MBL
Biological Discovery in Woods Hole
Catalyst

Founded in 1888 as the Marine Biological Laboratory

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Science That Makes a Difference

How basic research at the MBL solves real-world problems

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MBL Catalyst

Spring 2009 Volume 4, Number 1

MBL Catalyst is published twice yearly by the Office of Communications at the MBL in Woods Hole, Massachusetts. The MBL is an international, independent, nonprofit institution dedicated to discovery and to improving the human condition through creative research in the biological, biomedical, and environmental sciences. Founded in 1888 as the Marine Biological Laboratory, the MBL is the oldest private marine laboratory in the Americas.

About the cover: A boy in L'Acul, Haiti, where MBL experts are teaching sustainable methods of freshwater-fish farming to give villagers a reliable source of protein and much-needed income. (Photo by Bill Mebane. Story on page 12.)

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From the Director

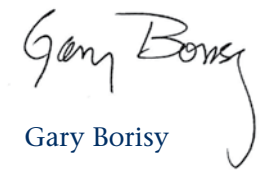
Dear Friends,

At the MBL, we continually look ahead by pushing the frontiers of the biological sciences. We know that these fundamental studies will pay off in the long run, and will bring great benefits to medicine and the welfare of society. Yet we also know that translational results—such as new medical therapies—began with the most basic biological research. In this issue of *MBL Catalyst*, we highlight how MBL basic research has translated to important applications, sometimes in unexpected ways. And we spotlight current activities that may lead to solutions to some of our most important social challenges.

We are tremendously encouraged by recent support, at both the state and national levels, for basic research as a crucial investment and stimulus for economic growth. Last year, Massachusetts Governor Deval Patrick spearheaded and signed into law a $1 billion Life Sciences Act, $10 million of which was awarded to the MBL. And President Obama's American Recovery and Reinvestment Act makes the largest investment in basic research funding in the nation's history. Clearly, the MBL is at the forefront of an invigorated era in science and technology. While our basic research programs are laying the foundation for great advances in medicine and environmental management, our educational program is training future leaders in the biological and ecological sciences.

One very promising avenue at the MBL is our new initiative in regenerative biology and medicine, which builds on several of the MBL's longtime strengths. In this emerging discipline, scientists are laying the groundwork for future medical therapies to restore lost, damaged, or aging cells and tissues in the human body. Many animals are able to regenerate a wide range of tissues and organs, from the cornea to the complete nervous system. We seek to understand these stem-cell driven regenerative processes, taking advantage of the MBL's renowned expertise in developmental biology and the remarkable ability of aquatic organisms to regenerate. With a generous contribution from the Bell family, we have established an annual visiting scientist research fellowship in this area, and we are partnering with scientists at UMass Dartmouth, Brown and elsewhere to develop collaborative opportunities in this important field.

I wish to extend my thanks to Josh Hamilton, guest science editor for this issue of *MBL Catalyst*. As the MBL's chief academic and scientific officer, Josh is a key member of our leadership staff. Under his guidance, the Brown-MBL Graduate Program is flourishing, and Josh is also identifying opportunities for intellectual property transfer from the MBL. Given the MBL's success in scientific education and discovery, both responsibilities are keeping him very busy.



Gary Borisy

Director and Chief Executive Officer
Marine Biological Laboratory

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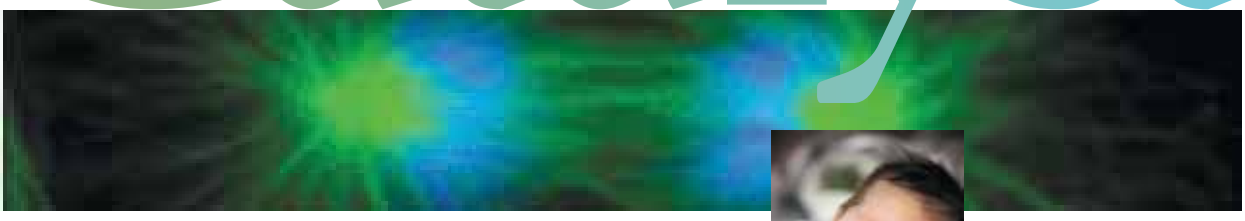

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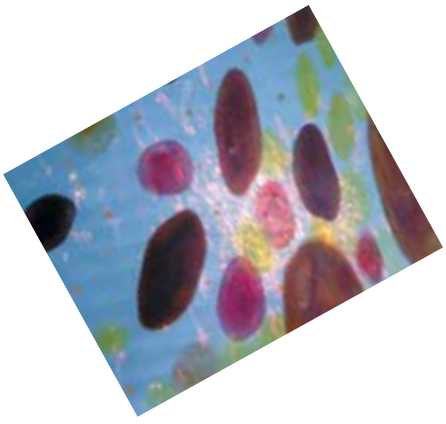
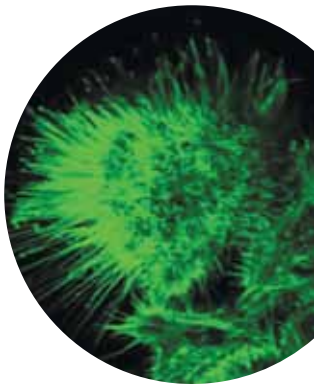


