Catalyst

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Osamu Shimomura Wins Nobel Prize in Chemistry for Discovery of Green Fluorescent Protein

Dear Friends,

These are thrilling times for the MBL. As this issue of MBL Catalyst *was going to press, we received news that MBL distinguished scientist Osamu Shimomura had been awarded*

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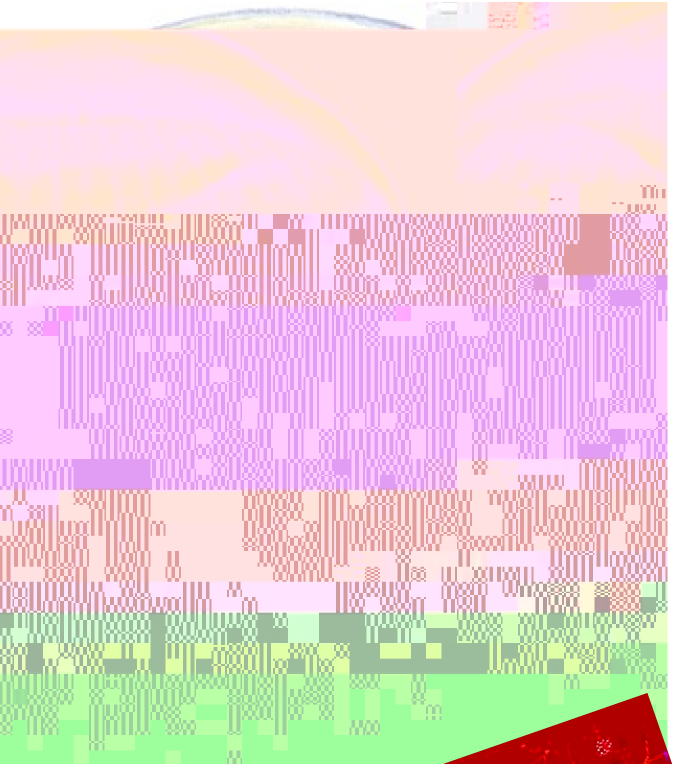

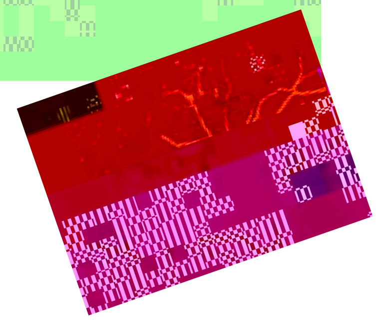

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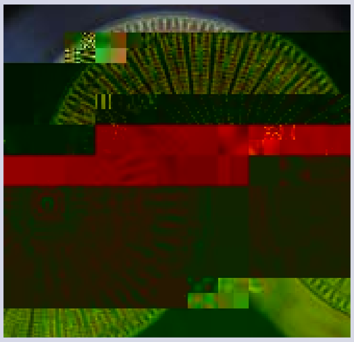
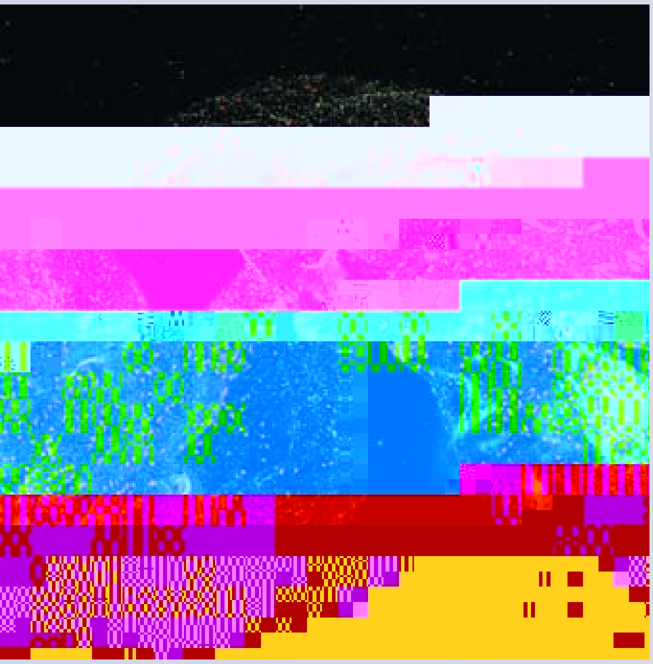
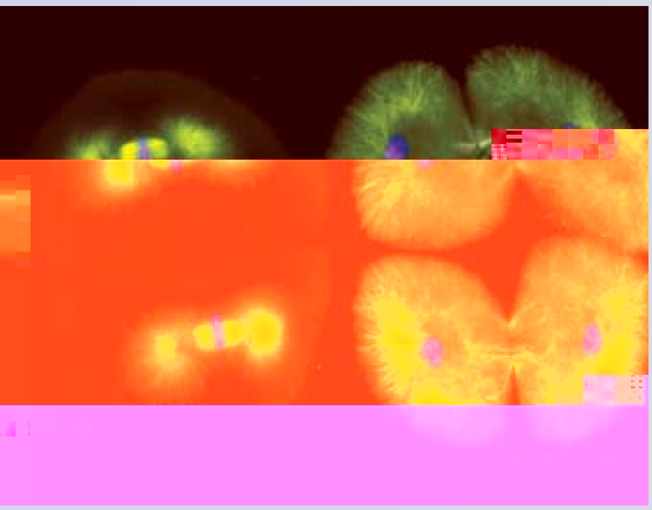


