Mount Desert Island Biological Laboratory
Annual Report 2011

Discovery
Inspired by Nature
Opposite: Planaria with brains, neurons, and digestive systems labeled with fluorescent proteins. Sánchez Alvarado lab, HHMI and Stowers Institute
The Mount Desert Island Biological Laboratory is a truly innovative research institute. Every day, our scientists and students advance a new paradigm for 21st century biomedical research based on comparative biology and transdisciplinary collaboration. Our unique approach yields important new insights into tissue repair and regeneration, disease, and aging, and often challenges and in some cases overturns long-held dogmas. If you are a scientist, student, or supporter of science, I can’t think of a more exciting place to be.

MDIBL’s collegial, informal environment breaks down artificial barriers and boundaries, creating an interdisciplinary research center that attracts some of the world’s most creative and inventive scientists. Because it lacks the bureaucratic silos often present in large universities and medical centers, MDIBL excels at creating partnerships with diverse research institutions, industry, and government. Our research community consists of all kinds of scientists and physicians – cell, molecular, and evolutionary biologists; physiologists, environmental scientists, computational biologists, neuroscientists, kidney and liver specialists, to name just a few – but there are no academic departments. Nothing impedes the free flow of ideas, the lifeblood of discovery. You can read about some of these scientists and partnerships in this report.

At MDIBL, we use comparative biology to understand the fundamental processes that make our bodies function, heal, and age. We study a variety of organisms to make comparisons across species and to decipher the role of evolution in our health. Our research model is based on the premise that important insights are likely to be gleaned from new, often unexpected, sources. Our success in finding new routes to effective treatments and cures demonstrates the value of our approach.

The growing number of professional courses we offer the scientific community are quickly gaining an international following. Medical students and physicians who come to Salisbury Cove discover a deeper understanding of the diseases they treat every day and, often, an affinity for research. Our hands-on research training programs for undergraduates and high school students continue to incite a passion for science and help launch new scientific careers.

Those of us at MDIBL have also enjoyed an increasing level of engagement with the community through the MDI Science Cafés, Community Environmental Health Laboratory, and our new initiative exploring connections between science and art. Science is part of everyone’s life, and an important part of our mission is to foster the community’s curiosity, enthusiasm, and support for science. Thank you for being part of this vibrant network of investigation and discovery.
Dustin Updike, Ph.D., is MDIBL’s newest faculty member. He studies small cellular structures called germ granules in the tiny roundworm *C. elegans* to learn about pluripotency, or the ability of a cell to develop into any number of tissue types.

“The potential for regenerative medicine to treat disease is tremendous,” Updike says, “but to realize that potential, we need to understand the cellular and molecular mechanisms of tissue regeneration and how those mechanisms change with aging. MDIBL understands this and has brought together a great team of investigators to discover these mechanisms.”

Updike passed up offers from leading academic centers to move his family to Maine and come to MDIBL. “I feel the environment at MDIBL, as well as its proximity to The Jackson Laboratory, provides me with what I’ll need to make significant advances in the fields of aging and regenerative biology. I’m also amazed by the fact that I’ll be able to do this important research in one of the most beautiful places in the country.”

Sandra Rieger, Ph.D., joined the Kathryn W. Davis Center for Regenerative Biology and Medicine at MDIBL in November 2011. Her laboratory investigates the interplay between nerve growth and wound healing, a matter of vital importance to the millions of people who suffer from peripheral neuropathy, a common complication of diabetes that often results in amputations.

“MDIBL offers exceptional support and mentorship for new investigators setting up their own labs and establishing their research priorities,” Rieger says. “And the visiting scientist program means we work with a wide range of outstanding scientists. I’ve already started major collaborations with new colleagues.” (See p. 9)

Rieger’s laboratory was the first to move into the new Davis research building. As MDIBL grows, it offers unique opportunities for new faculty. “It’s a great institution, and I feel that I can be part of it’s development and help shape it,” Rieger says. “That’s exciting.”
From Basic Science to Medical Breakthroughs

MDIBL scientists discover mechanisms that control biological activity by taking a comparative approach, studying fundamental processes in a variety of organisms. These advances in “basic” science can lead to new understandings of human disease and injury, and often generate medical treatments and diagnostic tools that improve or save lives. Physicians like James Boyer of the Yale Medical School have always been well represented among MDIBL researchers, and partnerships with medical centers, such as the reMAINE Healthy initiative, mean that discoveries made at MDIBL can be “translated” into new, effective clinical practices.

