The Coral Whisperer

LIZ BURMESTER HOPES TO FIND A WAY TO KEEP THE WORLD'S CORAL REEFS ALIVE / BY RICH BARLOW

By the time we realize that a reef is in trouble, it's too late.

LIZ BURMESTER scrapes a bit of tissue from a colony of coral, then studies the healing process.

IN A SANCTUM THAT FEW outsiders glimpse—the laboratory at the New England Aquarium—Liz Burmester pushes through two swinging doors signed The Coral Room (or the Room of Requirement). The parenthetical, a reference to the ever-morphing chamber in the Harry Potter books, attests to the room's multiple purposes. Mesmerizing blue blubber jellyfish live here, for example, but the room is mainly about coral. Against one wall, 16 fish tanks, stacked on 2 parallel shelves, hold trays containing 400 *Astrangia poculata* (northern star corals) for Burmester's experiments.

Burmester (GRS'16) dons a white lab coat and protective glasses and takes a small specimen of a coral colony to a work counter. Using a scalpel, she scrapes a tiny bit of tissue from the colony, then cleans the wound with a Waterpik. Depending on this coral's resilience, it should heal over the next 30 to 60 days.

"I feel a little bad about it," Burmester, a vegetarian, says of the infliction, even though she knows that the coral's primitive nervous system almost certainly can't feel pain, and its cousins in the wild endure all sorts of injuries from predators, storms, and humans. Burmester talks like a loving pet owner about these

animals that look like rocks. "We feed them shrimp in a slurry," she says. "It's pretty cute. We use a turkey baster."

Corals are nature's mishmash: animals with stony skeletons and a plant-like hunger for sun-derived energy, obtained from symbiotic photosynthesizing algae living inside the coral. Dubbed the "rainforests of the sea," coral reefs house up to 25 percent of marine species—including an estimated one-tenth of the fish eaten worldwide—and that's just the beginning of their beneficence. They shelter coastline communities against storms and hurricanes; they're a source of proteins that appear to block HIV infection; and they're tourism magnets, with the United Nations estimating that a square kilometer of reef powers at least $100,000 of business annually.

IN THE LAB BURMESTER can observe her 400 northern star specimens in a wide range of conditions: with reduced algae levels, in warm water or cold, or with an injury. These observations, she hopes, will yield insight into why this species is so robust.

Yet around the world, coral reefs are dying. Pollution, coastal development, harmful fishing practices, and warming and acidifying waters from fossil fuel emissions have conspired to threaten 75 percent of reefs worldwide, a percentage expected to swell to almost 100 percent by mid-century, says John Finnerty, a College of Arts & Sciences associate professor of biology. He is a faculty mentor to Burmester, who studies *A. poculata* in hopes of finding better diagnostic tools for sick reefs. Her work is part of a collaboration, called Coral Whisperer, between BU and the Virginia-based environmental group Conservation International.

A. poculata does not congregate in huge reefs, and the largest one Burmester has seen was about the size of a tennis ball. Its value as a research stand-in for larger reef corals comes partly from its biological similarity (it's a coral, after all) and from its distinctiveness.

Like its reef-building brethren, northern star corals live in warm waters. But they also thrive in the colder depths off New England, where Burmester collects corals during scuba dives in Rhode Island. Therein lies a vital trait for scientific research: northern stars are the tough guys of the coral world, able to survive with only small amounts of algae. That's because northern stars derive less than half of their energy from algae's photosynthesis; mostly, they feed on plankton they snare with their tentacles. By contrast, reef-building corals are much more dependent on photosynthesis for food; when they undergo prolonged bleaching (algae-shedding, something brought on by the world's warming waters), they can sicken or die.

In the lab, Burmester can observe her 400 northern star specimens in a wide range of conditions that other corals could not withstand: with reduced algae levels, in warm water or cold, or with an injury. These observations, she hopes, will yield insight into why this species is so robust. Is its advantage genetic? (Burmester has specimens' genes sequenced.) Or does it gain hardiness from its symbiotic relationship with its algae?

