A Nobel Tradition

The MBL and the Nobel Foundation were created in the same era, and their shared histories weave a distinguished portrait of life-sciences research from the 1880s to today. Swedish industrialist Alfred Nobel, the inventor of dynamite, specified in his will that his fortune be used for “prizes to those who . . . have conferred the greatest benefit on mankind.” In 1901, the first Nobel Prizes were awarded for achievements in Physics, Chemistry, Physiology or Medicine, Literature, and the promotion of Peace. The MBL was but 13 years old, but already it had a future Nobel laureate—**Thomas Hunt Morgan**—among its investigators and trustees.

Since that first prize ceremony, 53 Nobel laureates have performed research, taught, or been a student at the MBL (see running list over the next eight pages). It is hard to even imagine science and medicine today without their contributions. From **Otto Lowei**, often called the “Father of Neuroscience,” who first described the chemical transmission of the nerve impulse . . . to **James D. Watson**, who co-discovered the “double-helix” structure of DNA . . . to **Eric Wieschaus** and **Christiane Nüsslein-Volhard**, who found genetic mechanisms that control early embryological development . . . this is an extraordinary record of discovery.

The Nobel laureates affiliated with the MBL largely defined what we know about the biology and chemistry of life today.

In the next few pages, we profile just four of the Nobel laureates who have been, or still are, part of the MBL community. And we respectfully salute all our affiliated Nobel laureates, past and present, for sharing their knowledge with the MBL and for the benefit of mankind.

NOBEL LAUREATES AFFILATED WITH THE MBL

1920 August Krogh
Physiology or Medicine

1922 Otto Meyerhof
Physiology or Medicine

1931 Otto Warburg
Physiology or Medicine

1933 Thomas Hunt Morgan
Physiology or Medicine

1936 Otto Loewi
Physiology or Medicine

1937 Albert Szent-Györgyi
Physiology or Medicine

1943 (Carl Peter) Henrik Dam
Physiology or Medicine

1946 Hermann Muller
Physiology or Medicine

1946 John Northrop
Chemistry

Thomas Hunt Morgan and members of his "Fly Room" converse with fellow MBL investigators in 1919. Clockwise from left: T.H. Morgan, Calvin Bridges, Franz Schrader, Ernest Everett Just, Alfred H. Sturtevant, and an unidentified person. (MBL Archives)

The Birth of Experimental Genetics

Thomas Hunt Morgan

MBL investigator, 1890-1942
MBL trustee, 1897-1945

1933 Nobel Prize in Physiology or Medicine, "for his discoveries concerning the role played by the chromosome in heredity"

Early in the summer of 1910, Thomas Hunt Morgan made his customary trip to the MBL, where he settled into his laboratory in the Crane Building. Morgan, a professor at Columbia University, and his family enjoyed their summers in Woods Hole, especially the company of their neighbors, the Edmund B. Wilson family. This year, though, Morgan had exciting new results that would keep him exceedingly busy over the ensuing months. This summer would turn out to be a watershed in his career.

Two years earlier, Morgan had become one of the first researchers to start using the fruit fly, *Drosophila*, as an experimental organism. Morgan began breeding fruit flies in order to test an alternative to Charles Darwin's theory of natural selection, which he thought was insufficient to explain the origin of new species. However, in the spring of 1910, Morgan noticed something striking in his stocks of flies at Columbia University—something that set him off on a new path of inquiry.

What Morgan noticed was a mutation—white eyes instead of the customary red—that showed up in male flies only. He wondered if the white-eye mutation were somehow linked to whatever determined "maleness" in the flies.

(How sex was determined was then a topic of vigorous debate and research, at the MBL and elsewhere. Edmund B. Wilson and others had proposed that chromosomes were responsible, but this was not yet experimentally proven.)

By June, Morgan had done enough experiments to be sure that maleness and white-eye were always inherited together. He wrote up his results in Woods Hole and submitted them to the journal *Science*; this paper, "Sex-Limited Inheritance in *Drosophila*," is now a classic in the history of genetics. Morgan soon demonstrated what was occuring: The "factor" or gene for white eyes was located on the chromosome that determined maleness.

By 1913, Morgan and his colleagues had invented a way to "map" the location of specific genes on chromosomes.

