Breaking Through

In This Issue
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Learning from Nature: Can Humans Regenerate Missing or Damaged Tissue?
What if we were able to trigger our innate abilities for regeneration?

It would mean restoring heart muscle tissue damaged by a heart attack, replacing kidneys that have failed, or repairing injured spinal cords. It would mean saying goodbye to organ transplant waiting lists, to kidney dialysis machines, to wheelchairs. It would mean improved quality of life and billions of dollars in health care savings.

We believe the capacity for regeneration is encoded in our genes, waiting to be activated by complex networks of genetic switches. With the sophisticated new tools that are now at our disposal, we can peer into the genes of highly regenerative animals to understand the genetic networks responsible for triggering these switches.

It sounds like science fiction. Yet we know many animals have the ability to restore the form and function of almost any body part. Babies can regenerate hearts; young children can regenerate fingertips; adults can regenerate portions of their livers.

We are testing the genetic networks for regeneration every day to figure out how they work. If we turn off a gene, will we disable the ability to regenerate? Can we reactivate regeneration with a small molecule that could potentially become a drug? How do the regenerative networks of highly regenerative animals compare with those of animals, such as mammals, with limited capacity for regeneration?

Much remains to be done to decipher the complex cascade of genetic signals that is responsible for regeneration. In this issue of “Breaking Through,” you will learn how we are laying the foundation for future advances in regenerative medicine by training a new generation of scientists from around the world in comparative regenerative biology and by recruiting outstanding new faculty to our institution.

The discoveries of the next generation can’t come soon enough. The need is urgent: as the population ages, more people than ever are suffering from age-related degenerative conditions. Thanks to your continued support, the MDI Biological Laboratory is at the forefront of research to develop new regenerative medicine therapies that could potentially help millions of people around the world.

We are deeply grateful for your confidence and support, and we look forward to partnering with you in realizing the transformative power of regenerative medicine.

With deepest appreciation and heartfelt gratitude,

Kevin Strange, Ph.D.
President
WHAT IS IT THAT ALLOWS A SALAMANDER TO REGENERATE A LIMB, OR A ZEBRAFISH TO REGENERATE A HEART? AND IF THESE ANIMALS CAN DO IT... Why Can’t We?

THESE ARE THE QUESTIONS that captivated students from around the world who attended the MDI Biological Laboratory’s signature course in comparative regenerative biology.
The idea that science could one day develop therapies for treating human disease by studying animals that regenerate was once considered farfetched. But with stem cells yet to fully disappear as they get older? Is unlocking regeneration simply a matter of turning on an already-existing program? If so, can that program be sufficiently enhanced to regrow an entire structure? The students came away with the skills, tools and knowledge to help answer these questions and to begin to decode the process of regeneration. They also came away with a sense of destiny: a shared awareness that as the next generation of regenerative biologists, they will inherit the responsibility of refining and developing the tools for working with regenerative animals and will chart the course of future discovery.

Everything old is new again
Course director Voot P. Yin, Ph.D., likens the comparative study of regenerative animals to an earlier era in which naturalists compared the physiological functions of various organisms to investigate how these functions work in humans. “We have a tendency to think we are smarter than nature—for instance, that we can replace tissue with cells grown in a dish,” Yin said. “But we are realizing that nature has perfected regeneration over millions of years of evolution and there is much we can learn from studying this process. The more regenerative species we can compare and the finer the resolution of our ability to study their cells, the more we can learn about regeneration in humans.”

The major difference between the REGEN2017 students and the 19th century naturalists, however, is technology. Today’s students use sophisticated new tools to peer into an organism’s genetic code. These tools offer the potential to answer the million-dollar question of why some species can regenerate tissues and organs, while others, including mammals such as humans and mice, have limited regenerative capacity.

Transforming the practice of medicine
The task of deciphering the cascade of genetic signals that allows regeneration to take place is highly complex. In order to regenerate an injured limb, for instance, an animal must regenerate skin, bone, cartilage, muscle, blood vessels and nerves; it must know how much of the limb to regenerate; it must know how to position the new tissue; it must know how to integrate the new tissue with the pre-existing tissue.