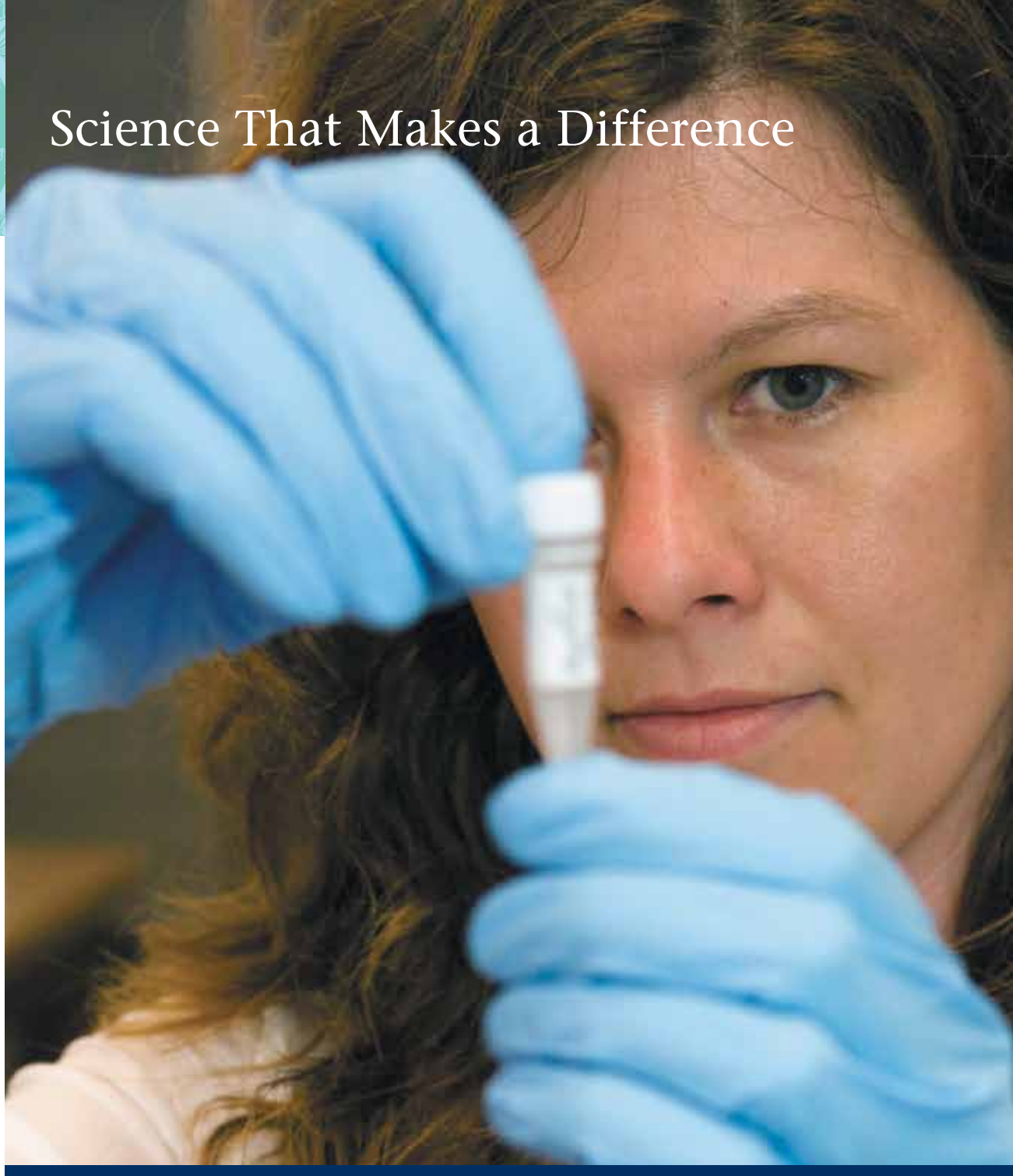


Departments

Science That Makes a Difference

"Science, no matter how basic or applied, has meaning and impact through its contribution toward the betterment of humankind."

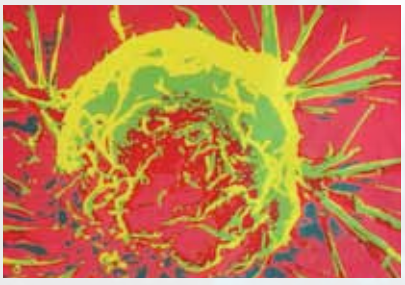
— Sheldon Segal, MBL Honorary Trustee



Every day at the MBL, researchers pursue the exacting, unbiased process of basic scientific inquiry into nature—from how a single cell develops to the ecological relationships that balance our biosphere. From this endeavor, many enormously important contributions to health and human welfare have sprung. In this issue of *MBL Catalyst*, meet some of these dedicated MBL scientists, and discover the remarkable—and sometimes surprising—applications of their knowledge to benefit society.

Basic research powers the engine of progress, and benefits us all.

Here are some examples from the MBL:

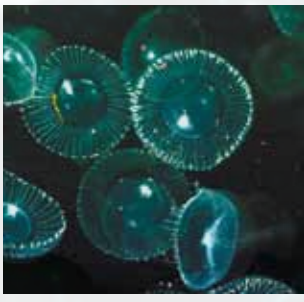


Tim Hunt discovered the protein cyclin at the MBL in 1982 and, more recently, cyclin's role in breast cancer has come to light. Today, therapies that target cyclin in order to block expansion of cancerous stem cells are under development.

In Type 1 diabetes, the insulin-producing cells in the islets of Langerhans, the region of the pancreas where hormones are produced, are selectively destroyed by an autoimmune process. Many researchers are seeking ways to engineer functioning islets of Langerhans for transplantation into diabetic patients. One novel approach is being developed by Peter J.S. Smith of the MBL Cellular Dynamics Program and Ron Pethig of University of Edinburgh. By manipulating the electrical field around insulin-producing cells, they are able to draw the cells into matrices that mimic islets of Langerhans.

The Oosight™ microscope, based on MBL technology, is used in fertility clinics to assess the health of eggs prior to *in vitro* fertilization. The imaging technology was developed by Rudolf Oldenbourg and Michael Shribak of the MBL's Cellular Dynamics Program, and is licensed to Cambridge Research & Instrumentation (CRi), Inc. CRi developed the microscope for clinical use in collaboration with former MBL investigators David Keefe and Lin Liu.

This food- and waterborne parasite, *Giardia lamblia*, is prevalent in developing countries and causes more the 20,000 intestinal infections a year in the United States. The MBL's Hilary Morrison and her colleagues sequenced the genome of *Giardia*, and identified several potential drug targets for the persistent giardiasis infection. New drugs for the infection are currently being investigated at other institutions.



MBL distinguished scientist Osamu Shimomura discovered the green fluorescent protein (GFP) in the *Aequorea* jellyfish in 1962. Today, researchers worldwide use GFP to illuminate cellular processes that were previously invisible. Roger Tsien, a co-recipient of the 2008 Nobel Prize in Chemistry with Shimomora and Martin Chalfie, is now developing fluorescent nanoparticles that will light up the edges of tumors for cancer surgeons as they operate.

On Fertile Ground

MBL research has helped millions of women to conceive and manage their reproductive years

Infertility treatment can be a long, trying journey, marked by monthly cycles of hope and disappointment. But some women conceive quickly, within the first few months of treatment, and usually it's because they have responded well to the drug clomiphene citrate (Clomid™). These women may know that clomiphene stimulates production of the hormones the ovaries need to ripen and release a mature egg. What they probably don't know is sea urchin research at the MBL played a role in Clomid's development—and in their happy state of expectant motherhood.

