MBL

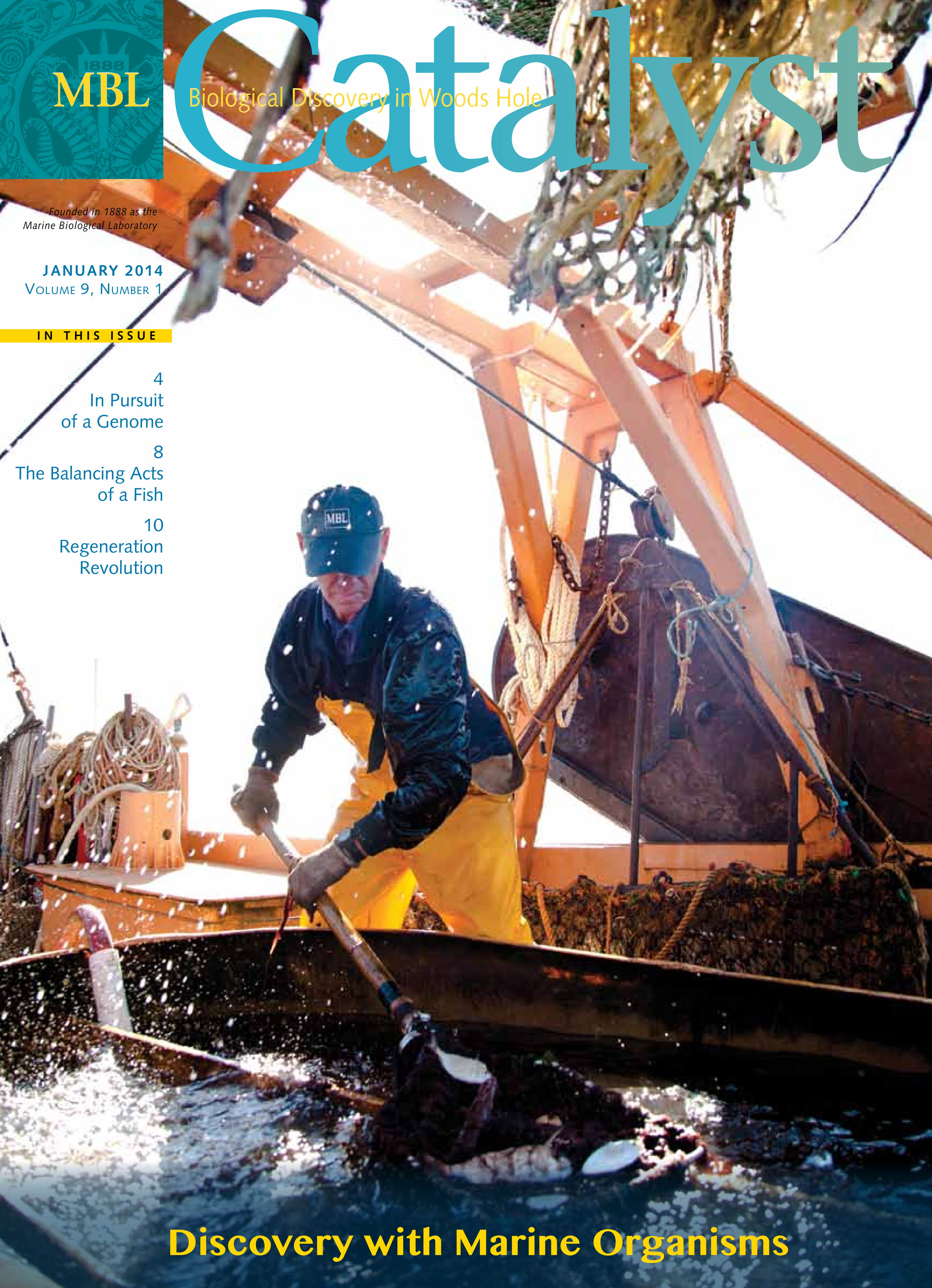
Catalyst

Biological Discovery in Woods Hole

Founded in 1888 as the Marine Biological Laboratory

JANUARY 2014
VOLUME 9, NUMBER 1

IN THIS ISSUE



Discovery with Marine Organisms

MBL **Catalyst**

JANUARY 2014 VOLUME 9, NUMBER 1

MBL Catalyst is published twice yearly by the Office of Communications at the Marine Biological Laboratory (MBL) in Woods Hole, Massachusetts. The MBL is dedicated to scientific discovery and improving the human condition through research and education in biology, biomedicine, and environmental science. Founded in Woods Hole, Massachusetts, in 1888, the MBL is a private, nonprofit institution and an affiliate of the University of Chicago.

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Images: *inside cover:* left background (Daniel Cojanu); MBL President and Director Joan Ruderman (Bachrach Studios); *P. 1*: gulls over harbor; smooth dogfish (*Mustelus canis*) (Daniel Cojanu); sea star illustrations (Mark Laughlin); toadfish (*Opsanus tau*) (Volker Steger); *P. 2*: The collecting net full of marine organisms on the deck of the *Gemma* (Daniel Cojanu); *P. 3*: red beard sea sponge (*Microciona prolifera*) (Xavier Fernández-Busquets); *P. 4*: squid (*Loligo pealei*) illustration (Barbara Harmon); *P. 6*: Frank R. Lillie (MBL Archives); marine plastic debris (Erik Zettler); *P. 7*: moon jellyfish (*Aurelia aurita*) (Brad Gemmell); *Xenopus* neural tube with ZIP12 RNA in blue (Mark Messerli); *P. 8*: toadfish (*Opsanus tau*) (Volker Steger); *P. 9*: MBL REU student (Allen Mensinger); *P. 10*: Planarian: nervous system in green, gut in red, photoreceptor eyes in yellow (Sarah Elliott and Lisandro Maya-Ramos, 2013 MBL Embryology course); sea star illustrations (Mark Laughlin); *P. 11*: Alejandro Sánchez Alvarado (Kevin Wolf/HHMI); *Xenopus* (Encyclopedia of Life); *P. 12*: David Remsen (Tom Kleindinst); *R/V Gemma* (Daniel Cojanu); eastern sea anemone (Andrew J. Martinez); smooth dogfish (*Mustelus canis*) (Daniel Cojanu); *P. 13*: MBL collector William Grossman unloading squid (Daniel Cojanu); *P. 14*: marine protist *Acantharian* (Linda Amaral Zettler); 2013 Physiology course students (Tom Kleindinst); zebrafish (*Danio rerio*) embryo (MBL Neural Systems & Behavior course); *P. 15*: DNA illustration (Dreamstime.com); *P. 16*: Jonathan Gitlin (Tom Kleindinst); *P. 17*: skate egg case (Tom Kleindinst); Selachii (Elasmobranchii) wall chart (Carl Chun, Rudolf Leuckart); *back cover*: Eel Pond and Woods Hole village (Tom Kleindinst)

ABOUT THE COVER: William W. Klimm III, captain of the MBL's collecting boat, the *R/V Gemma*, handles the catch at sea. (Daniel Cojanu)

Online extras: For full image descriptions, supplemental materials, and other information related to this issue, visit:

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FROM THE DIRECTOR

Dear Friends,

Since 1836, the windows of Candle House have looked out over many things, some familiar and some new and full of potential. The past year was an extraordinarily significant one at the MBL, marking both our 125th anniversary and our historic affiliation with the University of Chicago. This new partnership promises to bring exciting new initiatives in education and research to the MBL, with a renewed focus on marine organisms.

Constructed of beautiful granite, Candle House was built at the height of the whaling industry. Looking south, ships docked in the harbor across from Candle House; whales were hauled up and their oil was turned into candles inside the building's stone walls. Last summer, the sculpture "Flukes" by the artist Gordon Gund was installed in Waterfront Park on the harbor, reminding us of the many things that remain to be discovered beneath the surface of the ocean and the continuing power of marine organisms to reveal some of the secrets of life.