Over the next fifteen years, Morgan and his colleagues in the famous "Fly Room" at Columbia University moved their research program to the MBL every summer. "This did not mean any interruption in the *Drosophila* experiments," later wrote his close colleague A.H. Sturtevant. "All the (fly) cultures were loaded into barrels—big sugar barrels—and what you started in New York, you'd finish (in Woods Hole) and vice versa . . . This was the beginning of the detailed proof that genes were localized in the chromosomes."

When Morgan received the Nobel Prize in 1933, it was the first time the prize was awarded for discoveries in genetics. However, throughout his MBL career, Morgan actively investigated embryology and regeneration in marine organisms, even while his *Drosophila* genetics research was going on. "That was the way Morgan worked: he wasn't happy unless he had a lot of different irons in the fire at the same time," Sturtevant observed. Part of Morgan's broad scientific legacy is his book, *Regeneration* (1901), which today provides a useful and insightful perspective on regenerative biology and medicine.

Morgan was deeply involved with organizational matters at the MBL, serving as trustee from 1897 to 1936, at which point he became trustee emeritus. The early years of Morgan's trusteeship were a time of great struggle for the laboratory. Partly because it had grown so quickly, the MBL faced serious financial challenges and even "takeover bids" by the University of Chicago in 1901 and the Carnegie Institution in 1902. "In a halting and confused situation, no one could be more helpful than (Morgan), for with lightening-like rapidity he would isolate the main issue from the minor ones and go straight to a logical conclusion," wrote embryologist E. G. Conklin of Morgan's assistance during these years of "growing pains."

Morgan and his wife, biologist Lilian V. (Sampson) Morgan, had four children, and their home on Buzzards Bay Avenue in Woods Hole was usually full of friends and visiting relatives. In 1913, Lilian Morgan co-founded what is now the Children's School of Science in Woods Hole. The Morgan family certainly left their imprint on the MBL, not least in T.H. Morgan's place as the earliest MBL investigator to be awarded the Nobel Prize.

1946 Wendell Stanley
Chemistry

1953 Fritz Lipmann
Physiology or Medicine

1954 Thomas H. Weller
Physiology or Medicine

1958 George Beadle
Physiology or Medicine

1958 Joshua Lederberg
Physiology or Medicine

1960 Donald Glaser
Physics

1962 James Watson
Physiology or Medicine

1963 John Eccles
Physiology or Medicine

1963 Alan Hodgkin
Physiology or Medicine

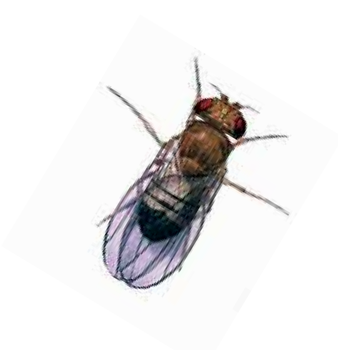
1963 Andrew Huxley
Physiology or Medicine

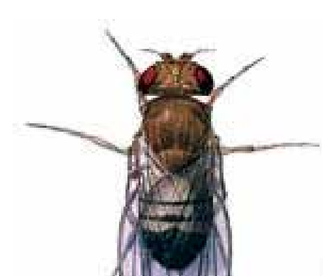
1964 Konrad Bloch
Physiology or Medicine

1967 Keffer Hartline
Physiology or Medicine

1967 George Wald
Physiology or Medicine

1969 Max Delbrück
Physiology or Medicine





If These Walls Could Talk

Jacques Loeb, Tim Hunt, and the Discovery of Cyclin

1969 Salvador Luria
Physiology or Medicine

1974 Albert Claude
Physiology or Medicine

1975 David Baltimore
Physiology or Medicine

1975 Howard Temin
Physiology or Medicine

1976 D. Carlton Gajdusek
Physiology or Medicine

1980 Paul Berg
Chemistry

1980 George D. Snell
Physiology or Medicine

1981 David Hubel
Physiology or Medicine

1981 Torsten Wiesel
Physiology or Medicine

1983 Barbara McClintock
Physiology or Medicine

1986 Stanley Cohen
Physiology or Medicine

1989 Sidney Altman
Chemistry

1991 Bert Sakmann
Physiology or Medicine

1995 Christiane Nüsslein-Volhard
Physiology or Medicine

Tim Hunt

Faculty member, MBL
Embryology course, 1979-1980, 1987 and Physiology course, 1980-1983, 2004
MBL investigator, 1985-1986
MBL corporation member, 1991-2006