"Leading directly from basic research to its applications rarely happens," says Sheldon Segal, a pioneering contraceptives researcher and former chairman of the MBL Board of Trustees. The remarkable path from sea urchin eggs to pregnant women was no exception.

Segal was a young scientist at the Rockefeller Institute in New York in 1957 when he was surprised by a phone call from the distinguished developmental biologist, Albert Tyler. "Albert invited me to his lab at the MBL," Segal remembers, and he didn't hesitate to accept—even though it meant sleeping on the porch of an MBL dorm all summer!

At Rockefeller, Segal had been studying compounds related to the synthetic hormone stilbestrol, and he had found one that seemed to be an effective contraceptive in laboratory mammals. "The question was, why?" Segal says. "Albert proposed I study the effect of this compound on the developing sea urchin at the MBL. If you are going to study embryos, it's hard to do in mammals, because you can recover only a few eggs per reproductive cycle. But if you use sea urchins or clams, you get thousands of eggs in a spawning season, and they are all dividing in synchrony. It's like a beautiful concert."

That productive summer in Tyler's lab would provide Segal with a "lifelong thrill and memory." Segal eventually found that the compound prevented pregnancy in mammals by accelerating the passage of eggs in the fallopian tube. And here's where the story takes an unexpected twist. The compound had been provided to Segal by a pharmaceutical company, William S. Merrell Company (later absorbed by Aventis), and they gave him permission to supply the compound in tablet form to Robert Greenblatt, a pioneering infertility clinician at the Medical College of Georgia. Greenblatt wondered if the compound might be used not as a contraceptive, but to induce ovulation.

"Greenblatt had tried everything, but he hadn't been able to help his anovulatory patients," Segal says. But when he gave them the tablets, "Lo and behold, they ovulated!" Greenblatt and the Merrell Company began working

on optimizing that compound and others like it, with Segal and others performing laboratory studies prior to Greenblatt's clinical studies. The Worcester Foundation for Experimental Biology, directed by MBL corporation member Thoru Pederson, played a major role in the evaluations. One of the compounds eventually became Clomid, while others turned out to be useful for treating breast cancer and osteoporosis.

"The body is full of surprises," Segal says of the compound's unanticipated therapeutic values. "That's not unusual in pharmacology, that you'll try one thing but something unexpected happens that is useful."

Segal had been so positively "overwhelmed by the MBL" and his sojourn in Tyler's lab that, in 1973, he came back and started up his own lab, which he ran for many summers. By then, Segal was a scientist at the Population Council in New York, where he was immersed in developing safe, long-lasting contraceptives to give women in impoverished countries a way to manage the size of their families. At the MBL, Segal continued basic research on fertilization in sea urchins and clams, and collaborated with other luminaries such as the late Luigi Mastroianni, whose groundbreaking work would pave the way for *in vitro* fertilization.

At the Population Council, Segal directed the research that led to the development of copper-bearing IUDs (intrauterine devices) and of implant contraceptives, such as Norplant™.

Today, an estimated 120 million women worldwide use the long-acting contraceptives, mainly various types of IUDs, that were developed by Segal's group.

Along with rolling up his sleeves as a scientist, Segal engineered visionary partnerships between industrial and nonprofit groups to deliver implant contraceptives to women all over the globe. Last year, those partners (Segal and the Population Council, the late Judah Folkman of Harvard University, Dow-Corning, and Wyeth) were honored for their work with the Prix Galien USA Pro Bono Humanum Award.

"I realized early in my career that you need such partnerships for the ultimate translation of any idea to the actual product," Segal says. "Developing a product is not just a lightbulb flashing. The scientific finding is just the beginning." •

–DK

Vital Statistics:

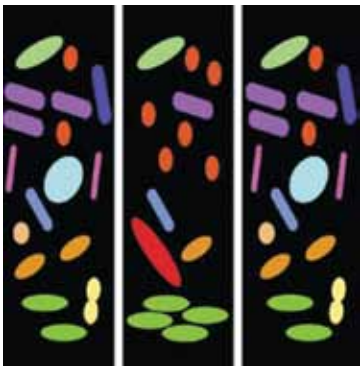
Sheldon J. Segal, Ph.D., M.D., h.c.,
Distinguished Scientist,
The Population Council

MBL CONNECTIONS:
Chairman of the MBL Board of Trustees, 1991-2002;
Trustee, Honorary Trustee, 1982 to present;
Corporation Member since 1973;
MBLWHOI Library Reader since 2002;
former Visiting Investigator

A Marine Marvel

During his first summer at the MBL, Sheldon Segal stepped into the illustrious tradition of using the sea urchin *(Arbacia)* to study fertilization and development. Summer is the reproductive season for this spiny creature in Woods Hole, and it casts its abundant, transparent eggs directly into seawater in the lab, where they are easily fertilized and studied. *Arbacia* research at the MBL has provided great insights over the past century, such as Ernest Everett Just's discovery in 1919 of how the fertilized egg blocks entry to other sperm. The sea urchin is so important in developmental biology that its genome was sequenced in 2006, with many MBL investigators taking part.

"You can stand on the corner of MBL Street and Water Street in Woods Hole and meet every currently and newly important scientist. No other place in the world has the kind of scientific ambiance that the MBL has."

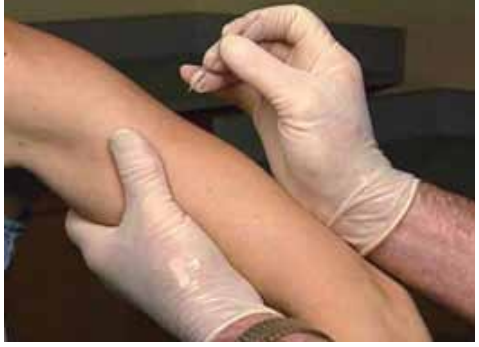


After Antibiotics, Your Gut Just Isn't The Same

Using a novel technique developed by MBL Bay Paul Center director Mitchell Sogin to identify different types of bacteria, scientists have completed the most precise survey to date of how microbial communities in the human gut respond to antibiotic treatment. Sogin and his co-authors at the MBL and Stanford University identified pervasive changes in the gut microbial communities of three healthy humans after a five-day course of the antibiotic Ciprofloxacin. Using very conservative criteria, the scientists identified at least 3,300 to 5,700 different taxa (genetically distinct types) of bacteria in the human distal gut, and antibiotic treatment influenced the abundance of about a third of those taxa. In all of the individuals tested, the bacterial community recovered and closely resembled its pre-treatment state within four weeks after antibiotic treatment, but several bacterial taxa failed to recover within six months. This raises questions about the health effects of changes to the human-microbial symbiosis in the gut. "When you change the microbial population structure in the gut, you may affect how that population is keeping indigenous pathogens at manageable levels," says Sogin. Bacteria that do not normally cause problems, for example, may begin to grow more rapidly, and cause or accelerate disease. (*PLoS Biology,* 6, No. 11, e280 doi:10.1371/journal.pbio.0060280, 2008) •

How Green are Your Biofuels?