Today, those south-facing windows look directly onto the docks of the Woods Hole Oceanographic Institution, founded in 1930 through the efforts of MBL Director Frank R. Lillie and others. A launching point for many research vessels engaged in the systematic study of the ocean, last fall the updated submersible *Alvin* was sent off, bringing back memories of spectacular new species discovered by now-MBL Speaker Colleen Cavanaugh in the 1990s in the original *Alvin*.

Looking west, Crane Building is Candle House's nearest neighbor. Built in 1913, it featured laboratories, a distribution system for seawater, and a library. One hundred years later, it is still home to biologists who carry out experiments that tackle questions of basic biological and biomedical relevance, many using marine organisms.

The view to the north includes the MBL's major collecting vessel, the *Gemma*, perhaps the best entrée to this issue of *MBL Catalyst*. Under captain Bill Klimm's direction for many years, the *Gemma* has brought back extraordinary numbers of marine organisms for use in MBL courses, the visiting investigator program, and resident scientific research. On many days, you can see the *Gemma* pull in with its precious cargoes, including live, healthy squid. A call from the vessel will have alerted squid users, who rush over to meet the boat in order to get the animals at their peak. You also see the smaller boats, the trailers, the trucks and—most importantly—the dedicated collecting staff members who know where and when to go to get all sorts of marine organisms that we scientists have requested. Finally, you can see the extraordinary Marine Resources building. Outside, its warm granite façade mirrors the original stones used for Candle House. Inside, a wizardry of plumbing, heating, cooling and aeration machinery, monitors, alarms, tanks and a variety of gizmos create a magical place where an amazing array of marine organisms stand ready to help solve the next generation of biological and biomedical questions.

Many thanks to Jonathan Gitlin, who was a quick and thoughtful Guest Science Editor for this issue of *MBL Catalyst*. Jonathan became the MBL's Deputy Director of Research and Programs in October, and also directs the MBL's Bell Center for Regenerative Biology and Tissue Engineering.

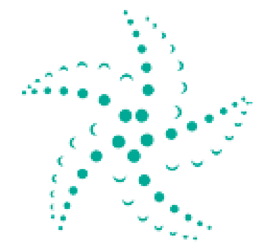
Joan Ruderman

Joan Ruderman, *President and Director*

IN THIS ISSUE

Catalyst

FEATURES



DEPARTMENTS

MBL

Discovery With Marine Organisms

September is a productive season on Cape Cod in many ways. The cranberries are ripe, ready for harvest mid-month. Clams, haddock, and sea scallops are plentiful; the oysters are plump. The schools reopen and fill with students.

In Woods Hole, amid other comings and goings, the "acorn worm group" reunites at the MBL. Arriving from several places—often Harvard, Stanford, Caltech, and Georgetown—these scientists pursue different research questions, yet congenially share lab space and resources. What draws them to the MBL is the spawning season of the acorn worm.

Throughout the month, mature acorn worms burrow into the sand near Woods Hole, usually in sheltered bays and other brackish sites. "We dig them up, bring them back to the lab, separate the males and females, and keep them alive in seawater," says Jessica Gray of Harvard Medical School. Through time-tested methods, many developed at the MBL, the organisms are stimulated to release their copious eggs or sperm. The scientists can then fertilize the eggs *in vitro* and observe the cascade of changes as the embryo develops.

These scientists are interested in the acorn worm not for its own sake, but to learn more about human evolution and development. Though little more than a squishy sac, the acorn worm sits in an interesting place in the evolutionary tree: it shares a common ancestor with the vertebrates. Moreover, its genome has been sequenced, so it can be compared with that of humans. Recent work has led to fascinating discoveries of shared genetic "parts" between this ancient organism and humans, and revealed ancient developmental patterns that, though evolutionarily changed, still make us tick today.

For generations of MBL scientists, marine organisms have offered deep insights on basic biological processes and what happens when they go awry. Scientists draw on the expertise in the MBL's Marine Resources Department, an advanced facility designed for collecting, maintaining, and culturing more than two hundred organisms for biological and biomedical research. As genome sequencing has become easier and cheaper, the special advantages of using marine and other aquatic organisms to address specific evolutionary and biomedical questions have multiplied.

MBL scientist Jennifer Morgan and colleagues, for instance, helped sequence the sea lamprey genome last year, which brought immediate rewards for her research on spinal cord repair. Among other discoveries, the team found lamprey genes that are linked to human disorders including Alzheimer's disease, Parkinson's disease, and spinal cord injury. This greatly enhances Morgan's use of lamprey, she says, "as a powerful model to drive forward our molecular understanding of human neurodegenerative disease and neurological disorders."

Other MBL scientists seek to understand, and even replicate, some strikingly useful animal feature, such as instantly camouflaging skin or the ability to regenerate a lost limb. In "discovery science" like this, having whole genome sequences can open many new doors for investigation.

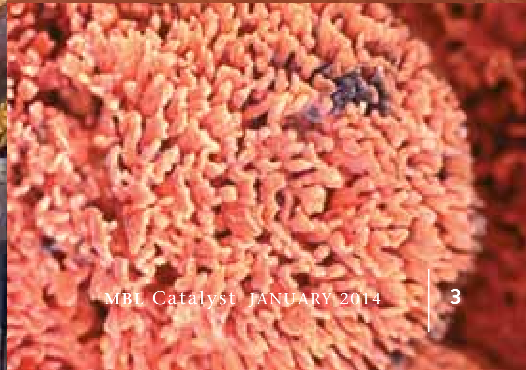
This issue of *MBL Catalyst* highlights several aspects of MBL research with marine and aquatic organisms. Some of the most long-valued models have been sequenced, while others await that day. "Ideally, we will sequence them all," says Jonathan Gitlin, the MBL's Deputy Director of Research and Programs. "The more species we sequence, the more we find out." • —DK

Surprises From the First Decade of Marine Animal Genomics

The first marine genomes to be sequenced were those of the sea squirt and puffer fish, in projects led by physicist Daniel Rokhsar of the University of California, Berkeley, in the early 2000s. This caught the attention of the MBL Embryology course directors, who invited Rokhsar to teach in the course in 2001 (which he still does today). Seeing the wide diversity of animals studied at the MBL, Rokhsar says, inspired him to plunge further into comparative genomics. Over the next decade he led sequencing projects for several basal marine organisms, including the starlet sea anemone, whose genome (to everyone's surprise) turned out to be almost as complex as that of human's.

The surprises kept coming, as several groups sequenced about twenty bony fish and lower marine organisms. When MBL scientists and others published the sea urchin genome in 2006, it revealed more than seven thousand genes in common with humans. But perhaps the most startling results came from one of the most ancient creatures, the sea sponge, sequenced in 2010 by Rokhsar and colleagues.

The sponge's genome, they discovered, contains instructions for the very features that define "animal," including cooperation between cells, division of labor among cell types, adhesion of cells, and innate immunity. Strikingly, many of the sponge genes involved with these "quintessentially animal features," Rokhsar says, are the same genes whose dysfunction is associated with cancers today. "It's an interesting contrast in the positive and negative aspects of the same genes," he says.



IN PURSUIT OF A Genome

WHILE THE FAST-MOVING SQUID HAS BEEN STUDIED FOR DECADES, ITS DNA IS STILL NOT SEQUENCED

Two years ago, as a meeting of cephalopod researchers in Italy drew to a close, the discussion turned to future research. Clifton Ragsdale, a neurobiologist at the University of Chicago, recalls that just one issue was on the delegates' minds. "It was virtually an obsession among the people there that we needed at least one cephalopod genome sequenced," he says. With that, a mission was born.

"The squid is like an intelligent alien. There aren't many other organisms that we consider to have really advanced neurological processing."

— C. Titus Brown, MBL visiting scientist from Michigan State University

With their large brains and sophisticated sensory organs, cephalopods—a class of mollusks that includes squid, octopus, cuttlefish, and *Nautilus*—have become crucial models for scientists studying human physiology, behavior, and disease.

