by the now-burgeoning knowledge about how nature builds.

Swiss-born billionaire Hansjörg Wyss, a Harvard Business School graduate, liked the idea so much that he donated the single largest gift in Harvard history, $125 million, to make it happen. The school tapped Ingber to run the show.

**Sole Searching**

Ingber and I stop inside a gleaming, 500-square-foot laboratory space with airy, high ceilings. Standing at a black counter-

**Cancer-Fighting Factory**

Bioengineer David Mooney has packed a cancer-fighting factory into what looks like a tablet of aspirin. With this new technology, he aims to improve treatment of melanoma, a deadly skin cancer that can claim up to 85 percent of patients diagnosed after metastasis. To start, Mooney’s team members biopsied a mouse tumor, isolated some of its proteins, and loaded them into the tablet, a biodegradable plastic device so porous that it is 90 percent air. They also filled the tablet with GMC-SF (granulocyte macrophage colony-stimulating factor), an inflammatory protein known to attract immune cells.

Then they implanted the tablet under the mouse’s skin. As expected, GMC-SF triggered a red alert, attracting immune cells that flooded the tiny device. Once inside, these immune cells came in contact with the tumor proteins and learned to recognize them as well. Before too long, contents of the tablet, including the trained immune cells, were trafficked to the lymph nodes, biological garrisons that help the body recognize and fight germs. Once ensconced inside, the trained immune cells taught naïve counterparts to recognize the tumor and attack. “We’re able to shuttle millions of cells through this device, generating a very potent immune response against the cancer cells,” Mooney says.

In 2009, Mooney reported that the device led to a complete regression in 40 percent of mice with metastatic melanoma. Yet the project might have stalled if not for the Wyss, where Mooney has been working with collaborators to develop efficient and low-cost manufacturing techniques and to prepare the cancer-fighting factory for human trials. The first tests, in fewer than a dozen patients, will take place at the Dana-Farber Cancer Institute this year.

Filled with tumor-specific proteins and implanted under the skin, the porous plastic disk David Mooney developed reprograms the body’s immune system to attack tumors.
Concussion in Miniature

Bioengineer Kit Parker, a major in the U.S. Army, was on duty in Afghanistan in 2009 when an explosive struck the lead vehicle in his convoy. The driver and vehicle commander suffered major concussions in the crash. Their behavior suggested the soldiers had suffered traumatic brain injuries, or TBIs, which can have devastating long-term effects, including cognitive and psychiatric disorders, seizures, and early-onset Alzheimer’s disease. “I thought to myself, ‘There’s no first aid for this,’” Parker says. If the men had suffered a broken limb, he could have tied a splint, but he knew there was no way to immediately stop the cascade of damaging chemical events happening in those soldiers’ brains. So he went back to his lab to find one himself.

The solution Parker hit upon is a “brain on a chip,” a model of the traumatized brain that is a first step toward understanding the effects of TBIs and how to halt them. To replicate the brain in miniature, Parker and his team started with an elastic substrate about the size of a fingernail, then added a layer of cells on top to mimic networks of blood vessels in the brain. To replicate the traumatic effects on vascular tissue from an improvised explosive device, Parker and his team used a high-speed motor to stretch the elastic substrate by one-fifth of an inch in just a few microseconds, then release it. When they analyzed the samples of the substrate about 90 minutes later, they found no evidence of increased cell death or even simple tearing. But they did find that the stretched cells were hypersensitive to a protein that promotes constriction of blood vessels. To Parker, the results suggest that head trauma kick-starts a chemical chain of events leading to a narrowing and reshaping of blood vessels in the brain. Over time, Parker speculates, the effect contributes to longer-term consequences such as depression and a wide variety of neurodegenerative diseases.

Parker hopes to eventually use the “brain on a chip” to test drugs that can halt the process. If a compound administered immediately after the simulated explosion were to stop the cascade of chemical events, then it could be used at the site of an injury, just as a soldier would tie a splint on a broken limb.

In Parker’s “brain on a chip” (top), brain cells cultured on silicone form neural networks (bottom). Rapidly stretching the cells at high speed mimics mechanical blast forces.
Aizenberg is now working with the Wyss Advanced Technology Team to find the first applications for her invention, dubbed slippery-liquid-infused porous surfaces, or SLIPS. One of the lubricants they tested is FDA-approved for contact with blood, so they are exploring the possibility of using the material in blood transfusions and medical devices—including Ingber’s sepsis device.

The slippery-liquid-infused porous surfaces (SLIPS, right) was inspired by the pitcher plant (inset), whose slick leaves capture insects and escort them to a watery demise.

but unfulfilled inventions. But when Collins joined the Wyss in 2010, Ingber encouraged him to revive the project. Working with the institute’s Advanced Technology Team, composed of industry veterans, Collins improved the inserts’ comfort and reined in manufacturing costs. Now, the inserts have morphed from monstrosities resembling orthotics for Andre the Giant into a sleek, small form. They are about to enter a clinical trial, and if successful, they could be sold soon afterward.

Not all Wyss inventions are so readily identifiable. The next contraption that stops Ingber looks mundane enough, with a square base, a smartphone-size LCD screen, a pair of red plastic knobs, and a few docks for blood collection tubes. He removes half of the rounded, plastic top to reveal a far more complicated interior structure filled with valves, motors, and electronics. This invention magnetically pulls pathogens out of a sample of blood to diagnose sepsis, a deadly inflammatory condition caused by a range of bacteria but also fungi and viruses. Sepsis infections kill more than 1,400 people worldwide every day. Normally it takes days for doctors to identify the causative pathogen by growing it in culture. And until they know the precise cause of the problem, they can’t choose the appropriate treatment.

The device in front of us borrows a tool of the human immune system: molecules known as opsonins, which bind to pathogens, marking them for destruction. The opsonins inside this device are genetically modified variants of naturally occurring ones, each one stuck to the surface of a microscopic magnetic bead. When infected blood courses through the machine, the opsonins latch onto pathogens. Magnets built into the device then pull on the beads, washing them out of the blood, pathogens in tow. Finally, an internal microscope scans the filtered pathogens, enabling scientists to identify the culprit or culprits so they can provide speedy treatment.

The magnetic beads were Ingber’s idea, a remnant of work he’d begun at Yale. A member of the Advanced Technology Team, Michael Super, is an expert in opsonins, so he took charge of genetically modifying the molecule to make it more efficient. Even the nuts and bolts of the machine can be traced back to Wyss production lines. Ingber snaps out a chamber that holds the blood and other fluids, explaining that it was manufactured on a 3-D printer a few steps away.

The device excites Ingber not only because it is his brainchild. From the tour, it is clear that he is proudest of the inventions that are edging out of the lab and into the world: The institute’s true measure of success, he says, will be the companies started and technologies licensed over the next five years. Ingber is confident the Wyss will succeed. “We’ve built a new model for innovation,” he declares, that should produce technology solutions “at an unprecedented rate.”

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