As part of President Obama's plan to end the nation's dependence on foreign oil, 60 billion gallons of advanced biofuels would be incorporated into the U.S. energy supply by 2030. Many scientists are urging that if this goal is adopted, it be met in an environmentally sustainable way. Among them is Jerry Melillo, co-director of the MBL Ecosystems Center. Melillo is collaborating with scientists at MIT to model how biofuels production would play out in different regions of the globe in the context of a changing climate. "If all is done well, biofuels can help us to meet the climate change challenge," says Melillo. "Critical issues are where and how you grow the biofuels feedstocks. If you burn forests to establish biofuels 'plantations,' you release a significant amount of carbon into the atmosphere. In terms of an energy budget, you are taking a large 'carbon loan' from nature that will require decades to centuries to pay back before biofuels become part of the climate change solution." In addition, Melillo notes that the biofuels picture gets more complex and less attractive "when you account for energy you have to put into the biofuels plant-growing process in a given region, such as by adding fertilizer or irrigating." The scientists are running alternative biofuels scenarios through economic and environmental models to identify the most sensible places to base this emerging, global industry. •



Database for New Tropical Disease Drugs is a Hit

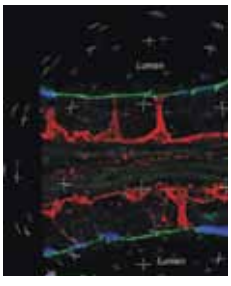
Infectious tropical diseases pose major challenges, but the discovery of new therapeutics to combat them has lagged. One reason is a limited understanding of potential drug targets in the microbes that cause the diseases. To remedy this, the World Health Organization has organized an international consortium of public and private partners, including Robert Campbell of the MBL Bay Paul Center, to create The TDR Targets database (tdrtargets.org). This open-access, ongoing database compiles data on genes and proteins in tropical disease pathogens, along with information on their potential as drug targets. (*Nature Reviews Drug Discovery* 7, doi: 10.1038/nrd2684, 2008) •

Buried Treasure: A New Approach to Coastal Water Pollution

A strolling passerby might not realize it, but buried along the shoreline in the Cape Cod town of Falmouth is a potential solution to nitrate pollution of the area's coastal waters. Four years ago, MBL Ecosystems Center scientists Ken Foreman and Joseph Vallino, working with an engineering firm, buried wood chips mixed with lime (NITREX™) in trenches along the shores of Waquoit

Bay and the Childs River. The scientists then tested whether these wood chip barriers could intercept the nitrates in Cape Cod groundwater before the water reached the coast. Nitrates, most of which originate from septic systems, overstimulate the growth of algae and bacteria, which can lead to low-oxygen conditions in bays and estuaries that kill marine life. In their evaluation, Foreman and Vallino found the barriers removed more than 90% of the nitrates from incoming groundwater. A cost analysis suggests that such a barrier system could be built for less than 30% of the cost of constructing a traditional municipal wastewater treatment system. Research to optimize the barriers continues.•

Toward a Treatment for Male Infertility



Among couples that face infertility, about a third of the cases involve male reproductive problems. One important regulator of male fertility is the pH level inside the epididymis and the vas deferens, two tubular ducts where sperm matures. Relative to most of the human body, the environment in these ducts is acidic, which keeps sperm cells quiescent while they mature, but this pH level can be disturbed by exposure to toxins such as cadmium, which is present in tobacco smoke. In a recent paper published in *Cell*, Peter J.S. Smith, director of the MBL BioCurrents Research Center, and his collaborators at Massachusetts General Hospital report progress in understanding this acidification regulatory process. Using a hydrogen probe developed at the MBL, the team discovered that basal cells in the lining of the epididymis extend long, slender projections into the cavity of the duct, where they act as sensors of pH level. The basal cells then report their findings to neighboring clear cells, which respond by increasing acidification in the cavity, if needed. By understanding these mechanisms in the male reproductive tract, the researchers hope that eventually clinicians can intervene and manipulate acidification to treat male infertility. (*Cell* 135: 1108-1117, 2008) •

Colorful, changeable animal skin provides "bio-inspiration" for materials of the future

Smart

by Roger Hanlon and

Colors and patterns surround us every day: in our homes, cars, clothes, buildings, entertainment devices, and, of course, in the natural world. We mostly take this for granted, but look around you for just five minutes—regardless of where you are—and you will notice a staggering array of designs with multiple colors, contrasts, contours, and textures.

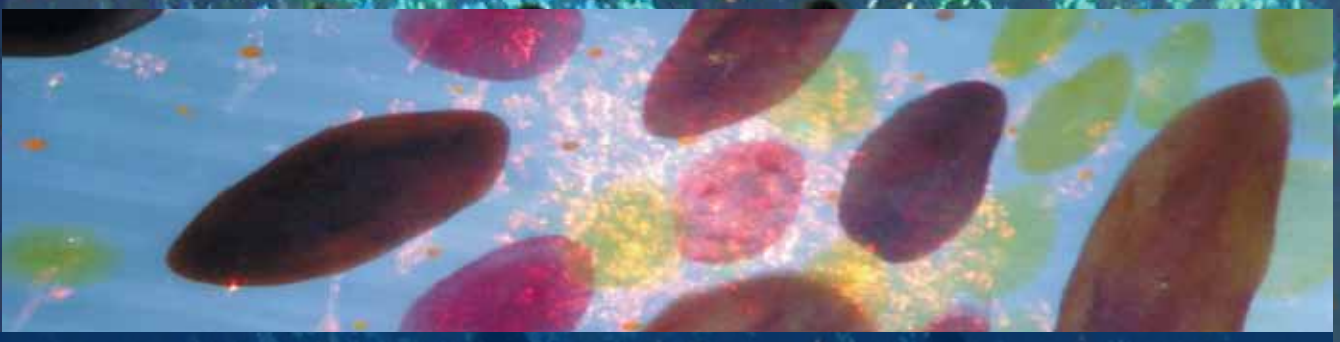
Humans are visual, inventive creatures who have engineered many of these colorful devices with increasingly diverse technology and materials. There is keen interest in creating changeable colors and patterns for many applications, such as in palmtop computers, or PDAs. Yet there are substantial energy costs involved. Your palmtop's screen, for example, may have dazzling graphics, but it requires a continual energy source to emit white light, color, and pattern; even then, bright light (such as sun) will overwhelm it. Thus, engineers and materials scientists are looking to nature for inspiration on how to manipulate light in more energy-efficient, yet still visually rich ways.