One member of the class, the squid *Loligo* (recently reclassified as *Doryteuthis*) is famous for the Nobel Prize-winning insights it has offered on nervous system function (see sidebar). Cephalopods also provide "the best invertebrate models of complex behavior," says Roger Hanlon, who directs the MBL's Program in Sensory Physiology and Behavior.

It is surprising then, that while many model organisms have been sequenced, cephalopod researchers are still working "in the dark," without a single genome. "Scientists from all sorts of disciplines are keen to get their hands on the squid model, but they really need the genome to do that," Hanlon says.

That day is arriving. After the clarion call in Italy, Ragsdale organized a meeting of cephalopod researchers with the goal of producing a manifesto on the need for cephalopod genomes. That white paper was published (*Stand. Genomic Sci.* 7:1, 2012) and scientists are drawing on it for grant applications. The meeting also sparked the formation of the Cephalopod Sequencing Consortium, a group committed to advancing the state of cephalopod genomics. Among the members of the "CephSeq" steering committee are Ragsdale, Hanlon, and C. Titus Brown, an MBL visiting scientist from Michigan State University.

"Genomics will allow us to do a lot more picking and choosing of the elements in the systems we want to understand," says Hanlon, who is particularly interested in the skin pigmentation organs that give cephalopods their amazing camouflage abilities.

One feature of the squid that has been prized by generations of researchers is its large nerve fibers, or "giant axons," that run the length of its body. These axons, which are fifty times wider than any human nerve fiber, have evolved to allow the squid a quick getaway from predators. Scientists value the squid giant axon not only for its advanced neural capacities, but also for its visibility to the naked eye and ease of manipulation.

"The squid is like an intelligent alien," says Brown. "There aren't many other organisms that we consider to have really advanced neurological processing."

Scott Brady of University of Illinois at Chicago, for example, uses the squid giant axon to study human neurodegenerative diseases at the MBL. He hopes that sequencing the squid genome will provide compelling evidence for using squid as a human disease model. "You get people who say, squid don't get Alzheimer's or Parkinson's disease, so why do you think the things you study in the squid will have the same pathways in a mammalian system?" he says. The best way to convince them is to demonstrate that the relevant genes and regulatory networks are the same in the squid and human genomes. Knowing which parts of the genome are conserved across species will also help scientists develop the best tools to probe both systems, he adds.

However, sequencing the squid genome is not a straightforward matter. It is almost the size of the human genome and contains repeat DNA sequences that complicate the effort. Members of the Consortium are working away on genome analysis in squid and other cephalopods, says Ragsdale, and he hopes data will start to emerge next summer. In the meantime, scientists at MBL are also sequencing squid transcriptomes—"snapshots" that reveal what genes are expressed in different cells, tissues, and organs at different developmental stages and under different conditions (see story on p.15).

Having a greater understanding of cephalopod genomes and transcriptomes will transform the field, says Brown. "It will move us from talking about individual genes to talking about how collections of genes work. And we know that collections of genes are closer to what, biologically, actually matters." • —CdL

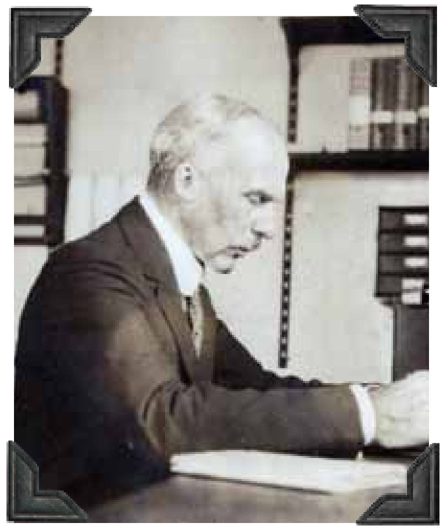
From Nervous Impulse to Drug Discovery

"Not only is the squid a beautiful animal, but boy, is it generous as far as allowing us to understand the nature of what we are," says Rodolfo Llinás, an MBL visiting scientist from New York University School of Medicine, who uses the squid as a system for studying human neurodegenerative disease and for drug discovery.

MBL scientists have been placing electrodes in squid giant axons to measure the nerve impulse since the pioneering work of Kenneth Cole (Columbia University) in the 1930s. Using an improvement on Cole's voltage clamp measuring system, Andrew Huxley and Alan Hodgkin pursued similar research in Plymouth, England. Their fundamental description of the "action potential" to explain the nerve impulse brought Huxley and Hodgkin the Nobel Prize in 1963.

In the early 1980s at the MBL, Scott Brady and Ray Lasek, then of Case Western Reserve University, developed an important new way to study the squid giant axon: they removed its membrane and freed its internal axoplasm. This axoplasm preparation paved the way for the subsequent discovery at the MBL of kinesin, one of a family of motor proteins, which are biological machines that move cargoes within cells, contract muscles, and enable cell movements. Last year, the Lasker Award for Basic Medical Research was awarded to Ron Vale of University of California-San Francisco, Michael Sheetz of Columbia University, and James Spudich of Stanford University for their kinesin and motor protein-related discoveries.

At the MBL today, Brady and his colleagues are introducing proteins implicated in neural diseases, such as Alzheimer's, into the squid axoplasm to see how they affect the transport of organelles. They have identified a number of molecular mechanisms involved in these diseases and gained a better understanding of how they progress in mammalian systems. "None of this research could have been done anywhere except in isolated axoplasm preparation," Brady says. "It all came from the squid." • —DK



F.R. Lillie, longtime MBL director and University of Chicago faculty member

University of Chicago, MBL Announce Lillie Research Innovation Awards, Scholarship Program

Soon after their formal affiliation last July, the University of Chicago and the MBL launched two opportunities: a new research award program and an undergraduate scholarship. The Frank R. Lillie Research Innovation Awards will provide funding for scientists to develop novel, collaborative projects based at the MBL. Collaborators from the worldwide MBL research community are eligible for the awards, including year-round MBL scientists and scientists from other institutions who are or propose to participate as MBL visiting researchers or course faculty. Also announced was the University of Chicago–Marine Biological Laboratory Scholarship for undergraduate study at the University of Chicago, to be awarded annually to the child of a year-round MBL employee. Beginning with the application cycle for fall 2014, the University of Chicago will offer one full-tuition, merit-based scholarship to a qualified applicant. It will be renewable for four years, pending the recipient's good academic standing and parent's continued MBL employment. More information on both programs is available on the MBL-University of Chicago Affiliation web site (mbl.edu/uc-affiliation). •

Scientists Discover Thriving Colonies of Microbes in Ocean "Plastisphere"

MBL associate scientist Linda Amaral-Zettler and her colleagues have uncovered a diverse multitude of microbes colonizing and thriving on flecks of plastic floating in the oceans. The scientists have dubbed the human-made flotilla of microbial communities the Plastisphere, a novel ecological habitat. Working with Erik Zettler (Sea Education Association) and Tracy Mincer (Woods Hole Oceanographic Institution), Amaral-Zettler analyzed the bacteria associated with marine plastic debris collected from several locations in the North Atlantic Ocean. Most of the plastic pieces were millimeter-sized fragments. Using scanning electron microscopy and gene sequencing techniques, they found at least 1,000 different types of bacterial cells on the plastic samples, including many species yet to be identified. The scientists say the Plastisphere raises a host of questions including how it will change environmental conditions for marine microbes and larger marine organisms, and impact the overall ocean ecosystem. The scientists also found evidence that Plastisphere microbes may play a role in degrading plastics and hydrocarbons. "Now we have to figure out what they are by [genetically] sequencing them and hopefully getting them into culture so we can do experiments," says Amaral-Zettler.
(*Environ. Sci. Technol*. 47 : 7137–7146, 2013) •

Built for Efficiency, Not Speed: Scientists Discover New Propulsive Mechanism in Jellyfish