"If I have seen farther than others, it is because I was standing on the shoulder of giants."— Sir Isaac Newton

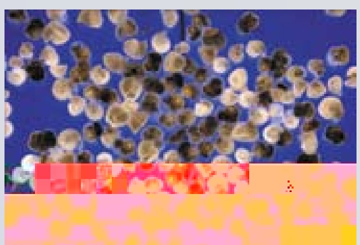


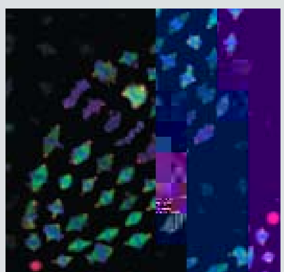
he story of microscopy and imaging at the MBL is a multitude of tales. It's as colorful as the field itself, which is in the midst of a renaissance. Scientists are pushing the boundaries of vision to places once thought impossible, and are amazed to see—and ask questions about—basic processes of life that could never be seen before.

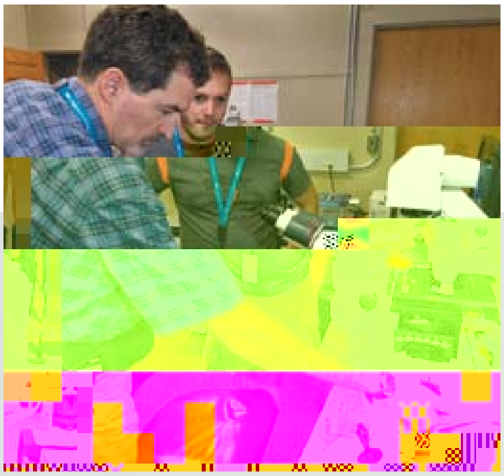
Such questions now seem answerable, thanks largely to a miniature "flashlight" called green fluorescent protein (GFP). Osamu Shimomura, a gifted chemist and MBL distinguished scientist, first purified GFP from the jellyfish *A* in 1961. Decades later, scientists realized they could produce GFP inside the cells of an experimental animal, shine blue light on the GFP, and it would fluoresce green and illuminate the cells in briliant detail. GFP has revolutionized biological imaging, and the scientists behind the breakthrough, Shimomura included, received the Nobel Prize in Chemistry this year. As this issue of demonstrates, ingenious ways to use fluorescent proteins to explore the microscopic world are continually being discovered at the MBL.



Photos: clockwise from top: an efflorescence of squid; Microscope Facility manager Louie Kerr and Physiology Course student Paul Miller; innervation of an ascidian oral siphon; ascidian's cerebral ganglion; filamentous cyanobacteria; mitotic spindles; various developmental stages of foraminifer; microtubles and DNS staining in the 2 to 4 cell division stage of sea urchin embryos; metamorphosed; diatom *A*. Center: aster





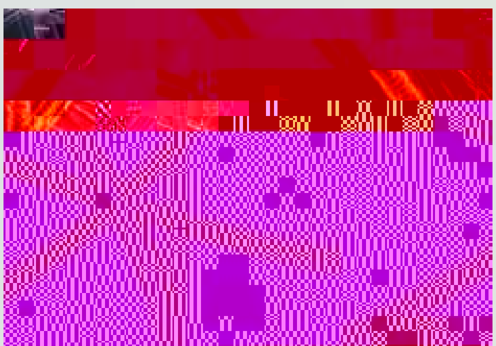


No less visionary is the work of another MBL distinguished scientist, Shinya Inoué, whose inventions in microscopy pioneered the imaging of live cells and ushered in the modern era of electronic imaging. Inoué has provided keen insight into cell division, the intricate process at the heart of embryonic development, growth, and many illnesses, such as cancer. Today, Inoué inspires an international,

innovative group of researchers at the MBL who are developing a predictive model of the dividing cell.