Nowhere in the animal kingdom is changeable color and pattern better developed than in the cephalopods—the squid, octopus, and cuttlefish. These marvelous animals live in competitive marine environments and have evolved a completely unique skin system that instantaneously changes its appearance. They are the acknowledged masters of camouflage, but they also produce dozens of skin patterns for communication with one another.

How do they do this, and what are the photonic structures in the skin that enable such optical diversity? The first of these questions is the theme of much of our research. The short answer is that the cephalopods use visual information—they have sophisticated eyes—to control their body patterns mainly by direct neural control of pigmented organs (chromatophores) in their skin.

But answering the second question —what are these biophotonic skin structures?—can lead us toward some potentially novel ways to manipulate light within man-made products.

One theme that is emerging from our research on animals with changeable skin patterns (cephalopods, fish, chameleons, etc.) is this: All of the animals seem to combine pigment cells in the skin with structures that reflect light. This "simple" idea has seldom been implemented in man-made systems. In our laboratory, we have been studying the gross and fine structure of the cephalopod skin, and measuring the light that is absorbed or reflected by the skin's various pigments, reflectors, and diffusers.



Skin

Lydia Mäthger

To our surprise, we have found that there are only three pigments in the cephalopod skin: yellow, red, and brown (or sometimes black). So where do the blues, greens, and other colors in their glorious skin patterns come from? Blue, green, pink, red, yellow, or silver is produced when incoming light reflects off other cells, called iridophores, at a particular angle. Iridophores are changeable; they can be turned on and off by a chemical signal from the animal, and then tuned to different colors. Remarkably, the reflecting material in iridophores is a translucent protein called reflectin. Other researchers have manufactured reflectin and placed it on man-made thin films; the proteins self-organized and reflected light!

Yet for these beautiful skin colors to be visible, the animal skin needs a base layer of white to provide contrast. And how does the cephalopod skin do this? In cuttlefish and octopus, specialized cells called leucophores produce white in the bottom layer of the skin. These cells are very efficient: they "collect" all the available wavelengths in the ambient light field, collate them, and then diffuse the resultant light field in every direction equally well, and with high reflectivity. No other photonic structure yet described in nature can do this with similar efficiency. Moreover, they do so without using muscles or nerves; i.e., they do it passively and without direct energy.

Cephalopods are the acknowledged masters of camouflage, but they also produce dozens of skin patterns for communication with one another.

This is a wonderful, biological example of "passive display technology," which is a burgeoning industry with widespread appeal and applicability throughout society. Presently, titanium dioxides are used for bright-white reflectivity in many passive-display products, but they are physically abrasive, which may impact industrial production processes. In contrast, leucophores are soft, flexible proteins that produce comparable white-light diffusion, and may inspire new materials construction.

"Bio-inspiration" has worked its way into many areas of life, from electronics to nanotechnology. In the textile industry, for example, fabrics have been designed that are based on the principles of spider silk, proteins, and plant fibers. By exploring and understanding one of nature's most impressive displays of biophotonics—the cephalopod skin—we may also create products with a rainbow of changeable patterns and colors. •

Ready, Aim:

Cancer

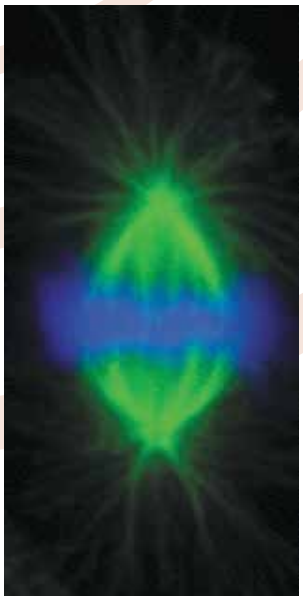
In the search for a cure, a scientist follows the evidence from cell division to cell death

A cancer cell is a formidable foe. Not only is it rapidly dividing, it can mutate and invade other tissues where it doesn't belong. A good way to stop cancer in its tracks, then, is to develop drugs that block the cancer cell from dividing, right?

If you ask Tim Mitchison of Harvard Medical School, he'd respond, "Maybe." What the drug may also need to do, he suspects, is

force the cancer cell to commit suicide.

Mitchison, a longtime investigator of cell division at the MBL, has been exploring ways to stop cancer for over a decade. In the late 1990s, his basic research at Harvard led to the discovery of a novel class of cancer drugs that block cell division. Those new "antimitotic" drugs, which are still in clinical trials, are similar to the classic chemotherapy drugs, such as the taxanes (Taxol™ and others), which also block cell division but through a different mechanism. Taxanes have been on the market for nearly two decades, and they are FDA-approved to treat ovarian, breast, lung cancers and Karposi's sarcoma.



In the dividing cell, the mitotic spindle (shown in green) attaches to the chromosomes (shown in blue) and then moves the chromosomes to opposite poles of the cell. Drugs that disrupt this process in the cancer cell are called "antimitotic drugs."

CELL DIVISION DYNAMOS AT THE MBL

It seems Tim Mitchison was fated to come to Woods Hole.

The journey began with a fundamental discovery he made about the mitotic spindle, while earning his Ph.D. at the University of California, San Francisco. Though he didn't realize it at the time, Mitchison's discovery was in direct line with research begun by MBL distinguished scientist Shinya Inoué in the 1950s. In fact, Mitchison's research confirmed a mysterious property of spindle dynamics that Inoué had intuited years before.

So when Mitchison first met Inoué's protégé, Ted Salmon, at a scientific conference in the mid-1980s, it was like finding an old friend. "I remember having a fantastic conversation with Ted and realizing we converged on what the mitotic spindle was really like, and that we might be the only two people in the room who had that feeling," Mitchison says. Salmon, who is now at University of North Carolina-Chapel Hill, encouraged Mitchison to collaborate with him at the MBL, which they began doing in the late 1980s.