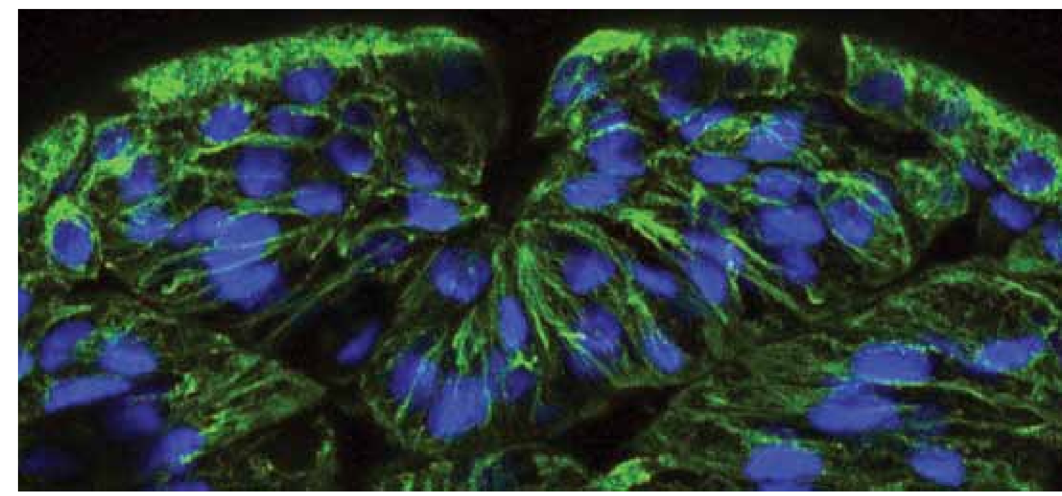
Jellyfish may not be fast, but they are one of the most efficient propulsors on the planet, report MBL visiting scientists Brad Gemmell and John Costello of Providence College and Sean Colin of Roger Williams University. The scientists' discovery may explain why jellyfish can "bloom" and overrun an ecosystem, outcompeting much swifter predators such as fish. "A jellyfish expends far less energy getting from point A to point B" than a fish does, Gemmell says, so for every gram of prey it eats, the jellyfish can put more of that energy into growth and reproduction, rather than locomotion. The key to the jellyfish's efficiency, the scientists report, is a previously overlooked part of its locomotive cycle. During the relaxation phase after the jellyfish contracts, which was primarily thought to be a period of reset for the next contraction, the scientists discovered that another vortex ring in the water comes underside the animal and gives it a second locomotive boost, a mechanism they call "passive energy recapture." Gemmell, who has accepted a research faculty position with the University of Texas at Austin, Marine Science Institute in Port Aransas, plans to return to the MBL this summer to continue the collaboration. (*PNAS* 110: 17904-17909, 2013) •

Long-Term Tundra Warming Study Provides Insight into Ecosystem's Resiliency

In 1989, MBL senior scientist Gaius Shaver and his colleagues set up a series of small experimental greenhouses on a hillside above the Toolik Field Station at the National Science Foundation Arctic Long-Term Ecological Research site in northern Alaska.

The clear, plastic-covered greenhouses increase average air and soil temperatures by 1-4° C and are used to observe the effects of sustained warming on the arctic environment. Today, this experiment is the longest-running climate warming study in the arctic region. Seeta Sistla (who received her master's degree in the Brown-MBL Graduate Program in Biological and Environmental Sciences), her doctoral adviser at University of California, Berkeley, Josh Schimel, Shaver, and their colleagues now report the results of this long-term warming experiment.

Their paper shows that 22 years of slow and steady warming did not change the amount of carbon in the soil, despite major changes in vegetation and in the soil food web. Whether or not this phenomenon—no net loss of soil carbon despite long-term warming—is a transient phase that will eventually give way to increased decomposition activity and more carbon release, remains to be seen. "This work demonstrates why long-term ecological research, and especially long-term whole-ecosystem experiments, are essential to understanding the long-term impacts of climate change," says Shaver. (*Nature* doi:10.1038/nature12129) •



MBL Researchers Find Zinc's Crucial Pathway to the Brain

A study by MBL scientists Mark Messerli and David Graham, in collaboration with scientists from the University of California, Davis, helps explain how parts of the brain maintain their delicate balance of zinc, an element required in minute but crucial doses, particularly during embryonic development. The research, conducted with the frog *Xenopus tropicalis*, shows that neural cells obtain zinc through a membrane transporter called ZIP12. "This particular transporter is an essential doorway for many neurons in the central nervous system," says Messerli. "You knock out this one gene, this one particular pathway for the uptake of zinc into these cells, and you essentially prevent neuronal outgrowth. That's lethal to the embryo." Previously, scientists thought that zinc could use more than one pathway to enter the cell during early brain development, as do other elements such as calcium. Zinc is essential for neural development, learning and memory; however, too much zinc can be problematic. The team is now investigating the implications of their results on processes including embryonic brain development and wound healing. (*PNAS* 110: 9903-9908, 2013) •

The BALANCING ACTS *of a Fish*

LIKE MANY CHILDREN WHO GREW UP WATCHING OCEAN EXPLORER JACQUES COUSTEAU, ALLEN MENSINGER YEARNED TO BECOME A MARINE BIOLOGIST, and he never wavered from his first-grade desire to study fish. Today, he's the only marine biologist at the University of Minnesota in Duluth, a city that lies 1,000 miles from the nearest coast. "I don't think I could be any further from salt water," he says. So each summer Mensinger travels to Woods Hole. In his lab at the MBL, he studies how the oyster toadfish—*Opsanus tau*—detects external clues in its environment and responds to them.

With their fleshy lips and flat heads, toadfish won't win any marine beauty contests. But what they lack in good looks, they make up for in hardiness. "You can't kill them," Mensinger says. Toadfish hold another advantage over other fish: Their sensory nerves are protected by only the thinnest bit of skull. By removing this plate of bone, researchers can directly access the fish's neural wiring to figure out what makes them tick.

Toadfish have been research subjects at MBL since the laboratory first opened in 1888, when zoologist Cornelia Clapp began studying their development for her doctoral dissertation at the University of Chicago. In the 1960s, MBL researchers prized the animals for research on insulin. In humans, insulin-secreting cells are scattered in islets throughout the pancreas. In the toadfish, however, these cells are largely found within a single islet, making them easy to locate, isolate, and study. This research revealed new ways to stimulate insulin secretion.

Stephen Highstein, now a senior scientist at MBL, began working with the toadfish in the 1970s. He is interested in the vestibular system in the inner ear, which controls equilibrium and balance. "It's a very convenient experimental animal," Highstein says. Because their heads are so broad, "the inner ear organ is quite a distance from the brain, which gives you a long length of nerve to work with." Highstein isn't put off by the fish's appearance. "I think they're handsome," he says.

Mensinger joined Highstein's lab in the 1990s as a postdoctoral associate, and that's when he began working with toadfish. Together they fitted toadfish with electrodes to record their nerve impulses and sent them into space as part of NASA's 1998 NeuroLab shuttle mission. "We wondered how the ear would respond to the lack of normal gravitational stimulus," Highstein says.

How did the space-traveling fish do? In the microgravity of space, the fish's inner ear "turned up" its sensitivity to gravitational stimuli, looking for the missing signal. "This seems to be a general principle in biology," Highstein says. "In Parkinson's syndrome, for example, when the brain decreases its production of dopamine, there is a genetic up-regulation of some dopamine receptors, looking for the missing dopamine." In space, "the perverted inner-ear signal regarding gravity conflicts with other vestibular and visual signals, creating a mismatch in the brain areas responsible for body and head orientation," he says. "We think this mismatch causes motion sickness, or space adaptation syndrome."

The Early Bird

Students need not choose a career path in elementary school, like Mensinger did. But college students who like science can start gaining real research experience at the MBL. In 2009, Mensinger helped launch Biological Discovery in Woods Hole, a Research Experiences for Undergraduates program funded by the National Science Foundation. The first year Mensinger and his co-director, Robert Paul Malchow of the University of Illinois at Chicago, received about 120 applications for ten slots. Last year, 400 students applied. "We've been quite successful," Mensinger says. The undergraduates spend ten weeks working on their own research projects, each advised by an MBL scientist. Last summer's students investigated questions ranging from the impact of injury on squid schooling to the population structure of oral bacterial films.