Comparative biology makes it easier to learn how genes, cells, and organs function. It can speed the rate of discovery and save money. As opposed to mammals, organisms such as zebrafish, the roundworm *C. elegans*, and sea urchins readily produce thousands of offspring and mature quickly. Their genes are easy to manipulate and their embryos transparent, allowing cellular processes to be easily visualized and studied. Mammals have a limited ability to regenerate their limbs and organs, so comparative biology offers the best way to learn about the extraordinary healing powers in "simpler" organisms, and how to possibly restore those powers in humans.
Teaming Up to Fight Kidney Disease

For the first time, scientists from MDIBL, The Jackson Laboratory, and the Maine Medical Center Research Institute (MMCRI) have joined forces with physicians at the Maine Medical Center in Portland to tackle a major health challenge. “Chronic kidney disease or CKD affects an estimated one out of nine adults and requires substantial national healthcare expenditures,” says Mark Parker, M.D., director of nephrology and transplantation at the Maine Medical Center in Portland. “We have formed a unique consortium in kidney research and have the potential to provide real innovations for kidney care.”

This alliance, known as reMAINE Healthy, highlights the benefits of comparative biology. Ron Korstanje, a research scientist at Jackson, initially identified genes in mice that might be involved in kidney disease. He then collaborated with Hermann Haller, director of the department of nephrology at the Hannover Medical School in Germany, and his research group at MDIBL to screen the candidate genes in zebrafish to determine if they cause kidney problems. Using zebrafish to prioritize the genes of interest saves both time and money.

Now the Maine Medical Center is preparing a study with the help of patients with CKD to see if markers for these genes can lead to better diagnostic and treatment tools. “The reMAINE Healthy program is a wonderful example of how collegial relations between investigators and leaders at our Maine research institutions can serve to advance health care,” says Donald St. Germain, director of MMCRI. “MDIBL continues to showcase the great value in bringing together innovative investigators who focus beyond their immediate interests to the larger issues in biology and medicine. The Laboratory is a wonderful asset and collaborative partner, not only for those of us in Maine, but far beyond our immediate borders.”

From Skates to Patients

James Boyer, M.D., professor and former director of the Liver Center at Yale Medical School and current chair of the MDIBL Board of Trustees, and Shi-Ying Cai, D.Sc., a research scientist in Boyer’s lab, have been studying skates at MDIBL for years. When Cai discovered a protein in the skate that helps the liver dispose of excess bile, he found that it was extremely sensitive to retinoic acid. Subsequent tests on human cells and rats demonstrated that they had found an effective way to turn off bile production in the liver.

Now their discovery is being tested in clinical trials as a treatment for a liver disease called sclerosing cholangitis, in which the liver is unable to rid itself of excess bile. There is currently no accepted treatment for the disease, and patients often end up requiring liver transplants. In the spring of 2012, however, Yale and the Mayo Clinic in Minnesota began enrolling patients for a 90-day trial using retinoic acid. Boyer says the “very preliminary” results look promising.

“For forty years I’ve worked on the basic biology of the bile secretory system in the liver,” Boyer adds, “as well as treating patients with sclerosing cholangitis. So to be able to have made a discovery scientifically from the bench that is now being taken to the bedside is very exciting. That’s what we all go into this business to do, and it doesn’t happen very often. And in this case, it wouldn’t have happened without MDIBL.”

Above left: Skate  
Left: Donald St. Germain and Mark Parker of reMAINE Healthy.
Exceptional physicians have a clear understanding of basic science and are able to integrate that knowledge into their care of patients. As Shoshana Herzig, M.D., of Harvard Medical School and her co-authors point out in a recent article about medical education at MDIBL, “A deep understanding of physiology and the underlying mechanisms of disease allows a physician to assimilate and apply knowledge from one situation to another slightly different, but conceptually similar, situation.”