The MBL has attracted great microscopists since its earliest days, from E.B. Wilson in the 1880s to Keith Porter in the 1930s to Bob Allen in the 1980s to the innovative scientists working today in the MBL's Cellular Dynamics Program. Many have seen and found things under the microscope that no one had seen or imagined before. Their accomplishments cannot all be described in this issue of ; some stories will be told later. In the world of imaging, the MBL is at the center of laudable past and a future of tremendous promise.

—James Galbraith,
National Institutes of Health



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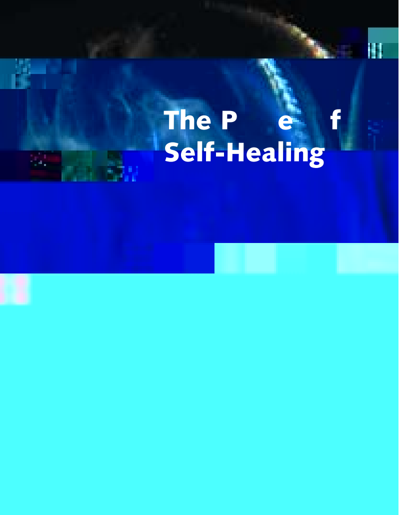
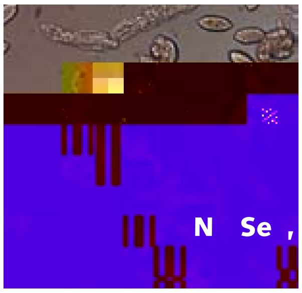
Ne Ec em i F ming a
We e n An a c ica Ra idl Wa m

Dramatic food-web shifts are emerging on the Antarctic Peninsula, where the climate is warming faster than anywhere else on Earth, report MBL Ecosystems Center co-director Hugh Ducklow and his colleagues in *A* . Working out of Palmer Station in Western Antarctica, the



The P e f Self-Healing

We'd save a fortune on bandages if we had the regenerative abilities of a comb jelly: Surgical scars would be a thing of the past and cuts would heal overnight. How a delicate, small, 500+ million-year-old creature can have this capacity, while humans don't, is the focus of ongoing investigation at the MBL. Ctenophores, or comb jellies, are one of the most ancient organisms on Earth, which is one of the reasons why Whitman investigator Anthony Moss of Auburn University finds them so intriguing. Moss and his graduate student, Matt Dodson, are investigating how the comb jelly can quickly repair its skin-like epithelium in a few minutes to a few hours—depending on the injury—without scarring. They use high resolution differential interference and fluorescence microscopy in addition to analyses of gene expression and electron microscopy to describe the cellular and molecular bases of wound healing in this jellyfish-like animal. Moss and Dodson hope to determine which molecules involved in ctenophore wound repair could be useful for a better understanding of human wound care. •