Answering these questions, by itself, won't save the coral reefs. But the markers of a robust constitution in a northern star coral could tell scientists what to look for in reef-building corals to determine whether they're healthy or threatened. It will also inform coral restoration efforts; Finnerty says some past efforts have simply tried to move coral into new waters, with no real knowledge of their survival needs. Preliminary results from Burmester's ongoing research suggest colder water hinders recovery in wounded coral.

With current knowledge, by the time scientists realize that a reef is in trouble, it's too late. "We're more undertakers than we are doctors," says Finnerty. "By the time you realize something is wrong, it's *very* wrong.

"We're hoping for better diagnostics," he says. "We could actually go out to the field and figure out, among corals that all look ostensibly roughly the same, who's doing well, who's not doing well, and why, and who's likely to survive the next five years and who's likely to succumb. You can actually tease apart the coral's role in resilience versus the algae's role in resilience, or the algae-coral combination. Basically, we can mess with this coral in a way that we can't mess with the tropical reef-building corals."

Burmester, who will continue the research until she receives her doctorate, has been funded by BU's Warren-McLeod Fellowship for marine biology research. Her other faculty mentors are Les Kaufman, a CAS biology professor, and Randi Rotjan, a lecturer in BU's Marine Program and a New England Aquarium associate research scientist.

PHOTOGRAPHS BY JACKIE RICCIARDI; INSET COURTESY OF LIZ BURMESTER

WEB EXTRA Watch a video about Liz Burmester's coral research at bu.edu/bostonia.

Regenerative Medicine Generates Hope

WILLINGNESS TO SHARE EARNS $2.7M

BY LESLIE FRIDAY

With the motto "Advancing Science to Heal the World," the BU stem cell scientists who founded the Center for Regenerative Medicine (CReM) could be pegged as starry-eyed idealists. Or, they could be seen as scientific pioneers who are willing to sacrifice some glory and profit for the advancement of science.

What CReM codirectors Darrell Kotton, Gustavo Mostoslavsky, and George Murphy are, undisputedly, is venturesome researchers who are willing to buck the long-standing practice of jealously guarding scientific breakthroughs. The trio's "open source biology" describes their desire to share their discoveries with almost anyone, with the conviction that more brainpower will speed medical progress. In August, their efforts won a five-year $2.7 million grant from the National Heart, Lung, and Blood Institute's Division of Lung Diseases, to make CReM's bank of lung disease–specific induced pluripotent stem cells available to researchers across the country.

Open source science is unusual in any field, but in a field as competitive as regenerative medicine, it is downright radical. One young researcher training at CReM recently approached Kotton, a School of Medicine professor of medicine, seeking advice on how to answer an outside request for a vial of stem cells that took several years and hundreds of thousands of dollars in federal grants to develop. The obvious answer, the trainee assumed, was to tell the researcher to wait until the report on the discovery was published.

CReM's stem cell research focuses on treatments for cystic fibrosis, emphysema, sickle cell anemia, and amyloidosis.

Kotton saw it differently. "Our mission is to decrease the burden of human suffering on the planet, help patients, and advance new knowledge," he told the trainee. "If this competitor of ours has the same goal, then we're obligated to share this cell vial with them, because that's going to achieve our mission... which is not to get credit and to stroke our egos."