There is growing concern that today’s medical school curriculum has not kept pace with the expanding scientific knowledge base of medicine and fails to reflect the importance of science in the practice of medicine. That’s why MDIBL’s courses for first-year medical students and residents are so important. Students from medical schools at Yale, University of Pittsburgh, Dartmouth, and University of Vermont as well as residents from Harvard’s Beth Israel Deaconess Medical Center and New York University come to MDIBL for a week each year to conduct experiments in comparative physiology. For many, it is their first real laboratory experience, opening their eyes to the possible rewards of a research career and illuminating the process of discovery that continues to transform the practice of medicine.

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Thinking Clearly

As an incoming chief resident in 2006, Shoshana Herzig, M.D., was enlisted to help plan the first MDIBL course for residents at the Beth Israel Deaconess Medical Center in Boston and “keep it medically relevant.” She has been a part of the course ever since. “We don’t think there’s anything else like this in other parts of the country,” she says. “That’s why we wrote the article.” Published in Academic Medicine, the paper outlines the rationale and methods used in the immersive comparative physiology course. “It’s definitely generated interest,” she reports.

Herzig now balances a hospitalist practice with academic work at Harvard Medical School, where she finds her approach altered by her experience with the MDIBL course. “The goal of the course, from our perspective, is to get residents to think more mechanistically and physiologically in their care of patients. It’s certainly had that impact on me.”

While she hopes other medical centers will initiate similar programs for their physicians, Herzig says the MDIBL experience will be hard to duplicate. “It’s a fantastic, state-of-the-art lab environment. The communal atmosphere encourages an exchange of ideas and doubly fosters the goals that we’re trying to achieve.” Some of MDIBL’s qualities are difficult to quantify. “There’s something about just being up there with the fresh Maine air and the ocean around you, with nothing else interfering in whatever analyses you’re doing. There’s a clarity, I think, that just makes your brain work better.”

A Transformative Research Experience

A first-year medical student at Yale, Jonathan Lorgunpai says he signed up for MDIBL’s one-week course in comparative physiology because he wanted to develop his research skills. “Also,” he says, “the upperclassmen that had taken the MDIBL course in previous years told me this was one of the most rewarding courses they’d taken in med school.”

The course did not disappoint. “I learned so much more and gained so much more confidence in my ability to think as a scientist than I thought was possible in a one-week course.” Though he had been involved in several research projects before coming to MDIBL, Jonathan reports, he had only taken one project from start to finish. “This experience was definitely different. The course was set up in such a way that we got to take part in the entire research process for a project, from coming up with a research question to analyzing and presenting the results. At MDIBL, the focus was on how to creatively and critically think about research questions and designs, as opposed to simply following protocols for various experimental techniques.”

The effects of his week at MDIBL will be long-lasting, Jonathan expects. “I believe that as a result of taking this course, I will be a much bolder researcher, daring to tackle questions that are more complex and significant than I would have pursued if I hadn’t attended the course.”
Collaboration and the cross-fertilization of ideas are hallmarks of MDIBL. The community is defined by its relatively small size, informality, interdisciplinary makeup, and collegiality, as well as its connection to nature. There are no academic departments or barriers; nothing separates scientists who use different model organisms or have different academic backgrounds and expertise. The campus is designed to promote casual interaction, and frequent seminars and chalk talks keep researchers and students in touch with each other’s latest projects and plans.

The visiting scientist program brings extraordinary vitality and vibrancy to the campus. Each year, fifty to sixty scientists come to MDIBL from around the world to collaborate with the resident faculty and each other. The cumulative effect is to give MDIBL the scope of a large institution, while maintaining the retreat-like atmosphere of a smaller center. This rich research environment spurs innovation and discovery, and propels MDIBL’s exceptional education programs.
Common Interests and New Collaborations

Malcolm Maden, Ph.D., a professor of biology at the University of Florida, has studied salamanders, mice (wild and lab-bred), rats, zebrafish, and chick embryos to identify the mechanisms of regeneration and to try to understand why humans have such limited regenerative capacity. So it was only fitting that Maden come to MDIBL to work with other researchers in the Davis Center for Regenerative Biology and Medicine as the Thomas H. Maren Visiting Fellow.