“Regeneration is incredibly complicated in a living system in which there are interactions and communications among different cell types,” Yin said. But the potential payoff is enormous. The aging of the world’s population has led to a surge in age-related degenerative diseases that has placed an enormous burden on patients, caregivers and the health care system. The study of the molecular mechanisms underlying regeneration could one day lead to the development of drug therapies to restore tissue and organs lost to disease and injury.

“If we see an unprecedented rise in the costs associated with treating chronic age-related degenerative diseases, we must identify new ways of combating them,” Yin said.

The students in the REGEN2017 course have a revolutionary mission: They are seeking nothing less than the replacement of major body parts such as hearts, limbs and spinal cords—in short, the transformation of the practice of medicine. Thanks to the REGEN2017 course, they are well equipped to move regenerative medicine one step closer to that goal.

LEARN MORE | Visit the Breaking Through blog for REGEN2017 student interviews (https://mdibl.org/breaking-through/rege2017-students/).

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The idea that science could one day develop therapies for treating human disease by studying animals that regenerate was once considered farfetched. But with stem cells yet to fully deliver on their promise, scientists are recognizing the tremendous benefits of studying organisms that have already perfected the miraculous ability to regenerate tissues and organs.

The senior graduate students, postdocs and junior faculty who attended REGEN2017 came to learn more about this comparative approach to regenerative biology from global leaders in the field. The week-long course provided participants with an opportunity to get their hands wet by interacting one-on-one with the champions of regeneration, namely the model organisms that nature has endowed with the ability to regrow hearts, limbs and other body parts. Attendees examined such intriguing questions as: Why can newborn babies regenerate their hearts while adult humans cannot? Why does the ability of children to regenerate fingertips disappear as they get older? Is unlocking regeneration simply a matter of turning on an already-existing program? If so, can that program be sufficiently enhanced to regrow an entire structure?

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James Godwin, Ph.D., attributes his interest in science in part to his childhood dog, Timmy. A cross between a fox terrier and an Australian kelpie, Timmy was a herding dog and the center of Godwin’s life as a boy in his native Australia.

“Why can some animals change the color of their coats, or work a herd of sheep or regrow limbs, while others can’t?”

UNDERSTANDING REGENERATION: A Monumental QUEST
He arrived at the MDI Biological Laboratory last year from the Australian Regenerative Medicine Institute with the goal of studying the role of the immune system in limb and heart regeneration in the axolotl, or Mexican salamander (see sidebar). The availability of new genetic tools, including a public catalog of its genes, have made the axolotl a powerful tool for understanding regeneration. “I’m like a kid in a candy shop,” he says of these tools, which allow scientists to study the axolotl at the molecular level. Because he holds a dual appointment with The Jackson Laboratory, which studies mice, he is also seeking insight into how to reverse-engineer the process of regeneration in humans by comparing the genetics of the axolotl, which can regenerate, with those of the mouse, which for the most part cannot.

Godwin recognizes that the task of understanding regeneration is a monumental one. “Basically, we know nothing about how regeneration occurs,” he says. But he is heartened by the “game-changing” progress enabled by the development of new genetic tools and thrilled to be a part of the discoveries these tools will make possible. “It’s a good time to be involved,” he says. “It’s going to be an interesting ride.”

The Axolotl: ‘A Sustainer of Life’

With its pink skin, blue eyes and headdress of feathery gills, the axolotl, or Mexican salamander, has captivated exotic pet enthusiasts and scientists for decades.

The axolotl is also a favorite for the study of regeneration. Unlike other amphibians such as frogs, which lose their ability to regenerate when they metamorphose from an aquatic to a terrestrial stage, the axolotl remains in a juvenile state, which means it retains the ability to regenerate throughout its life. This quirk of evolution has earned it a position as nature’s champion of regeneration: It can regenerate limbs and organs hundreds of times with no loss of form or function.

The axolotl was once considered a “sustainer of life” by the Aztecs, who venerated it for its powers of regeneration. Indigenous to the lake area of Xochimilco, now a borough of Mexico City, it is quickly disappearing due to loss of natural habitat, predation by non-native fish and use for food. As food, it is valued for the symbolic power that derives from its regenerative capabilities as well as for its delicate flavor, which has earned it the sobriquet “food of the lords.” Once so plentiful that Cortes’ army subsisted on it, it is now on the verge of extinction. Unless its habitat is protected and the dwindling population restored, it could become extinct in the wild in a matter of years. Mexico’s Nobel Prize-winning poet Octavio Paz called the axolotl a “hanging bridge between eras.” Though extinction threatens its role as a bridge across time, its use as a model in regenerative biology ensures it will live on as a sustainer of life through its potential to help patients regenerate lost and damaged tissue and organs.