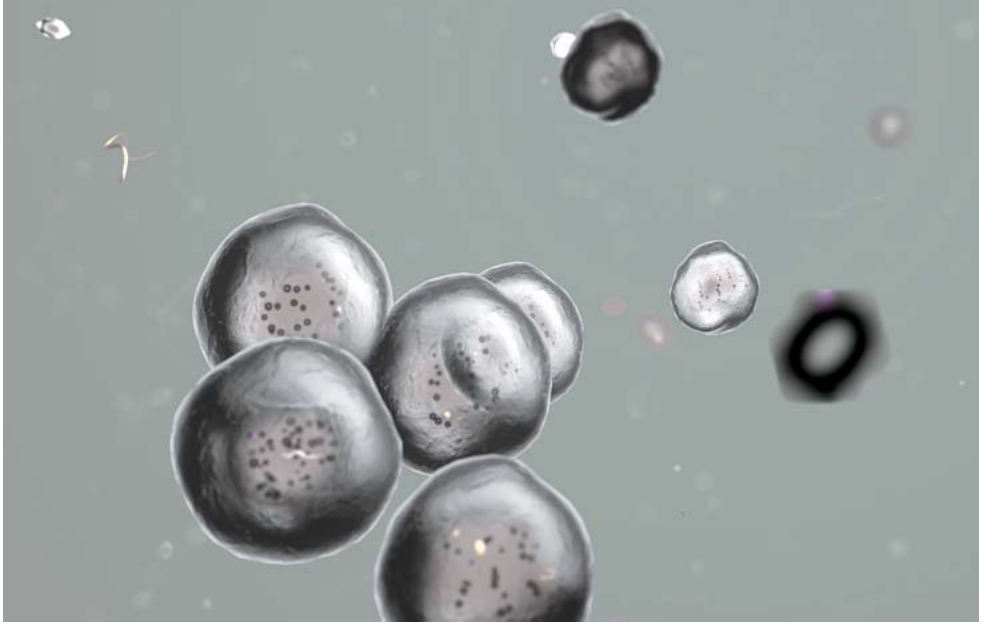
"Here's the thing that nobody talks about," says Kotton. "If you behave in this way, people in our community quickly get the idea that the BU/Boston Medical Center CReM are the good guys of science. At some point, the equation gets so lopsided that people

Stem cell scientists Gustavo Mostoslavsky (from left), Darrell Kotton, and George Murphy are willing to buck the long-standing practice of jealously guarding scientific breakthroughs.

almost feel embarrassed that they're not sharing with you and so they tell you stuff, and the whole field starts to move forward."

That was the theory anyway, and now, in fact, CReM founders are being asked by increasing numbers of researchers to collaborate on grants; foundations have begun to recognize that funding a CReM project very probably means that resulting knowledge, expertise, and reagents will be shared with other academic or nonprofit laboratories without restriction or exclusivity.

"I can't emphasize enough how unique that was for the community," says Mostoslavsky, a MED assistant professor of gastroenterology. "We have dozens of emails that testify to that, saying, 'I must tell you this is the first time in my 30 years of being a scientist that someone replied and sent me stuff the same week I asked for it.'"



In 2008, Mostoslavsky developed a more efficient tool to generate stem cells. His invention is now the industry standard.

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Still, Mostoslavsky says, there is a fine balance between freely sharing their work and protecting it once research has advanced to the clinical stage. "It's very expensive—no academic institution can support it—so we do need a company to move forward," he says, which also means they'll need patented protection of intellectual property.

SCIENTIFIC SOUL MATES

Kotton, Mostoslavsky, and Murphy met as Harvard postdoctoral fellows in the lab of stem cell scientist Richard Mulligan, who is famous for his rigorous research and forthright style of mentorship. "It was more of a sink-or-swim methodology, where you really had to prove yourself," says Murphy, a MED assistant professor of medicine. "Coming out of there, we were battle-tested and bombproof."

Kotton, Mostoslavsky, and Murphy have followed the rapid advance of stem cell biology since 2006, when scientists at the University of Kyoto reprogrammed adult cells to develop into what are called induced pluripotent stem (iPS) cells—which resemble embryonic stem cells and can be used to create heart, lung, liver, or other cells. A tinkerer at heart, Mostoslavsky was fascinated by the Kyoto process, but felt he could go one better. In 2008, he developed a more efficient tool to generate stem cells, called the stem cell cassette (STEMCCA). BU patented the tool, and it has become the industry standard.

In 2010, with STEMCCA and multiple publications under their belts, the trio established a virtual Center for Regenerative Medicine, with its own website, seminar series, and iPS cell bank carrying branded labels.

As the number of stem cell biologists, physician-researchers, and biomedical engineers grew on both BU campuses, the affectionately labeled CReM brothers felt it was time to pitch a physical center to BU President Robert A. Brown, who firmly backed the idea. Boston University and Boston Medical Center (BMC) invested jointly in the endeavor, and in November 2013, CReM opened in its newly remodeled space at 670 Albany Street.

CReM's mission is to advance stem cell research and regenerative medicine for the treatment of patients, in particular those at BMC, with diseases such as cystic fibrosis, emphysema, sickle cell anemia, and amyloidosis. Investigators collect blood or skin cell samples, usually from patients at the Alpha-1 Center, the Center of Excellence in Sickle Cell Disease, and the Amyloid Center, and reprogram them into iPS cells.