2001 Nobel Prize in Physiology or Medicine, "for the discovery of cyclins, key regulators of the cell cycle"

The news coming out of the MBL in late 1899 was a headline writer's dream at *The Boston Herald*:

> "Creation of Life. Startling Discovery of Prof. Loeb. Immaculate Conception Explained. Wonderful Experiments Conducted at Woods Hole."

The occasion for the excitement was Jacques Loeb's demonstration, at the MBL, that sea-urchin eggs will divide and form early larvae when immersed in a certain salt solution. Here was apparent fertilization and development—with no sperm required! The press had a field day with Loeb's experiment, which he called "artificial parthenogenesis," and Loeb was compared to "creators" of life from Faust to Frankenstein. The event put the MBL on the map for the general population. It was, in the words of historian Philip Pauly, "the first major manipulation of the reproductive process to reach the public."

Scientists were more circumspect than the press, of course, but after artificial parthenogenesis was repeated using other animals, its usefulness for studying development—and its implications for manipulating human reproduction—were widely acknowledged. In 1901, Loeb was a finalist for the very first Nobel Prize in Physiology or Medicine.

Jacques Loeb

Loeb, who died in 1924, left a big footprint at the MBL and everywhere else. His belief that life could be reduced to physics and chemistry—without invoking vital forces—largely set the tone for 20th century biological research worldwide. On the very spot where Loeb's small, wooden laboratory once stood is now the three-story Loeb Laboratory, the main teaching facility on the MBL campus. The students and faculty who have passed through the doors of Loeb Laboratory comprise a who's who of international biology. If only those walls could talk, we would hear countless stories of learning and discovery at the cutting edge of biological research.

And perhaps those walls did talk, in the summer of 1982. That year, Tim Hunt of Cambridge University made a profound discovery in Loeb Laboratory, one that would later bring him the Nobel Prize. It is most fitting that Hunt was on the faculty of the MBL Physiology course, which Loeb had founded in 1899.

It was late July. The formal portion of the Physiology course was over and a post-course research period had begun. Hunt was trying to make inroads on a stubborn research problem, with the help of a few students, but he wasn't having much luck. Three years earlier, in the MBL Embryology course, Joan Ruderman and Eric Rosenthal of Harvard Medical School had noticed that, just after surf clam eggs were fertilized, unknown proteins were synthesized in the eggs. Hunt, Ruderman, and Rosenthal began to study those proteins. What were they for? What activated their synthesis? Hunt was still mulling over these questions in the 1982 Physiology course. By then, he was trying out various hypotheses using sea urchin eggs.

"We had almost run out of ideas. It was thus a good moment to perform a simple experiment," Hunt later wrote. He decided to parthenogenetically activate sea urchin eggs—as Loeb had first done—and compare their patterns of protein synthesis with fertilized sea urchin eggs. The result was startling—in the fertilized eggs only, one protein abruptly declined in intensity just before the eggs divided, and then came back afterwards. These oscillations persisted for several hours after fertilization. "From the start, I felt in my bones that we had made an important discovery about control of the cell cycle," Hunt wrote, and indeed he had.

Hunt had discovered a class of proteins, the cyclins, whose synthesis is absolutely required for cell division to be sustained over time.

He and his collaborators first announced their results at the MBL General Scientific Meetings that summer, and published them in the MBL's journal, *The Biological Bulletin*. In 2001, Hunt was awarded the Nobel Prize in Physiology or Medicine for his discovery.

And as for Jacques Loeb's legacy to the MBL? It just continues to grow. In 2009, a $25 million renovation and modernization of Loeb Laboratory will begin. The biological discoveries to happen on that spot of earth, in all likelihood, have only begun.

The Story Unfolds

Tim Hunt's 1982 discovery wasn't the end of the cyclin story at the MBL. In subsequent years, Joan Ruderman of Harvard Medical School (above) cloned the cyclin genes and showed how they worked at the molecular level. Ruderman, who is currently President of the MBL Corporation, also discovered that cyclins are overexpressed in human breast cancer cells.