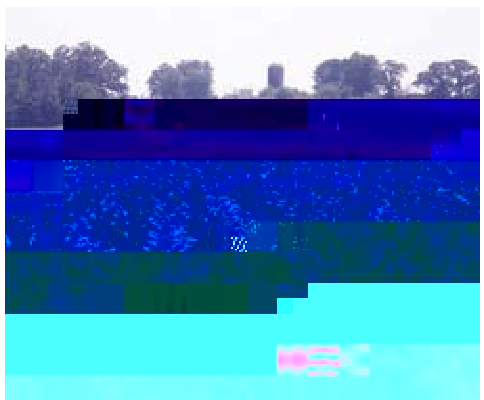


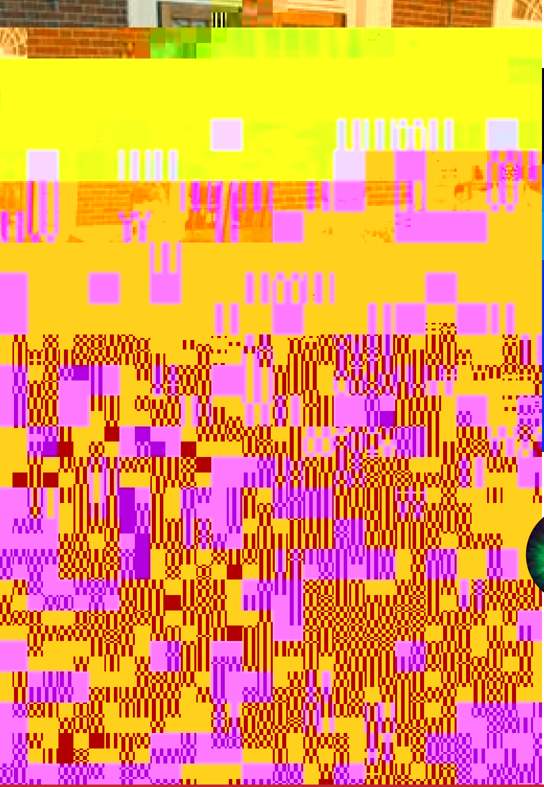
N Se , B Plen f Gene T an fe

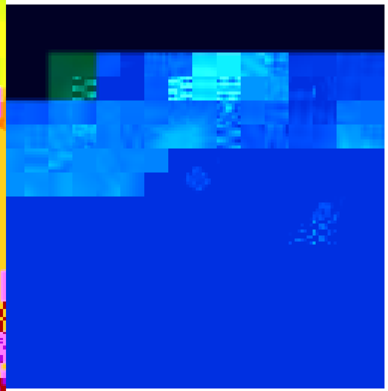
Where do you get your genes? If you are an animal, you inherit them from your parents at the moment of conception, and that's about it. Unless you are a bdelloid rotifer, that is. In a paper published in , Irina Arkhipova and Matthew Meselson, scientists at the MBL's Bay Paul Center and at Harvard University, and Harvard graduate student Eugene Gladyshev describe a startling discovery of numerous chunks of foreign DNA in the genome of the bdelloid rotifer, an asexual, microscopic, freshwater animal that has managed to diversify into more than 360 species over 40 million years of evolution. The results provide evidence for massive horizontal gene transfer—from bacteria, fungi, even from plants—into the bdelloid rotifer genome. While horizontal gene transfer is common in bacterial species, it was unheard of in the animal kingdom on such a massive scale—until this study. "It is quite amazing that bdelloids are able to recruit foreign genes, which were acquired from remarkably diverse sources, to function in the new host," says Arkhipova. "Bdelloids may have the capacity for tapping into the entire environmental gene pool, which may be of (evolutionarily) adaptive significance during expansion into new ecological niches, and may even contribute to bdelloid speciation," she says. (320: 1210-1213, 2008) •

Thinking i Th gh: Scien i Call F P lic G ide Bi f el Ind T a d S ainable P ac ice

As the U.S. and other nations commit to the path of biofuels production, a group of scientists is calling for sustainable practices in an industry that will, as MBL Ecosystems Center co-director Jerry Mellilo says, "reshape the Earth's landscape in a significant way." In a paper published in , Melillo and 22 co-authors call for science-based policy in the emerging global biofuels industry, which by 2050 could command as much land as is currently farmed for food. While the industry has significant momentum, no environmental performance standards are currently in place. Earlier this year, the 2008 Farm Bill was passed, which provides subsidies for growers of biofuels crops and for refiners who convert those crops to ethanol. Also, the U.S. Legislature approved a mandate in 2007 for the production of 16 billion gallons of cellulosic ethanol per year by 2022. "We have a lot of information that can help policy makers think through the long-term consequences of this kind of mandate," Melillo says. "We can help society avoid, or at least reduce, some of the negative consequences of the expansion of biofuels programs in the United States and around the world. Science can help all of us use renewable resources, such as biofuels, in a sustainable way." (322: 49-50, 2008) •







Imagine building a microscope that lets you peer beneath the surface of life. Imagine devoting whole days and nights to improving its optics. Imagine discerning movement at hidden levels, where molecules line up, form visible structures, then suddenly disperse and disappear. Imagine turning this instrument on the cell, and seeing into the mystery of how it divides. This is what Shinya Inoué did.

But his peers didn't always understand what he was up to. "Shinya was ahead of his time," says cell biologist Greenfield ("Kip") Sluder of University of Massachusetts Medical School. "People didn't know what to do with his work. Scientists were skeptical, they wanted to argue, or had their own pet theories." But after many years, Inoué was proven right. "And then everyone just said, of course!" Sluder says.