“I’m like a kid in a candy shop. Being able to study the axolotl at the molecular level and having access to a diverse range of tools is game-changing.”

JAMES GODWIN, PH.D.
MDI Biological Laboratory
Assistant Professor

When he saw a television documentary about how some animals’ coats turn white in winter, Godwin wondered why Timmy couldn’t do the same. When he visited his grandparents’ farm, he wondered how the city-bred dog instinctively knew how to control errant sheep, a mystery that was compounded by his grandfather’s explanation that it was “in his blood.” But it was a documentary on the ability of salamanders to regrow limbs that really piqued his curiosity. “By that stage, I knew people who had experienced serious injuries,” he says. “I’d been told that the body couldn’t repair itself. But yet the salamander had overcome these limitations. Why don’t we know how to do this? I wondered. The most important question for me became, Why can some animals change the color of their coats, or work a herd of sheep or regrow limbs, while others can’t? I wasn’t interested in looking into the cosmos. I wanted to understand the biology underlying these qualities.” That quest eventually led Godwin to a doctorate in immunology from Melbourne University, followed by post-doctoral work at University College London. “Those nature documentaries have a lot to answer for,” he jokes.
Inspiring Future Discoveries

Thanks to you, our scientists are making potentially life-changing discoveries – discoveries like those made by Voot P. Yin, Ph.D., that led to a potential breakthrough drug, MSI-1436, for the treatment of heart disease (see back cover). Your generous support also allows us to share our knowledge with a new generation of scientists from around the globe who participate in our unique courses. In this profile, University of California, Santa Barbara post-doc, Susannah Kassmer, Ph.D., discusses how the REGEN2017 course is helping her create the tools upon which future biomedical discoveries will be based.

Your support of this work has never been more important. Together we will continue to inspire future scientists like Kassmer to make their own breakthrough discoveries.
Susannah Kassmer, Ph.D., has spent the last four years studying how bone marrow stem cells from the mouse differentiate into mature lung tissue. Her research was an outgrowth of studies showing that bone marrow stem cells can differentiate into lung, heart, liver and other types of cells, which raised the possibility that stem cells could be transplanted into humans to treat disease. But recently Kassmer switched from studying stem cells in mice to studying highly regenerative animals. This interest prompted her to enroll in REGEN2017, a signature course in comparative regenerative biology at the MDI Biological Laboratory. “Transplantation of stem cells into damaged organs has not achieved the improvements we were hoping for,” she says, reflecting the MDI Biological Laboratory’s view that the study of highly regenerative species is the key to realizing the transformative potential of regenerative medicine.

Kassmer, 38, who earned her doctorate in immunology in her native Germany, would like to head her own lab some day. Because she believes in the need to study a variety of animals that have the ability to regenerate, her goal is to develop the molecular tools to use the sea squirt, or colonial ascidian, as a research model. “The colonial ascidian has a lot to teach us,” she says. The colorful undersea creature is the only chordate (the phylum, or category of organisms, that also includes humans) that can regenerate its entire body from only a few cells. “The more we know about how different species regenerate,” Kassmer says, “the more we know about how humans can regenerate. That’s why this work is so important.”

“I wanted to interact with a community of scientists studying regeneration and that’s what’s happened here. It’s been a real bonding experience.”

— Susannah Kassmer, Ph.D.
NOVO BIOSCIENCES INC., an MDI Biological Laboratory spinoff, has received a two-year, $1.5 million Small Business Innovation Research grant from the National Institutes of Health for the development of MSI-1436 as a potential regenerative medicine therapy for the treatment of heart attack patients. The grant will allow Novo Biosciences to move ahead with studies of MSI-1436 in the pig, the critical next step in moving it into clinical trials in humans.

Learn more about this and other discoveries on our “Breaking Through” blog, where you’ll gain an in-depth look at our work, hear directly from our scientists and stay informed.

mdibl.org/breaking-through