"Any cell can be reprogrammed," says Mostoslavsky. "It's a true biological rejuvenation. The cells really go back in time." Researchers now have the ability to coax iPS cells—which uniformly carry a patient's genetic mutations—into their desired cell line, such as lung, liver, or blood. (CReM's iPS cell bank stores at least 13 such cell lineages.) Mostoslavsky says the resulting cells are "still a work in progress," compared to those found in nature, but the process allows researchers to watch how an iPS-derived lung cell develops the early stages of cystic fibrosis. What took years to unfold in a patient takes days in the lab.

CReM investigators can screen drugs against patient cell lines to determine which medications are most effective for a specific genetic mutation—the "clinical trial in a test tube," as Murphy calls it. "In theory," he says, "you could develop therapies that are molded [*more*] →

PHOTOGRAPHS BY JACKIE RICCIARDI (FACING PAGE); COURTESY OF CReM (ABOVE)

← [*from page 21*]

specifically for a particular patient with a particular disease."

Developmental biology and drug screenings are now CReM's bread and butter, but its founders keep in mind what they call their long-term "Apollo projects," such as genetically engineering iPS cells to correct patients' mutations. The resulting healthy cells could be cultured and multiplied to regenerate a transplantable organ that wouldn't be rejected by the patient's body.

Kotton has been collaborating with a team of Massachusetts General Hospital researchers using a technology called lung decellularization and recellularization, which strips the organ of its cells and repopulates it with genetically engineered copies that lack the patient's original mutation. Theoretically, the reprogrammed cells could multiply, fill the lung's scaffolding, and someday be used for transplantation.

WEB EXTRA
Watch videos about how CReM researchers use iPS cells to study disease development, conduct drug screenings, and correct genetic mutations at bu.edu/bostonia.

Kotton, who thinks it will be possible eventually to re-create lungs via 3-D printing technology, is collaborating on this with Christopher Chen, a College of Engineering professor of biomedical engineering.

Meanwhile, Murphy dreams of brewing blood. "The human body makes 2.5 million red blood cells every second of every day," he says. "How does one contend with that from a research platform?" He thinks they will be able to "harness molecular cues" that exponentially increase the amount of artificial blood they can produce in vitro. Such a discovery could eliminate the need for blood donation in the United States and—even more urgent—in developing countries, where the practice is not widely accepted.

Another one of Murphy's Apollo projects is boutique blood, or the development of small batches that could be produced for people who suffer from sickle cell anemia or the blood disorder beta thalassemia and require transfusions of rare blood types.

When Good Fat Goes Bad

STUDY LOOKS AT WHAT A FAST-FOOD DIET DOES TO BROWN FAT / BY BARBARA MORAN

WHITE AND BROWN FAT ARE THE YIN AND YANG OF METABOlism. We're all familiar with white fat, the squishy stuff that bulges around our waists after a few too many doughnuts. But brown fat is more mysterious. It's the good twin—it burns energy, produces heat, and may hold clues to combating obesity.

A new study led by Kenneth Walsh, director of the School of Medicine's Whitaker Cardiovascular Institute and a MED professor of medicine, sheds light on the life—and death—of brown fat cells and illustrates the important role that brown fat plays in metabolism.

The study, published in the May *Journal of Clinical Investigation*, shows that feeding mice a high-fat, high-sugar diet causes their brown fat cells to malfunction, a process that Walsh likens to a "death spiral." While it's long been known that humans lose brown fat as they age, the study is the first to describe exactly how brown fat cells "whiten," effectively becoming more similar to white fat.

"The biggest driver today for cardiovascular disease is obesity and metabolic dysfunction," says Walsh. "That's what's bringing people into the clinic. This study further demonstrates the complex interplay between the cardiovascular and metabolic systems."

White fat looks white because it's full of molecules called lipids, which the body uses for long-term energy storage. Brown fat has lipids, too, but it is constantly using them like fuel to stoke a fire. Brown fat looks brown because it is packed with mitochondria, the tiny cellular

KENNETH WALSH, with research instructor Gladys Ngoh, is the lead author on a study that sheds light on the life and death of brown fat cells and illustrates the important role of brown fat in metabolism.