Inoué's striking vision first began to attract attention when he was a Princeton University graduate student who spent his summers at the MBL. In 1951, Inoué premiered a film of dividing cells at the MBL that showcased the power of his hand-built, polarized light microscope for viewing live cells, which at the time was very difficult to do.

What was even more exciting, Inoué's film clearly showed the action of the

"The modern revolution in microscopy started at the MBL, when Shinya Inoué, Nina Allen, and Bob Allen began using video cameras and computers to image the interior of cells. What they saw was absolutely fantastic, things that no person had seen before."

— Ron Vale, HHMI/UCSF

Inoué's hunches—and his gadgets—have indeed been very good over the years. With his polarized light microscope, for example, Inoué clearly saw that the spindle was made of bunches of fibers, which themselves were made of even finer fibrils. But what most excited his eye was seeing that the fibrils weren't static, but fluctuated dynamically as the cell went through division (called mitosis). By experimenting, Inoué found that the fibrils disappeared when he

ortunate hunches."

cooled the cell or exposed it to certain drugs—and reappeared when he reversed the conditions. Inoué sensed that this submicroscopic movement of the fibrils must be related to an essential job for the spindle: to attach to the chromosomes and accurately separate them during cell division.

So in the late 1960s, Inoué proposed the counterintuitive idea that the spindle fibrils—which by then were known to be microtubules—repeatedly fall apart and reassemble, and that this action creates forces to pull or push chromosomes during cell division. This was far from a mainstream idea—most biologists conceived of the spindle as a stable structure, like a muscle—and it was met with incomprehension and resistance for many years. Still, in the 1970s and 1980s, Inoué and Salmon made significant progress to confirm the energetics of the

brain POWER

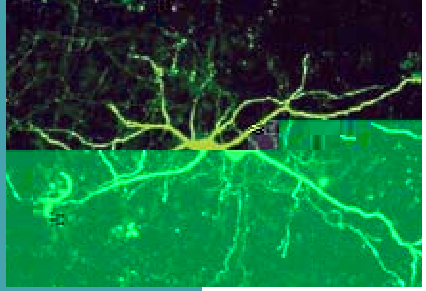
the MBL neurobiology course takes on the greatest imaging challenge of all

Some things in life are easy to visualize, say, the vacation of your dreams. The brain, with its intricate circuitry, is definitely not one of them.

"It is unimaginably complex. We don't have anything to compare it to," says Jeff Lichtman of Harvard University, who has taught imaging in the MBL Neurobiology course for more than 20 years. "You look at any little piece of the brain and you are amazed at how much stuff is in there."

In even the simplest animal, a maze of cells and wires is packed in the brain, while humans have hundreds of billions of neurons and trillions of synapses, or neural connections. Just getting a picture of neural circuits—let alone understanding how they work—demands all the prowess that modern imaging has to offer. These goals are actively pursued in the Neurobiology course, whose faculty include some of the best imagers in the world.

"What the faculty do," says course co-director Holly Cline of The Scripps Research Institute, "is bring certain ideas and tools to the course, maybe a certain kind of transgenic animal, and they lay them out as a smorgasbord for the students." The students learn diverse approaches to the ultimate challenge of visualizing neural circuits, and then they pursue a research project around one of the faculty options. "Many wonderful things, many scientific papers, have come out of the imaging section of this course," Lichtman says.



One of the wonderful aspects of what Jeff Lichtman calls “the green fluorescent protein revolution” is it’s not just green—it’s a rainbow of color. Over the past decade, GFP has been modified to emit light at dozens of different frequencies, primarily by Roger Tsien, who shared this year’s Nobel Prize in Chemistry. Proteins discovered in other sea creatures, such as corals, have broadened the spectral range of fluorescent proteins even further.