Now Mitchison and his wife, Christine Field, also a cell biologist, own a home in Woods Hole and come with their children to the MBL every summer. From 2004 to 2008, Mitchison co-directed the MBL Physiology Course with Ron Vale, and their re-vamping of the course to tackle cutting-edge problems in cell biology received high praise from students and faculty alike.

Mitchison continues to collaborate with Salmon in the MBL Cell Division Group, which they founded in 1999. "It's a great collaboration, with Ted's students and mine at the MBL," Mitchison says. "We've published several scientific papers listing the MBL as the primary institution, and they have been bedrock in my thinking about spindle organization."

"In lung cancer treatment, the combination of Taxol and Carboplatin is used a lot," says Anthony Letai of Dana Farber Cancer Institute, who collaborates with Mitchison. "It doesn't work great, but it's probably as good or slightly better than anything else available. Nothing works great on advanced epithelial (tissue) cancers."

One huge challenge is what Mitchison calls "the central unsolved problem" with all cancer drugs that block cell division: "We need drugs that kill dividing cancer cells, while sparing, as much as possible, dividing normal cells in the bone marrow and gut." All the antimitotic drugs, in one way or another, ultimately "poison" the mitotic spindle, a transient structure that the cell builds in order to divide. But what is puzzling is all antimitotic drugs aren't equal in terms of their toxicity to bone marrow cells—which suppress immune function when knocked down—or to gut cells, which when damaged cause the nausea associated with chemotherapy.

"We don't understand why that is," says Mitchison. "That has led me just to try to understand how drugs that poison the mitotic spindle work and don't work. To me, it raises a very important scientific issue. We just don't understand how (poisoning the spindle) blocks mitosis, and we don't understand how that kills cells. Just trying to block mitosis in new ways is unlikely to give us a better cancer drug. But if we understand how cancer cells die, and how bone marrow cells die, we have a chance of perhaps building a more specific cancer drug to target cell division that is less poisonous to the human body."

To that end, Mitchison has teamed up with Letai to study how the antimitotic drugs "communicate to the cell that the cell has to die," says Letai. "Before I studied cell death, I had a very simplistic view of what made cells die, and that was once they accumulated enough damage, they basically had no choice but to die, like a person whose heart has stopped working." But it seems that another form of cell death called apoptosis, in which the cell recognizes it is sustaining damage and "commits suicide" for the benefit of the rest of the organism, is what really kills cancer cells that are hit by chemotherapy. Currently, Mitchison and Letai are looking at the degree to which various antimitotic drugs trigger the cell-suicide pathway in cancer cells, as well as in the normal cells that one would want to spare.

"What is the connection between a drug getting to a cell and tickling it just right, so it forces the cell to commit suicide?" Letai says. "Most of our chemotherapy drugs do this, in ways we don't understand. So we have to start bird by bird; we have to choose one drug and try to understand how it triggers apoptosis. This is what Tim and I are doing with the antimitotic drugs."

Although Mitchison has long been fascinated by the mitotic spindle, which he calls a "beautiful structure," his research is increasingly complemented by the study of how cells die. It may not be scientific territory he ever thought he would explore. But when your goal is cancer therapies, he says, "you can't just choose a (research) problem because it appeals to you, or because you have a hunch. You have to look at a disease like cancer squarely in the eye." • –DK

MBL Moment

From Sunlight to Sustenance

...with

Bill Mebane

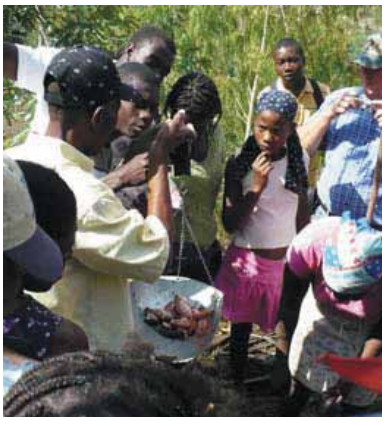
Director, MBL Sustainable Aquaculture Initiative

Bill Mebane is superintendent of aquaculture engineering at the MBL's Marine Resources Center facility and director of the MBL's Sustainable Aquaculture Initiative. A native of Philadelphia, Mebane received his B.A. in biology from Ohio Wesleyan University in 1981. He previously worked as a fisheries biologist for Philadelphia Electric and as international marketing manager at Zeigler Brothers, a commercial feed company. Mebane joined the MBL in 1992.

In Haiti, one of the world's poorest nations, widespread malnutrition is an ongoing challenge. Subsistence farmers in the rural areas have nearly exhausted soil fertility, creating a pressing need for new ways to sustainably produce food. Since 2002, the MBL's Sustainable Aquaculture Initiative (SAI) has been building fish ponds in Haiti and developing fish-raising strategies to offer Haitians a reliable source of protein and even income. Working in collaboration with the Comprehensive Development Project in L'Acul, Haiti, the SAI has improved 52 existing ponds and helped to build 21 more that individual Haitians then take over and maintain. Below, SAI program director Bill Mebane shares his thoughts on translating scientific aquaculture into a way of life for impoverished Haitians.

MBL What is the initiative trying to accomplish in Haiti?

BM We are introducing a technique called periphyton aquaculture technology, which we believe is the best way to raise tilapia (a freshwater fish) in the Haitian ponds. Periphyton is the green, slimy, algae-like growth that develops on submerged objects in almost any aquatic environment. It is an extremely nutritious protein source for higher aquatic organisms. We have trained the Haitians to install substrate in the ponds for the periphyton to grow on, and taught them how to maximize the growth using composting methods. Basically, we are showing them how to use sun and waste products to make fish food. It's kind of like baking a cake using just the things in your kitchen that you don't need. Take the dust from the floor, the sun coming in the window, the water from the spigot, and make something that's nutritious; that's what we're trying to do.



MBL How is this different from traditional aquaculture?

BM Our focus is to provide a system that is totally sustainable. The MBL can leave Haiti, and the fish will just keep on growing. The hardest part has been getting the Haitians to buy into this concept. It was really difficult, at first, to get them to believe that there was anything going on in these green and stagnant ponds. It's paradoxical that the Haitians, in one of the most primitive areas in the Western Hemisphere, are using a fish-rearing technique that many advanced countries are beginning to implement, because it produces a value-added, organic crop without the use of fish feed.

"In Haiti, cause and effect are not always linked by science, as we are trained to understand it... It's a fascinating culture to work in."

MBL Why did you choose Haiti as the location for this project?