In the early 1990s, Avram Hershko of the Technion-Israel Institute of Technology began coming to the MBL to collaborate with Ruderman, who had developed a test-tube system for studying cyclin degradation in clam egg extracts. Hershko wondered whether a certain protein, ubiquitin, mediated the periodic destruction of cyclin during the cell cycle. Hershko found that this was the case, working in collaboration with Ruderman and Robert Palazzo, then of University of Kansas. In 2004, Hershko was awarded the Nobel Prize in Chemistry for his earlier work in the 1980s to establish the basic mechanism of ubiquitin-mediated protein degradation.

(NOAA)

Toward A Peaceful Environment

The Intergovernmental Panel on Climate Change (IPCC), and Al Gore Jr.

2007 Nobel Peace Prize, "for their efforts to build up and disseminate greater knowledge about man-made climate change, and to lay the foundations for the measures that are needed to counteract such change"

"I would like to pay tribute to the scientific community, who are the winners of this award," said R.K. Pachauri, chairman of the Intergovernmental Panel on Climate Change (IPCC), on the day the panel was named a laureate of the 2007 Nobel Peace Prize. With these words, Pachauri warmly saluted the hundreds of scientists who had contributed to the panel's work, including Jerry Melillo, then co-director of the MBL Ecosystems Center.

Melillo served as a lead author for the panel's first two assessment reports on global climate change, published in 1990 and 1995. The IPCC, which is part of the United Nations, publishes scientific reports every five to six years that assess climate change with regard to degree, causes, consequences, and potential counter-measures.

The panel created a firm scientific foundation for a very complex and controversial global issue, the Nobel Foundation acknowledged. "There was for a long time great doubt about whether global warming was man-made. Thanks to the IPCC, there is very little such doubt today," noted Nobel Committee chairman Ole Danbolt Mjøs at the award presentation ceremony in Stockholm.

(T. Kleindinst)

Jerry M. Melillo

Senior Scientist, MBL Ecosystems Center

"The evidence continues to get stronger and stronger that humans are responsible for much of the recent climate change," says Melillo. "The IPCC reports have had a tremendous effect on policymakers."

In the IPCC's first assessment report, Melillo was a convening lead author of a chapter on the effects of climate change on ecosystems. That report became one of the basic documents at the U.N. Conference on Environment and Climate in 1992. In the panel's second assessment report, Melillo co-authored a chapter on terrestrial responses to environmental change and resulting feedbacks to the climate system. That report provided key input to the negotiations that led to the adoption of the Kyoto Protocol in 1997.

In choosing a panel of ecosystems scientists and Al Gore as Peace Prize laureates, the Nobel Foundation highlighted the fraught connections between climate stability and world peace.

"One of the great fears is that the various aspects of climate change—sea level rise, changes in precipitation patterns, drought, and so on—will create large numbers of 'environmental refugees,'" says Melillo. "That has the potential to be tremendously disruptive to global peace."

Climate change has many adverse impacts that threaten the security of populations that are forced to migrate, Pachauri said in his Nobel lecture. These include water and food shortages, unstable health conditions, and loss of environmental resources such as arable land. The recent "climate wars" in Darfur and across the Sahel belt of Africa, brought on by tribal dislocations due to the continuing advance of the Sahara desert, are an early warning of the link between climate change and conflict.

For decades, Melillo has focused his research on how land systems and changes in land use feedback to the climate ecosystem. "For example, if one clears large swaths of forests by burning, this releases carbon dioxide to the atmosphere, which basically promotes climate change by adding to the greenhouse gas load," he says. Today, Melillo evaluates various scenarios for mitigating and adapting to climate change—such as the commitment of large parcels of land to biofuels crops—and how these scenarios may lead to unintended consequences. "I think one of the jobs that scientists have to take on is to consider these consequences for policymakers," says Melillo, who recently completed a report on human activities and climate change for the U.S. government.