In particular, Maden came to MDIBL to collaborate with Sandra Rieger, MDIBL assistant professor. “We’ve been working on the role of nerves in regenerating tissue and looking at this new signaling pathway based on hydrogen peroxide,” Maden says. “She’s already studied that in zebrafish tail wounds, so I’ve been looking at it in axolotls, the salamander species I’ve been working on for a long time.”

Once he arrived, Maden discovered more reasons to be at MDIBL. “I knew about Voot Yin’s work on regeneration in zebrafish before, but I’ve never talked about it in such detail. So that was another benefit of coming here.” David Evans, a colleague of Maden’s at the University of Florida who has been coming to MDIBL for 40 years, urged Maden to apply for the Maren Fellowship. “I’m glad he did,” Maden says. “A community of committed researchers is a good place to be. And it’s beautiful. It’s great to be put into such an environment.”

New Approaches to Understanding the Health Effects of Arsenic

“Nobody really understands how very low doses of arsenic affect cell function,” says Bruce Stanton, Ph.D., a visiting professor at MDIBL since 1997 and professor at the Geisel School of Medicine at Dartmouth, where he also directs the Dartmouth Toxic Metals Superfund Research Program. “But after hearing Voot Yin talk about his work with Ben King (two MDIBL faculty members) on microRNAs in zebrafish, it seemed to me that it was at least possible that arsenic works through microRNAs.” MicroRNAs are small molecules that regulate gene activity.

By “low doses” of arsenic, Stanton means amounts less than even one part per billion, or the kind of doses found in people who drink well water in the states of Maine and New Hampshire. Studies have shown that people exposed to arsenic in drinking water have a fifty-fold increase in respiratory disease.

After consulting with Yin and King, Stanton conducted experiments that showed that part of the effect of arsenic is indeed mediated through the regulation of microRNAs. Those microRNAs affect the production of cytokines, proteins that recruit immune cells to eliminate the bacteria in lungs.

“Our experiments say, yes, these low doses do have an effect on the lung immune system and the ability to clear bacteria. The concept of looking at microRNAs likely never would have occurred to me had I not heard Voot give a seminar on his work. That’s the power of MDIBL.”
New Models for Research and Partnership

“MDIBL is nimble and forward thinking, willing to take risks and think outside the box, and able to adapt quickly to a dramatically changing climate for science and the biotech and pharmaceutical industry,” says Lew Kinter, a longtime friend of the Lab and a senior director at the pharmaceutical company, AstraZeneca. As a result of its institutional agility, MDIBL is accelerating scientific innovation and building new partnerships with industry, academic medical centers, and government agencies.

These partnerships help bring discoveries made in MDIBL’s laboratories to fruition as new treatments and diagnostic tools that benefit all humanity. With support from the U.S. Department of Defense, MDIBL scientists are investigating mechanisms that may make severe wounds less disabling. Partnerships with industry and academic medical centers, such as the reMAINE Healthy initiative, allow the translation of basic research findings into efforts focused on developing new therapeutics.

MDIBL’s growing focus on regeneration and aging means that its scientists are making discoveries that will have major implications for treating such difficult conditions as Alzheimer’s, traumatic brain injury, heart attacks, and stroke – and make the Lab an exceptional partner for individuals and organizations committed to improving human health.
Adventurous Perspectives on Regeneration

“Through its comparative regenerative biology program, MDIBL under Dr. Kevin Strange’s leadership has positioned itself to occupy an important place at the table of biomedical research,” says Alejandro Sánchez Alvarado, Ph.D., an investigator with the Howard Hughes Medical Institute and Stowers Institute for Medical Research. Sánchez Alvarado was instrumental in developing the planaria, a flatworm capable of regenerating an entire organism from a fragment 1/279th the size of the original animal, as a powerful model for studying the mechanics of regeneration.

As a member of MDIBL’s Board of Scientific Counselors, Sánchez Alvarado plays a vital role in shaping and evaluating the Lab’s research programs. He’s a firm believer in approaching biological problems as an explorer, rather than a hunter, and bemoans the current funding climate that often expects researchers to know exactly what they’re looking for. In a recent profile in the March 2012 issue of The Scientist, he says, “There are all these pejorative terms for exploration, like ‘fishing expedition,’ but it’s a valid way to do science. [To] suggest that we have a thorough comprehension of all the fundamental principles that make life possible is fanciful.”