BM Haiti is fairly close; it's a 90-minute plane ride from Miami. We have really good contacts there. We work out of a missionary compound that has clean drinking water and a generator, and where we are safe. Haiti has so many things going against it—political turmoil, no infrastructure. It's a real boot camp for making something sustainable work. It does have a great climate, though. We knew that if the project worked in Haiti, it could work anywhere along that latitude of our planet where there is water and sun.

MBL How is working in Haiti different from being in Woods Hole?

BM In Haiti, cause and effect are not always linked by science, as we are trained to understand it. This may have roots in the Voodoo belief that the results of an action can be attributed to what we would call "non-scientific" forces. If you're feeling sick, it may be because you have done something wrong, or because someone who doesn't like you put some spirit towards you. And those ideas translate to the fish farming. For example, if you throw papaya leaves into the ponds, the fish will eat them and grow. If we teach the Haitians that, they'll think it's some magic that we bring, not that it's related to the nutrients in the leaves. But if they see the leaves fall into the pond, and they see the fish eat them, then they'll believe it works and start to supply the ponds with leaves themselves. It's a fascinating culture to work in.

MBL How well is the fish-farming initiative taking root?

BM During our last visit to Haiti, we heard a rumor that new fish ponds had been built up in the mountains, about a six-hour hike from the road. SAI project coordinator Nick Warren, our intern Vansa Chatikavanij, and I walked to the site and found 21 ponds that the Haitians had dug, without any prompting from anybody. They were beautiful ponds, and they had the right amount of fish in them. It was textbook. They had done that with no money, no prompting, nothing. That was really encouraging.

MBL What is the initiative's biggest challenge for the future?

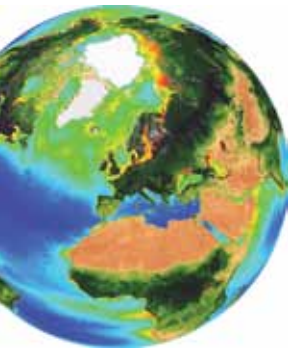
BM Tilapia are not an easy fish to catch. The Haitians harvest the fish by draining the ponds. Then they have this mass of flesh to bring to the market in an area where it'll spoil in a day or so. We are trying to convince the people that eating the fish every day is good, and that the fish will actually grow better if they harvest them more frequently. One way to do this is through the kids. We will start training schoolteachers to harvest some fish and feed it to the kids, who will hopefully go home and pester their parents for more fish. But also, to get them to harvest the fish daily, we need to develop methods for them to catch the fish without draining the ponds.

MBL Last year at the MBL, the Sustainable Aquaculture Initiative hosted a round table for periphyton experts from around the globe. What did you learn?

BM The takeaway message was patience. Understand the culture. It's a systems approach. We have to drop back and look at the whole culture. Hunger is a cultural problem, not just a scientific problem. The science is easy. We could increase the production of these fish ponds tenfold, easily. But if the culture doesn't buy into it and accept it and understand it, we won't succeed. That is the biggest challenge. •

–DG

Gifts & Grants



The National Science Foundation awarded $5.6 million for "Palmer, Antarctica Long Term Ecological Research Project." Ecosystems Center co-director Hugh Ducklow is the principal investigator.

The National Institutes of Health awarded $1.6 million for "Dartmouth Superfund Program Project: Arsenic as an Endocrine Disruptor." Chief academic and scientific officer Joshua Hamilton is the principal investigator.

Former MBL board member **George W. Logan and his wife Harmon** have pledged $1.5 million to endow the Science Journalism Program and $100,000 to support the Annual Fund (2009-2011).

Dart Neuroscience, LLC awarded $1 million for a program in learning and memory.

The National Institutes of Health awarded $1.1 million for "Enhancing Organism Based Disease Knowledge via Name Based Taxonomic Intelligence." Adjunct scientist Neil Sarkar is the principal investigator.

The National Institutes of Health awarded $1.1 million in support of the Neural Systems and Behavior course and $893,847 for the Neurobiology course.

Accolades

MBL Trustee **Douglas Melton**, co-director of the Harvard Stem Cell Institute, was recently featured in a *Time* magazine cover story for his work on diabetes causes and cures.

Ecosystems Center senior scientist **Zoe Cardon** was named president of the Ecological Society of America's Physiological Ecology Section. She is the first woman to hold this post.

The International Society for Eye Research awarded **John Dowling**, MBL Trustee and Gund Professor of Neurosciences at Harvard University, the Paul Kayser International Award in Retina Research at the 2008 International Congress of Eye Research in Beijing. While in China, Dowling also presented a centennial lecture at Lanzhou University to an audience of 1,000 university members.

Associate research scientist **Irina Arkhipova** and adjunct scientist **Matthew Meselson**'s paper, "Massive Horizontal Gene Transfer in Bdelloid Rotifers" (*Science* 3320: 1210-1213), was cited among *Discover Magazine's* top 100 science stories of 2008 and named a 2008 research highlight in *Nature* magazine.

MBL affiliated scientists including **Gary Borisy**, **Scott Brady**, **Andrew Huxley**, **Shinya Inoué**, **Tim Mitchison**, **Tom Pollard**, **Tom Reese**, **Conly Rieder**, **Joel Rosenbaum**, **Mike Sheetz**, **Albert Szent-Györgyi**, **Edward Taylor**, **Ron Vale,** and the late **Robert Allen** were cited in 12 of the 25 "Milestones of the Cytoskeleton" compiled by *Nature* magazine.

The **Encyclopedia of Life** project was named by *Nature* magazine as one of the top science stories of 2008.

The Combinatorial Imaging group (L to R): Rudolf Oldenbourg, Gary Borisy, Mitchell Sogin, Chris Rieken, Alex Valm (Brown-MBL student), Jessica Mark Welch, Yuko Hasegawa (Brown-MBL student), Louis Kerr

Battling the Matrix

Chronic bacterial infections are the Achilles' heel of the antibiotic age. For the patient, they can range from being irritating—such as chronic sinusitis or middle-ear infections—to life threatening, such as lung infections in children with cystic fibrosis.

Why do infections become chronic? Often, the offending bacteria are no longer free-floating in the body but have adhered to a surface, colonized, allowed other microbes to pile on top, and become encapsulated in a protective matrix called a biofilm. Once bacteria enter a biofilm state, they become resistant to antibiotic therapy, and more aggressive medical strategies are needed.