Highstein, an MD/PhD, continues to value the fish for basic biomedical research. "A few times in my research career, I've been lucky enough to discover something in the toadfish that, because of my clinical background, I recognized its relationship to human malfunctions of the inner ear," he says.

Mensinger today works in the field of neuroethology, which explores the neural basis of natural animal behaviors. Research in this field has typically been carried out on a single sensory system—hearing, vision, or smell. However, "when fish are out there, they're getting all this sensory information from multiple sources," Mensinger says. He wonders how they absorb and process this wealth of input.

Male toadfish, for example, attract females by producing a long, low sound uncannily like a fog horn. How the fish hear this mournful call is something of a mystery. The hearing organ in fish is internal and consists of fluid-filled canals and bony structures called otoliths. These organs perform double duty, allowing fish to hear and to maintain balance and equilibrium when swimming.

"When the fish is stationary, it's not receiving any movement input. When it starts moving, all these systems that are designed to detect sound are also designed to detect movement," Mensinger says. "So we're not sure how the fish can filter that movement out and still hear." They may not be able to do both at the same time. Mensinger has observed female fish taking short hops toward the sound of a male toadfish rather than swimming directly. One possibility is that the females are pausing to listen. Or perhaps the brain has a way to filter out sensations associated with movement. "That's one of our experiments coming up," he says.

To explore these mysteries, Mensinger has developed an implantable device that can record sensory nerve impulses and transmit the data wirelessly. Most behavioral studies involve fish that are anesthetized and restrained. Mensinger's device enables researchers to gather real-time data from free-swimming fish, which are likely to behave more naturally.

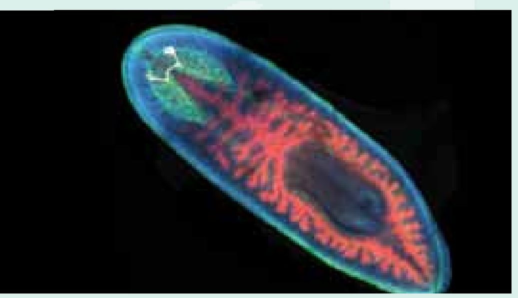
Mensinger has spent nearly every summer at the MBL for the past two decades. Packing up and migrating to Woods Hole can be inconvenient, but it's worth it, he says, because "I need interaction with colleagues." By summer's end, he's happy he came. • —CW

Regeneration Revolution

No one is more familiar with the regenerative powers of marine organisms than Alejandro Sánchez Alvarado. He spent the entire summer of 1996 at the MBL dividing sea creatures in two. He experimented with bristle worms and flatworms, starfish and crabs—even organisms he couldn't name. "I would grab any specimen that the Marine Resources Department would give me," he says. Then a recent graduate of the MBL Embryology course, Sánchez Alvarado had decided to focus his research on regeneration, and he was searching for a model organism. At the time, dogma held that relatively few organisms could regrow new tissue. "But almost everything I cut regenerated just fine," he says. "So then I began to wonder, 'How unique *is* regeneration?'"

"There are species in every phyla that will do some truly remarkable regenerative feats."

— Alejandro Sánchez Alvarado, MBL Embryology course co-director and HHMI investigator



If scientists can figure out the mechanisms that control regeneration, our ability to grow tissues for medical use may improve.

Not unique at all, it turns out. "Regeneration is broadly distributed," says Sánchez Alvarado, who today co-directs the Embryology course and is a Howard Hughes Medical Institute investigator at the Stowers Institute for Medical Research. "There are species in every phyla that will do some truly remarkable regenerative feats."

Often considered to be poor regenerators, even mammals can display a robust ability to regenerate. Last year, researchers reported that at least two species of African spiny mice can rapidly replace large patches of skin and hair. But there's little rhyme or reason to the pattern of distribution. Two nearly identical species that inhabit the same environment may not possess the same regenerative capabilities.

When Sánchez Alvarado entered the field, regeneration was not a hot research topic. Many scientists dismissed it as a curiosity, a capacity only a few organisms possess. Others argued that the secrets of regeneration could be revealed simply by studying tissue formation during embryonic development. Sánchez Alvarado didn't buy it. "In an adult animal, [to regenerate], you're asking tissues that are already committed to a particular fate to all of a sudden make a new tissue and then functionally integrate it into the existing tissue," he says. "That never happens in embryogenesis."

One day, while wandering the stacks of the MBL's library, Sánchez Alvarado stumbled across a 1901 book on regeneration by Thomas Hunt Morgan, a longtime MBL visiting scientist, Nobel Prize laureate, and pioneer of genetics. Sánchez Alvarado spent much of that night and the next morning reading. "I couldn't put it down," he says. In the pages of that book he found his model organism: planaria, a tiny freshwater flatworm with a tremendous capacity for regeneration. "Here was a body of work that was already available, beautifully executed," he says. No one had applied the modern tools of molecular biology to study regeneration in these worms.

Over the past fifteen years, Sánchez Alvarado has established planaria as a model organism for studying the molecular mechanisms that underlie regeneration. He and his colleagues developed new tools for silencing genes in planaria and identified genes important to the regenerative process. Many of the fundamental questions in the field when Morgan published his book remain unanswered. "How do animals *do* this?" Sánchez Alvarado asks. If scientists can figure out the mechanisms that control regeneration, our ability to grow tissues for medical use may improve.

There's another big question lurking, too: What is the evolutionary history of regeneration? Did regenerative organisms inherit the ability from a distant ancestor, or did it evolve independently in every phylum? And why does regeneration taper off as you approach the mammalian branch of the evolutionary tree?

"These questions are of particular interest to regeneration studies, but of general interest to the life sciences," Sánchez Alvarado says. While the MBL Embryology course doesn't focus on regeneration, students work with many of the organisms commonly used to address these questions—hydra, planaria, fruit flies, and more. "The answers will likely illuminate many aspects of both embryonic and post-embryonic development," he says.

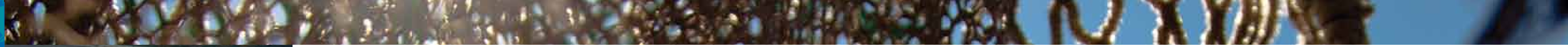
The MBL also hopes to answer some of these questions within the Eugene Bell Center for Regenerative Biology and Tissue Engineering, which opened in 2010. The Bell Center aims to highlight the extraordinary regenerative capabilities of marine and aquatic organisms. "This is a specific niche that MBL can fill," says Jennifer Morgan, who studies spinal cord regeneration in the sea lamprey and is the Bell Center's associate director. "The fact that we can sequence genomes and transcriptomes and do so relatively cheaply and fast means that we can really start to tackle those questions," she adds.

Sánchez Alvarado believes that solving the mysteries of regeneration will require that scientists look beyond the standard model organisms. That's one of the merits of having access to the sea, he says, because "that's where the vast majority of unknown organisms live. "Within the diversity of marine life, there are likely new, unstudied paradigms of regeneration. "I suspect that there are lot of surprises and discoveries waiting to be revealed," he says. • —CW

Frog Fates

Some organisms, such as the aquatic frog *Xenopus*, can regenerate body parts when young but then lose the ability. As a tadpole, *Xenopus* can regrow a tail or limb or eye. Once it becomes a frog, it can't. This makes it an interesting model for regeneration research, says Marko Horb, an MBL scientist who studies pancreatic development in the frog. Researchers can look at how the biological signals change as the frog matures and loses its regenerative powers.

In 2010, the MBL received a $3.4 million grant to establish the National *Xenopus* Resource, a one-stop shop for *Xenopus* researchers. This frog has long been used as a model organism in biology, but there has never been a unified resource center in the United States until now. Horb, who directs the center, says it is designed to be an intellectual hub as well as a repository of two species: *Xenopus laevis*, a frog traditionally studied by developmental and cell biologists, and *Xenopus tropicalis*, which is easier to manipulate genetically.