As one of the leaders in the field, Sánchez Alvarado knows that “regeneration remains one of the last untamed frontiers of developmental biology. It is amongst the oldest biological problems known to humankind, yet we’re still waiting for a satisfactory mechanistic explanation. It is my firm belief that this is the time to plumb the molecular depths of regeneration using non-traditional model systems.”

Left: Alejandro Sánchez Alvarado, who developed planaria (below and opposite) as a model organism for regeneration

At the Forefront of 21st Century Science

Lew Kinter, Ph.D., has spent over thirty years applying his training (Harvard doctorate in physiology) to discovering and developing new drugs and diagnostic tools, mentoring young scientists in non-academic careers, and developing non-traditional working relationships between academia and industry. He has led research and development efforts at numerous leading pharmaceutical companies. Growing up, he assisted his father, the late William Kinter, Ph.D., in his MDIBL laboratory, where the senior Kinter studied kidney function and the physiological effects of environmental pollutants.

“Because of its culture, MDIBL is in an excellent position to participate and develop new paradigms for 21st century biomedical research,” Kinter says. “The traditional relationships between large and small companies, academia, and government no longer work, and the ‘gloves are now off’ to find new relationships and business models. The Lab’s growing focus on using genetically tractable model organisms like zebrafish and C. elegans, and its growth of regenerative biology research puts it at the forefront of biomedical science. Regenerative biology has enormous potential for improving human health, and the Lab has strong leadership and a clear vision of where it wants to go.”
# The Mount Desert Island Biological Laboratory

**Statement of Financial Position**

**December 31, 2011**

(with comparative financial information as of December 31, 2010*)

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<thead>
<tr>
<th>ASSETS</th>
<th>2011</th>
<th>2010*</th>
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<td>Cash &amp; Cash Equivalents</td>
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<td><strong>17,914,380</strong></td>
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| Total Liabilities & Net Assets | 26,338,065  | 24,223,771  |

* prior year has been restated
The Mount Desert Island Biological Laboratory

Statement of Activities
Year ended December 31, 2011
(with summarized financial information for the year ended December 31, 2010*)

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<tr>
<th>OPERATING ACTIVITIES</th>
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<th>2010*</th>
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<th>Operating Expenses</th>
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<td>3,114,356</td>
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| Change in Net Assets from Operating Activities | (658,008) | 358,066 | 114,771 | (185,171) | (493,748) |

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<td>(61,722)</td>
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<td>(913,537)</td>
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| Total Change in Net Assets | 2,905,518 | (555,471) | 222,271 | 2,572,318 | 57,332 |
| Net Assets, Beginning of Year | 7,930,202 | 7,110,362 | 2,873,816 | 17,914,380 | 17,857,048 |
| Net Assets, End of Year | 10,835,720 | 6,554,891 | 3,096,087 | 20,486,698 | 17,914,380 |

* prior year has been restated

The financial statements of the Mount Desert Island Biological Laboratory for the fiscal year ending December 31, 2011, were audited by Horton, McFarland, and Veysey, LLC, and are available upon request.
2011 Officers/Trustees
As of July 28, 2011

James L. Boyer, M.D.
Chairman
Edward J. Benz, Jr., M.D.
Vice Chairman
I. Wistar Morris III
Treasurer
Alan B. Miller, Esq.
Secretary
Kevin Strange, Ph.D.
Director, ex officio

Peter J. Allen, M.D.
Phoebe C. Boyer*
Terence C. Boylan*
Maximiliaan J. Brenninkmeyer
Thomas R. Cech, Ph.D.
John A. Hays*
Richard M. Hays, M.D.
Frank L. Hohmann III
Barbara Kent, Ph.D.
Emily Leeser
Steen L. Meryweather
Margaret A. Myers, M.D.*
John B. Overton, Esq.
Bruce A. Stanton, Ph.D.
Clare Stone

Board of Scientific Counselors

Barbara Beltz, Ph.D.
Wellesley College

Marianne Bronner, Ph.D.
California Institute of Technology

Dennis Brown, Ph.D.
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