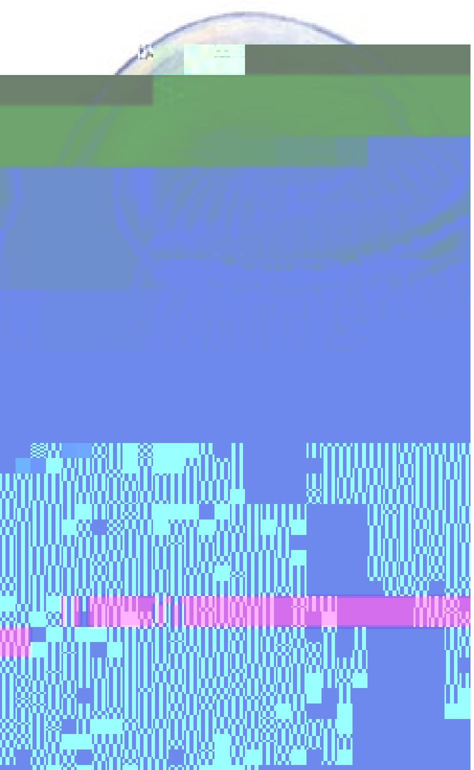
For years before Lichtman became co-director of the MBL Neurobiology course in 2000, he had sought a wayTf98 Tm[wayTctral rangeossage o)sTBTr se of the i3e0(0TBT/v)6arrayha

Accolades

MBL Distinguished Scientist **Osamu Shimomura** was awarded the 2008 Nobel Prize in Chemistry for his discovery of green fluorescent protein. Shimomura shares the prize with **Martin Chalfie** of Columbia University, New York, and **Roger Y. Tsien** of University of California, San Diego. Chalfie is a former lecturer in the MBL's Neural Systems and Behavior course and Tsien is a former lecturer in the MBL Neurobiology course. Tsien was also the Forbes Lecturer in 2005. Shimomura also recently received the Order of Culture, the highest honor given annually to citizens of Japan by the Emperor of Japan.

MBL Corporation Member, Honorary Trustee, and former Chairman of the Board **Sheldon J. Segal** and the Population Council in New York were awarded the Prix Galien USA 2008 Pro Bono Humanum Award for their science-based, global effort in support of reproductive planning and family health.

The American Academy of Arts and Sciences inducted **John Hobbie**, distinguished scientist and senior research scholar in the MBL's Ecosystems Center, into its 2008 class of fellows. Four MBL alumni and 10 course faculty, including Physiology course co-director **Timothy Mitchison** (HarAr4S2008 PrTm1an ive0(ector)]TJ4oi.(fort in suppc ht79 Tm[(H



Inside every cell are hundreds or thousands of proteins, each with a specific role to play in the life of an organism. Before we can understand how muscles contract, how the immune system defends, or how the nervous system performs, we must first understand how proteins work in cells. Yet proteins are too small to be seen by light microscopy alone. For decades, scientists could only deduce their behavior.

Green fluorescent protein (GFP) from the jellyfish *A* has changed all that. Discovered by Osamu Shimomura in 1961, GFP is now the gold-standard tool in microscopy for illuminating protein processes, with far-reaching consequences for research on conditions from cancer to AIDS. This year, Shimomura of the MBL, Martin Chalfie of Columbia University, and Roger Tsien of University of California, San Diego, received the Nobel Prize in Chemistry for

Scaling the Super-Resolution Peak

Jennifer Lippincott-Schwartz, a faculty member in the MBL Physiology course, is a senior investigator at the National Institutes

A Cell and its Fate

Edmund B. Wilson was one of the greatest cell biologists of the 20th century and, not by coincidence, he was also an uncommonly good microscopist. When Wilson made his masterful study of early development in the marine worm , in 1892, scientific illustration was a mature art and photomicrography was just coming into vogue. Wilson, a Columbia University professor and MBL trustee for nearly 50 years, collected , in Woods Hole, isolated and fertilized its egg cells, and then watched the original cells divide "all through the night," recording each stage with a camera, then adding fine details by hand to the camera sketch. Wilson credits his methods for fixing and staining the embryos for rendering "preparations of the utmost beauty and clearness," in which "the relations of the dividing cells may be studied with the utmost accuracy." After these cell lineage or cell fate studies, Wilson began to focus on the nucleus, and he and W. S. Sutton helped make the all-important connection between the chromosomes and inheritance. "The key to every biological problem must finally be sought in the cell," Wilson wrote, "for every living organism is, or at some time has been, a cell."

From E.B. Wilson (1892) "The Cell-Lineage of , . A Contribution to the Cytogeny of the Annelid Body," . , VI: 361-480. An original copy of this issue of the journal, which was edited by Charles O. Whitman, the first director of the MBL, is stored with "Selected Reprints of Edmund B. Wilson" in the MBLWHOI Library.

Catalyst

Translational Research

When Osamu Shimomura discovered a green, glowing protein in a jellyfish, he didn't dream it would be applied as a tool that has revolutionized biomedical research. Yet marine organisms are key to critical advances in