MBL Moment

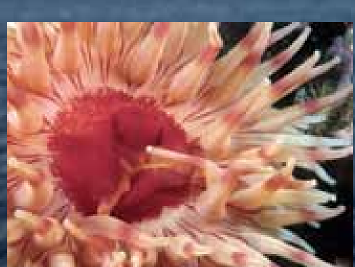
with …

David Remsen
Manager, Marine Resources

THE COLLECTOR'S NET

At the heart of the MBL is the Marine Resources Department, which collects, maintains, and supplies to researchers about two hundred different marine species, both animals and plants. Some of these species have been collected at the MBL for more than a century and have driven major fields of biological and ecological discovery. David Remsen, manager of Marine Resources, first worked as a diver and marine specimen collector for the department in the 1980s, while he was in college. After spending many years as a programmer at the forefront of biodiversity informatics, he returned to the MBL to manage Marine Resources in 2012.

David Remsen returned to the MBL in 2012 from Copenhagen, where he had served as senior programme officer at the Global Biodiversity Information Facility (GBIF) since 2006. At GBIF, Remsen oversaw a biodiversity informatics work program that contributed to the design and development of an international biodiversity data network. A native of Falmouth, Massachusetts, Remsen worked as a diver and specimen collector at the MBL from 1987 to 1991. He then worked in information technology at the MBL in a variety of positions, including systems architect of the MBLWHOI Library's uBio Project, which later became a core component of the Encyclopedia of Life (eol.org); manager of bioinformatics and systems developer in the Information Systems Division; and instructor in the Biomedical Informatics Course. He has performed information systems development, software development, and web administration for several marine organizations in the United States. Remsen holds a B.S. in biology from the University of Wisconsin-Milwaukee, and has completed post-graduate courses in information science, mariculture, and computer programming.



Which species are most popular, in terms of researchers requesting their supply from the Marine Resources Department (MRD)?

DR The priority species change with time. When I worked at the MRD in the 1980s, everybody wanted the surf clam (*Spisula*). Research on cell division using eggs of these clams was just going gangbusters, and we couldn't collect enough. But that has gone through its gold-rush phase and settled to a low boil. Squid, horseshoe crabs, many of the organisms we collect have been significantly important at different times. Right now, the starlet sea anemone (*Nematostella*) is really big and the demand for skate embryos (*Leucoraja*) exceeds our ability to supply them. Although we usually just collect wild animals and ship them to researchers, we have started breeding programs for the sea anemone and the skate to ramp up for demand. Both are used for research on embryological development and the evolutionary history of development. Sea urchins, another useful organism for studies of development, are also in high demand.

How do you collect the organisms?

DR We drag a net from our collecting vessel, the *Gemma*, for some species; others are collected by hand. We dive for organisms that are below the surface of the ocean floor or are too delicate to collect by other means. Surf clams and parchment worms (*Chaetopterus*) have to be dug by hand, for example.

The MBL can collect an unusually rich diversity of species within a 75-mile radius of Woods Hole. Why is that?

DR The species assemblages you find in the waters north of Cape Cod are very different from those found in the south. The purple-spined sea urchin (*Arbacia*), for example, is found in Woods Hole and south to the Gulf of Mexico, while the green sea urchin (*Strongylocentrotus*) is found in Cape Cod Bay and north into the Arctic. We collect the purple urchin when they are gravid [have eggs] from June through August, and we know how to keep them gravid at the MRD until November. Then the eggs of the green sea urchin come into season from December through February. If we keep them in cooler water at the MRD, rather than letting them warm up in the spring, they will stay gravid through April. That gives us almost ten months of urchin egg availability. Other organisms come into season at other times.

How do you know where to look for a particular organism?

DR It's an oral tradition. The collectors know. That's why they are so valuable. *Gemma* captain Billy Klimm is a commercial fisherman, so he knows how to operate the boat, but he also knows where to go and how to bring the animals back alive. Lots of people can go out and collect squid, if they can find them, for calamari. But to bring them back alive requires special handling, equipment, and know-how. Also, the landscape isn't stable: The animals move around; habitats change over time. We have to stay on top of that. We need a presence out there all the time, looking around, scouting.

Do you keep a record of where the organisms are found and when?

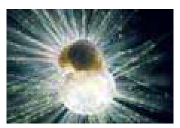
DR I am trying to get more of this written down. We have a great opportunity here. Imagine, if the all the MBL collectors over the last 125 years actually wrote down what they saw, where they saw it, how many they caught, etc. We'd have a time series of information regarding changes in distribution of species. We could use that for many scientific purposes, such as ecological niche models or trends in habitat distribution, as well as for our own department's activities. The MBL had a Systematics-Ecology Program in the 1960s that developed a key to the invertebrates of Woods Hole, but the key hasn't been updated since then. That field gave way to more "hard" science disciplines, but advances in molecular, genomic, and informatics tools now offer the means to revitalize the field and provide new applications for this sort of data.

One of my goals is to develop knowledge bases around all the organisms that Marine Resources provides. Each species is the focal point for an enormous amount of information. Look at all the research that has been done with squid, for example, all the collaborators, the methods they developed, the papers they wrote. That is tied to the features that make an animal a good model, such as the giant axon system of the squid, and those features are tied to the animal's natural history and its ecological niche. It's an enormous story to tell. I think there is great potential for a renaissance in the use of marine models, as the genomic tools have matured. It would be strategic for MBL to collate, coordinate, and present the information on these models, so incipient investigators can make the jump to start using them. • —DK

Gifts & Grants

The National Institutes of Health awarded $1,396,352 for a project titled "Cytosolic and Plasma Membrane Circuitry of Beta Cell Redox Control." Emma Heart is the principal investigator.

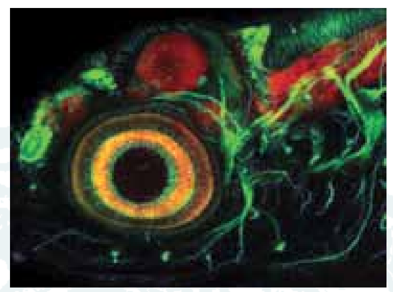
The Alfred P. Sloan Foundation pledged $1,250,000 in support of the Deep Carbon Project. Mitchell Sogin is the principal investigator.



The National Institutes of Health awarded $708,000 for a project titled "Interdisciplinary Training in Quantitative Cell Biology (Physiology)." Dyche Mullins is the principal investigator.

The National Institutes of Health awarded $455,975 for a course titled "Strategies and Techniques for Analyzing Microbial Population Structures (STAMPS)." William Reznikoff is the principal investigator.

The Grass Foundation awarded $450,000 in support of the Neural Systems and Behavior course and the Neurobiology course. •



Accolades

Ecosystems Center senior scholar **Bruce Peterson** was awarded the A.C. Redfield Award for Career Achievements in Aquatic Science from the Association for the Sciences of Limnology and Oceanography.

Ecosystems Center senior research scientist **Ivan Valiela** received the Odum Lifetime Achievement Award from the Coastal and Estuarine Research Federation.