The IPCC is a scientific body, and it is not policy prescriptive. However, it provides key scientific input to the U.N. Framework Convention on Climate Change (UNFCC), whose goal is to stabilize greenhouse gases at a level that has not yet been quantified. Melillo, and many others, hope this level will finally be set at the UNFCC convention in Copenhagen in December 2009. Once again, the work of the IPCC—which issued its fourth assessment report in 2007—will be critical.

"The Nobel Peace Prize to the IPCC was recognition of the long-term value of the scientific assessment process and a very high-level and credible dialogue between scientists and policymakers," says Melillo. "The next step is Copenhagen."

1995 Eric Wieschaus
Physiology or Medicine

1997 Paul. D. Boyer
Chemistry

1997 Jens C. Skou
Chemistry

2000 Paul Greengard
Physiology or Medicine

2000 Eric Kandel
Physiology or Medicine

2001 Leland Hartwell
Physiology or Medicine

2001 Tim Hunt
Physiology or Medicine

2002 Sydney Brenner
Physiology or Medicine

2002 H. Robert Horvitz
Physiology or Medicine

2003 Roderick MacKinnon
Chemistry

Burning the rainforest to clear land for oil palm plantations near the Bukit Tigapuluh Nature Reserve, Sumatra, Indonesia. (©WWF-Canon/M. Edwards)

In a Flash

Hours after becoming a 2008 Nobel Laureate in Chemistry, Osamu Shimomura meets the media at the MBL. (B. Liles)

Flashes of light have accompanied many milestones in Osamu Shimomura's life. On the morning of October 8, 2008, the camera flashes from an international crowd of journalists greeted him upon his arrival at the MBL. A few hours earlier, Shimomura had received the exciting call from Stockholm: He had been awarded the Nobel Prize in Chemistry for his discovery of green fluorescent protein (GFP), a naturally green-glowing molecule in the jellyfish *Aequorea*. Not only does GFP help the jellyfish glow, it is now used by scientists worldwide to light up living cells and their minute parts for microscopic study.

"(GFP) has become one of the most important tools used in contemporary bioscience," stated the Nobel Foundation in the prize announcement. "With the aid of GFP, researchers have developed ways to watch processes that were previously invisible, such as the development of nerve cells in the brain or how cancer cells spread."

Shimomura shared the Nobel Prize with Martin Chalfie of Columbia University, who first demonstrated the value of GFP as a luminous tagging tool in biomedical research, and Roger Tsien of University of California, San Diego. Tsien engineered GFP to glow in many colors, which allows scientists to tag and follow several biological processes at once. Both Chalfie and Tsien have served as faculty members for MBL training programs.

When Shimomura discovered GFP in 1961, he was trying to isolate a light-emitting substance from *Aequorea* that allows it to bioluminesce. Thanks to an unexpected flash of blue light, he finally succeeded.

2004 Avram Hershko
Chemistry

2004 Irwin Rose
Chemistry

2006 Roger D. Kornberg
Chemistry

2008 Martin Chalfie
Chemistry

2008 Osamu Shimomura
Chemistry

2008 Roger Y. Tsien
Chemistry

Osamu Shimomura

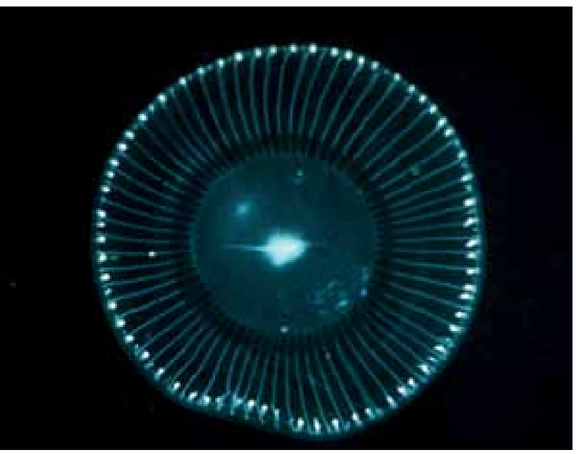
MBL distinguished scientist, 2008 to present
MBL senior scientist, 1982-2001
MBL corporation member, 1988 to present,
MBL library researcher, 2002 to present

2008 Nobel Prize in Chemistry, "for the discovery and development of the Green Fluorescent Protein."

MBL Distinguished Scientist Osamu Shimomura and his wife, Akemi, who worked for many years as his research assistant. (T. Kleindinst)

For several weeks, Shimomura and his mentor, Frank Johnson of Princeton University, along with Shimomura's wife, Akemi, had been collecting thousands of jellyfish in the waters off Friday Harbor Laboratories, University of Washington. They cut off the "ring" from each jellyfish where the light organs are located, and tried various chemicals and methods to isolate the light-emitting substance. Yet all their efforts failed. Johnson was convinced that the bioluminescence must be caused by the interaction of an enyzme, luciferase, with a substrate, luciferin, but Shimomura disagreed. The two were at an awkward impasse.