At the MBL, a new technique for identifying bacteria could translate into a rapid, inexpensive clinical test for bacteria in biofilms. "It could have a wonderful use in diagnostics," says Jessica Mark Welch of the MBL's Combinatorial Imaging group, which is led by Gary Borisy, the MBL's director and chief executive officer. "It allows the rapid identification of bacteria that are otherwise visually identical, and it can identify rare pathogenic bacteria in a sea of harmless bacteria."

At the heart of combinatorial imaging are fluorescent probes that "stick" to different species of microbes, such as bacteria. When viewed through a microscope, each bacterial type lights up in certain colors, allowing one to quickly see what microbes are in the sample, and where they are.

The technique could show, for example, the 3-D composition of dental plaque, identifying which bacteria are the original colonizers on the tooth surface, and which attached later. "You could take a sample of plaque, and then have the patient eat something different, and see if that changes the plaque composition," Mark Welch says. "You could identify which foods affect the proliferation of the plaque-causing organisms in that individual."

The Combinatorial Imaging group is just beginning to develop applications. Brown-MBL graduate student Alex Valm, for instance, is designing probes for the detection of dental plaque. "There are 500 to 700 different types of bacteria in the human mouth," says Valm. Visualizing such a diverse community "is a whole new ball game." •

Expecting the Unexpected

Joshua W. Hamilton is the MBL's chief academic and scientific officer (CASO). He provides leadership for all MBL academic programs, including the Brown-MBL Graduate Program in Biological and Environmental Sciences, as well as the resident and visiting research programs and the scientific infrastructure that supports these programs. He also oversees MBL policies relating to scientific research and commercial relations, including intellectual property and technology transfer. Prior to his arrival at the MBL, Hamilton was a faculty member in the Department of Pharmacology and Toxicology at Dartmouth Medical School. He was also founding director of the Center for Environmental Health Sciences at Dartmouth. Hamilton received his master's degree in genetics and his Ph.D. in genetic toxicology at Cornell University. In addition to his administrative responsibilities, Hamilton continues his basic and translational research program at the MBL. His laboratory focuses on molecular and environmental toxicology, especially how arsenic and other toxic chemicals in the environment affect biochemical processes in ways that might contribute to human disease risk.

By Joshua Hamilton

translate (v)*: to change from one language to another; to change into another medium or form, as in translate ideas into action; to put into different words, to interpret.* **Syn.:** *interpret, define, explain, elucidate, transfer, change, transform.*

Over the past two decades, "translational research" has become a buzzword in science. This is largely a response to pressure from Congress and the general public to have scientists focus their basic research efforts on solving real-world problems. As a result, government agencies and other funding sources have been increasingly pushing researchers to conduct translational research as a fundamental aspect of their basic research.

But what is translational research? It has become such a dominant idea that probably every scientist thinks he or she knows the definition, yet probably each of us has a different one. In simple terms, it is most often described as the process of moving laboratory findings to practical application. The biomedical industry often calls this "bench to bedside" or "mouse to man" with the idea that potential therapeutic drugs are moved rapidly from the lab to the clinic. When President Nixon declared a "war on cancer" that would lead to cures within 20 years, it was with this translational model in mind.

But that particular paradigm, with its intense focus on drug discovery—and its principal "bedside" application being to those who already have a serious illness—is a very narrow definition of translational research. It assumes that the primary goal of basic science is to come up with a "magic bullet" to cure some end-stage condition. But it also leaves out the critical first steps in the process that are the real engine of science: How did we get to the lab bench discovery or the mouse experiment in the first place? That is not so straightforward and rarely can be directed at the outset.

In this respect, both basic and translational research differ very much from their cousin, applied research. Applied research—sending someone to the moon is an example—takes existing and emerging technology and applies it to solving a particular tractable problem. But basic research is about understanding the natural world through open inquiry, hypothesis testing and development of empirical knowledge. Many—and we could perhaps argue most—great discoveries in science have been a by-product of this basic process of discovery and knowledge building, and what scientists call "serendipity"—a special kind of scientific luck (or as Louis Pasteur said, "Chance favors the prepared mind"). A scientist has an idea that leads to a hypothesis and experimentation. But what often comes of this inquiry is a discovery that was not anticipated, and which is often far more interesting than the original idea—a discovery that an unprepared mind might miss altogether or write off as a failed experiment. The scientific process trains scientists not only in how to do the initial inquiry, but also how to recognize that something else interesting happened, which then leads to further inquiry and discovery. It is the results of this process that ultimately provide the starting place for translation into real-world application, and often the best application is also unanticipated. •

Treasures from the MBL's Archives

Jack Levin, then of The Johns Hopkins University School of Medicine, collects the blue blood of the horseshoe crab, *Limulus*, in the MBL's Lillie Laboratory in 1977. *Limulus* blood is an exquisite indicator of the presence of bacterial endotoxins, and it is used to manufacture the LAL test, used worldwide to ensure sterility in medical settings. Levin also reported the first clinical studies demonstrating that the LAL test could detect endotoxin in the blood of patients suspected of being infected with a wide range of bacteria.

An Application Gels

For millions of years, marine animals have done just fine in the bacterial soup that is the sea. But how do the creatures respond when they encounter potentially lethal bacteria? Curious about this question, Frederik Bang in the mid-1950s at the MBL injected horseshoe crabs (*Limulus*) with samples of bacteria obtained at random from the sea. He found that one, the *Vibrio* bacteria, caused the crab's blood to gel, after which the crab died. Why this happened was a mystery until Jack Levin came to the MBL to work with his mentor Bang in the mid-1960s. Levin discovered that *Vibrio* and other gram-negative bacteria contain an "endotoxin" that can cause the blood of *Limulus* to clot. What's more, Levin showed that the rate at which the blood clots depends upon the precise concentration of bacterial endotoxin present. Thus was born the Limulus Amebocyte Lysate (LAL) test, now used in medical settings worldwide. These bacterial endotoxins, which are present in some pathogens such as *E. coli*, are potentially dangerous if they enter the human bloodstream. The LAL test ensures that injectable drugs, intravenous fluids, and medical devices are free of gram-negative bacterial endotoxins before they are used in the human body. •

Catalyst

IN THE NEXT *CATALYST*

Creature Feature: Biological Diversity and Discovery

Vanishing penguins in Antarctica. Frogs that can regrow a new cornea. Oysters resistant to shellfish disease. The shining "star" of neuroscience, the Woods Hole squid. These and many other wonderful creatures are central to MBL research, and they take the spotlight in the next issue of *MBL Catalyst*.

MBL | Biological Discovery in Woods Hole

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