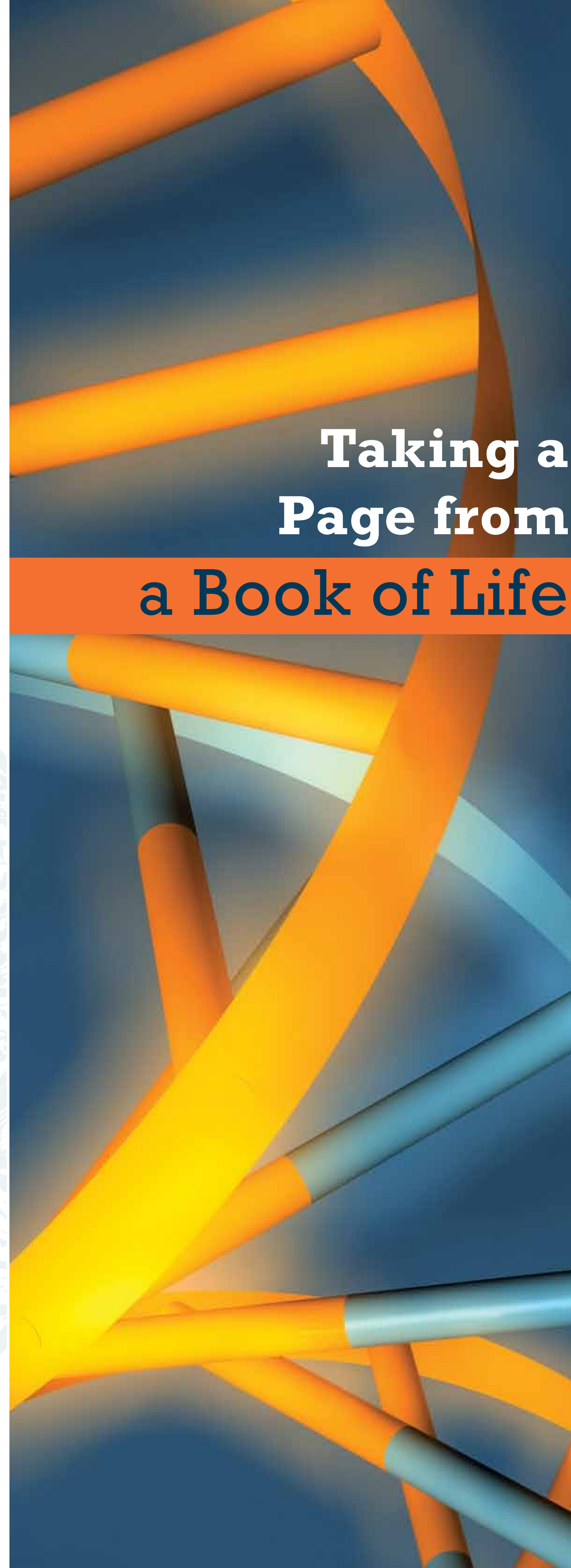
Sheila Nirenberg (Neural Systems and Behavior course student in 1986) was named a 2013 MacArthur Fellow by the John D. and Catherine T. MacArthur Foundation.

MBL Distinguished Scientist **Shinya Inoué** was designated as the second Honorary Scholar within the E.S. Morse Institute at the University of Washington's Friday Harbor Laboratories.

Cassandra Bilogan was the first Brown-MBL student to complete her Ph.D. in the Eugene Bell Center for Regenerative Biology and Tissue Engineering. Her MBL doctoral advisor was associate scientist **Marko Horb**.

Postdoctoral scientist **Paloma Gonzalez-Bellido** and her colleagues were awarded a 2012 Cozzarelli Prize by the editorial board of *Proceedings of the National Academy of Sciences* for the "scientific excellence and originality" of their study of prey detection and interception in dragonflies. The research was performed at Howard Hughes Medical Institute's Janelia Farm Research Campus, where Gonzalez-Bellido was a postdoctoral scientist prior to joining the MBL.

Martin Karplus (Physiology course student in 1950) was awarded the 2013 Nobel Prize in Chemistry "for the development of multiscale models for complex chemical systems." •



Taking a Page from a Book of Life

Biologists often want to know what's happening at a given place and time. For instance, when a cut on your finger is healing, which genes are active in the surrounding skin cells? To answer questions like this, the entire genome sequence of an organism isn't required. The answer can be found via transcriptomes: catalogs of the genes expressed in a cell or cell population at a given time.

"Imagine the genome is a dictionary," says C. Titus Brown, an MBL visiting scientist from Michigan State University. "A transcriptome is one particular book that's been written in that language." Because they result from selective gene expression, transcriptomes are easier to evaluate than entire genomes; one can focus on the genes expressed in a given cell or tissue that may have a direct functional role. Eventually, scientists want the dictionary too, Brown says, to understand the wealth of possibilities in the entire genome. But "to understand what genes are expressed when and where," he says, "you really only need the transcriptome."

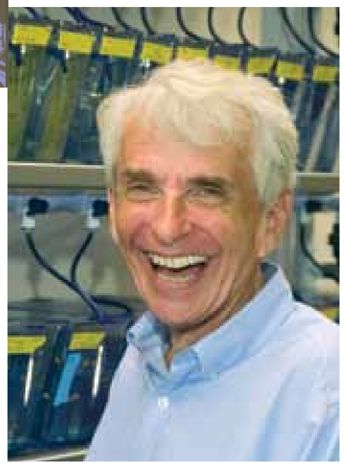
While a handful of methods exist to assemble transcriptomes, most researchers do not have the computing power needed to use them. That's why Brown and his colleagues—in particular Joshua Rosenthal of the University of Puerto Rico—spent last summer at the MBL adapting an existing transcriptome assembly protocol. They focused on making it simpler to use and available through a cloud server, so that even researchers with limited computing power can take advantage of it.

The scientists hope their protocol will be easy enough to use without in-depth computer training. Rosenthal has expertise in molecular biology and Brown is the bioinformatics brain behind the system, which they named the Eel Pond mRNAseq Assembly Protocol, after the Woods Hole pond. "I was the guinea pig for the protocol, the person who didn't know much about bioinformatics," says Rosenthal; a few months later, he is already using it to study RNA editing in the squid.

The pair is building the protocol using the squid, but they hope it will work with other organisms. The long-term goal is to build a searchable, collaborative database of transcriptomes and genomes from many marine organisms important to MBL research. This will allow scientists to compare data, such as searching for similar features in tissues of different organisms. "The goal is to bring this data out from behind closed doors and make it widely available, so we can concentrate on advancing the biology," says Brown. • —CdL