"I spent several days soul-searching, trying to find out something missing in my experiments and thought," Shimomura later wrote.



Aequorea *(O. Shimomura)*

Often, he took a rowboat out into the middle of the harbor, where he drifted and meditated on the problem.

One afternoon, Shimomura had a thought: the luminescence system must include a protein, even if it isn't luciferase. To test the idea, he could turn the protein's action off by simply changing the pH level inside the jellyfish rings.

Shimomura hurried back into the lab and performed the test, which did indeed show that luminescence stopped when a protein was inhibited. "But a big surprise came at the next moment," Shimomura wrote.

"When I threw the extract into a sink, it lit up with a bright blue flash."

The sink contained seawater from an overflowing aquarium, and Shimomura soon discovered that calcium, a component of seawater, activated the luminescence. The knowledge enabled him to devise an extraction method for *Aequorea's* bioluminescence protein, which he called aequorin, and for its companion protein, GFP.

Soon Shimomura was shipping out aequorin samples to researchers all over the world, who used it as a means to measure calcium in living systems. Nobody paid too much attention to GFP, on the other hand. It did interest J. Woodland Hastings and James Morin of Harvard University, who studied GFP at the MBL in the early 1970s. Shimomura characterized GFP in 1974, and in 1979 he elucidated the structure of its chromophore (the part responsible for its green fluorescence), which exists within its peptide chain. Yet it wasn't until Chalfie demonstrated GFP's utility as a fluorescent tag in 1994 that the molecule found its fame.

Shimomura, meanwhile, always remained interested in the chemistry of how the aequorin molecule emits light. He finally solved this puzzle in 1978 after enormous effort. (His work on *Aequorea* involved collecting 850,000 jellyfish over 18 summers.) "GFP was just a by-product in my work on aequorin," he says. "Even so, I'm very glad GFP has made huge contributions to science!"

The accomplishment is remarkable in its own right, but is even more so given another flash in Shimomura's life, a horrible one—the Nagasaki atomic bomb. On August 16, 1945, the 16-year-old Shimomura was working in a military plane factory 10 miles outside of Nagasaki. Like many of Japan's youth, he had been taken out of school to work for the war effort.

Shortly before 11 AM, an enemy plane flew over Nagasaki, and he and a friend ran outside and climbed a hill to watch it. Minutes later, thinking the danger had passed, Shimomura returned to the factory and sat down on his work stool.

"At that moment, a big flash came," he recalls. "It blinded me for about 30 seconds."

"I couldn't see anything because of the brightness. Then about 40 seconds later was a very strong, not a sound, but a pressure wave."

"I had pain in my ears, I couldn't hear for a couple of minutes. We wondered, what had happened? We knew it was an explosion. We didn't know it was an atomic bomb."

At 5 PM, Shimomura left the factory to walk home, three miles away. "On the way home, then started the black rain," he says of the nuclear fallout. "I was soaked. I was wearing a white shirt, and I became completely gray. When I got home, my grandmother saw me and quickly made a bath and washed everything off." Shimomura thinks this reduced the amount of radiation damage he received.

Shimomura feels extremely fortunate to have survived the Nagasaki atomic bomb, and to have been given an opportunity, in post-war Japan, to begin research on bioluminescence at Nagoya University. His success there at purifying the bioluminescent substance from the sea firefly, *Cypridina*, changed his life and led to a research post at Princeton.

"Before that time, my life was very dark. Since the atomic bomb, nothing was good. That success with *Cypridina* gave me some light, somewhere," he says.

Fortunately for science and for mankind, it lit Shimomura's path toward the discovery of GFP.