A Chaos of Delight

by Jonathan Gitlin

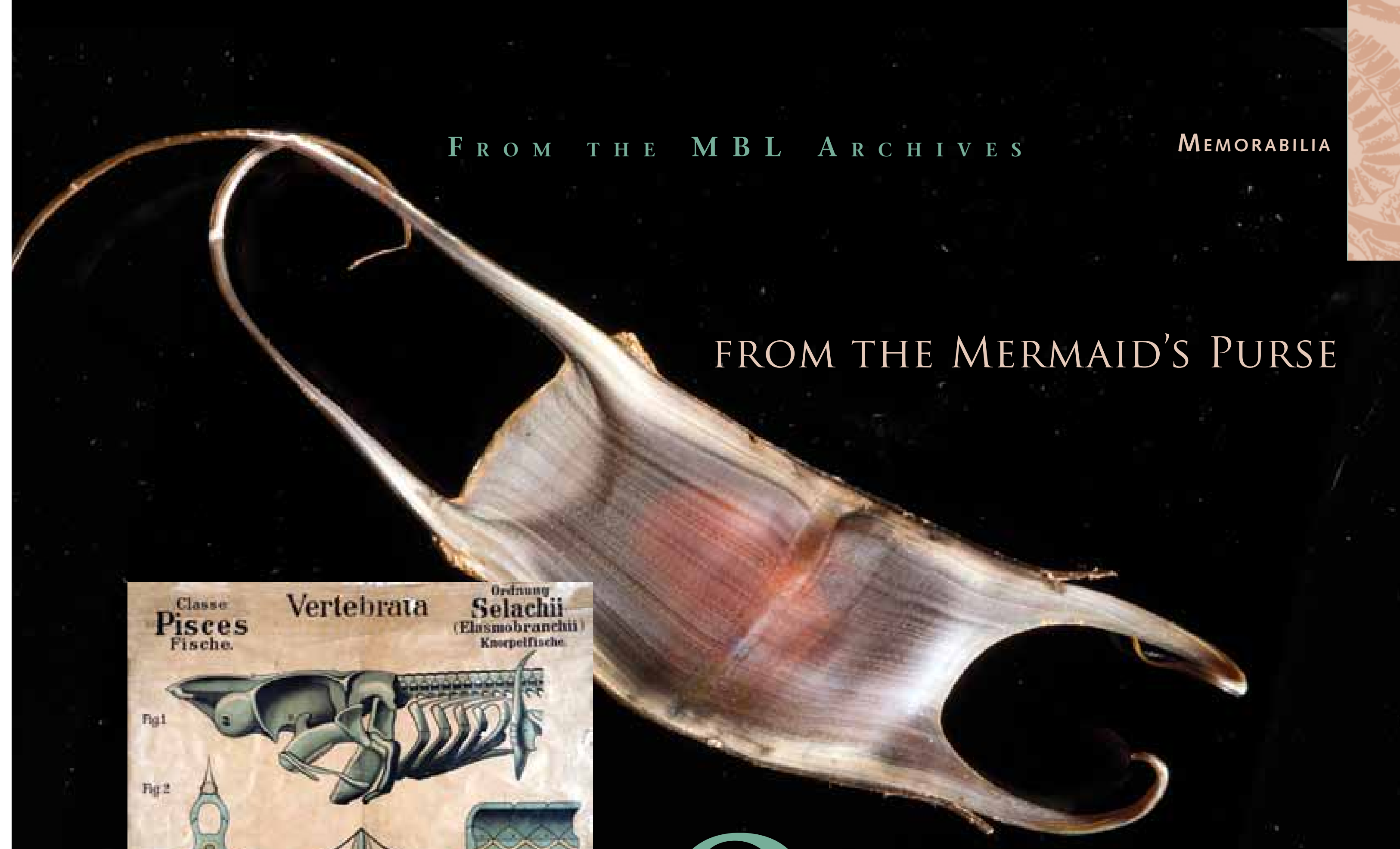


Jonathan Gitlin, M.D., Deputy Director of Research and Programs at the MBL, provides leadership for all scientific activities at the lab. He also directs and is a senior scientist in the MBL's Eugene Bell Center for Regenerative Biology and Tissue Engineering. Gitlin came to the MBL in 2012 from Vanderbilt University School of Medicine, where he served as Chair of Pediatrics and Physician-in-Chief at Vanderbilt Children's Hospital. He received his M.D. from the University of Pittsburgh and completed his residency and fellowship at Boston Children's Hospital. He served on the faculty at Harvard and at Washington University School of Medicine, where he was the Helene B. Roberson Professor of Pediatrics and founding Scientific Director of the Children's Discovery Institute. Gitlin is a specialist in newborn medicine and an expert on human genetic disease and has carried out fundamental research on the etiology of human birth defects. His many professional honors include election to the Institute of Medicine of the National Academy of Sciences in 2011.

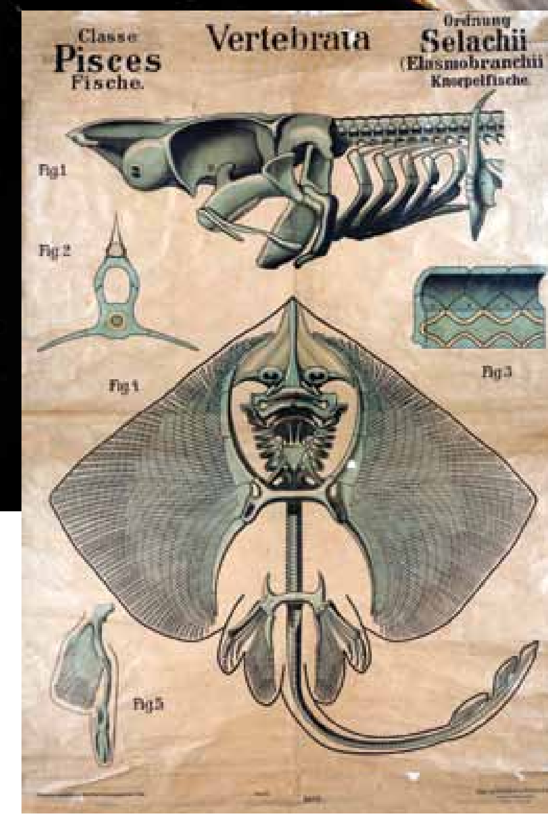
The great Danish physiologist, Nobel laureate, and MBL visiting scientist August Krogh, whose work elucidated the inner workings of capillary flow and function, noted that for every essential question in biology there is an organism ideally designed to provide answers. The truth to this idea lies in the principle of evolutionary adaptation and the "endless forms most beautiful" that have helped scientists unravel many fundamental biological problems. The diversity of marine organisms has contributed greatly to this approach, as exemplified by Alan Hodgkin's and Andrew Huxley's use of the squid giant axon to determine the ionic basis of the action potential and Eric Kandel's brilliant experiments with the marine mollusk *Aplysia* to discern the molecular basis of learning and memory. Here at the MBL, Joan Ruderman and Tim Hunt, studying protein synthesis in the rapidly and synchronously dividing eggs of the surf clam *Spisula*, revealed the first molecular insights into the workings of the cell division cycle. Also at the MBL, Ron Vale and colleagues, observing the movement of organelles within the squid axoplasm, discovered kinesin, the first in a family of molecular motors that drive intracellular transport.

Yet these examples and numerous others are behind us. Is there a future in this approach and in the principles that have made the MBL, in Lewis Thomas's words, America's "National Biological Laboratory"? Reflecting on his life in science, Isaac Newton wrote, "I seem to have been only like a boy playing on the sea-shore … whilst the great ocean of truth lay all undiscovered before me." Today, we must think of this metaphor in the most literal sense. Beyond our seashores, vast expanses of ocean cover three-quarters of the Earth's surface and define the physical and chemical forces that support life on our planet, yet remain virtually unexplored. The extraordinary advances in genomics that have transformed biology and medicine are now transforming research in marine biology, impacting our understanding of planetary geochemistry and the development and function of diverse ecosystems, and facilitating the discovery of organisms that will serve as emerging models to invigorate Krogh's principle.

The game is afoot. We face immense challenges, from climate change to cancer. The MBL stands firmly on 125 years of discovery and at the threshold of a revolution in marine biology. Our transformative partnership with the University of Chicago permits an unprecedented opportunity to accelerate this revolution; our questions are limited only by imagination and the answers by our creativity. What could be more exciting to a young scientist ready to embark upon a lifetime of discovery? Aboard the *HMS Beagle* for less than a year, the ever-curious, 22-year-old Charles Darwin sent a myriad of specimens from the Brazilian rainforest back to John Stevens Henslow, the Cambridge geologist who had taught him and secured his passage. As he explores all he sees, Darwin wrote, "the mind is a chaos of delight." If only he could see us now. •



From the Mermaid's Purse



Vertebrata: Pisces – Selachii (Elasmobranchii) *created by Carl Chun, produced by Rudolf Leuckart. A prominent 19th-century German zoologist, Leuckart designed and/or produced 114* Wandtafeln *(wall charts) that were used worldwide as teaching aids. The complete collection of Leuckart charts is archived at the MBL; donors of the charts included Louis Herlands, a former MBL summer investigator, and Ohio Wesleyan University. To see the collection online, please visit mblwhoilibrary.org.*

One of the nicest finds for a Cape Cod beachcomber is a "mermaid's purse," a lightweight, rectangular case with slender projections that once held the fertilized egg of a skate. It was likely deposited by a "little skate" (*Leucoraja erinacea*), a local species that has long been used by MBL scientists. A member of the Elasmobranchii group that includes sharks, rays, and skates, the little skate is one of the few among them that lays eggs, rather than giving birth to live young. With some care, one can open the egg case and remove the fertilized egg for study, making it an increasingly valued model for research on vertebrate development. Scientists also use the little skate to study the evolutionary transitions from fins to wings and limbs, by comparing how embryological development is controlled in animals that swim, fly or walk. This Elasmobranchii chart was produced by zoologist Rudolf Leuckart (1822-1898), whose students included Charles O. Whitman, later founding director of the MBL. Through his fine anatomical descriptions, Leuckart loaned support to the new idea that evolution could be illuminated by studies of organismal structure and embryonic development. "Evo-devo" research, now energized by molecular methods, flourishes at the MBL to this day. • —DK

MBL Biological Discovery in Woods Hole

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