Biologists Search for New Model Organisms

The bulk of biological research is centered on a handful of species. Are we missing a huge chunk of life’s secrets?

By Emily Singer

Ever since he was a student in the late 19th century, the Columbia University zoologist Thomas Hunt
Morgan would flee the city heat to spend his summer in the seaside village of Woods Hole, Massachusetts. The Marine Biological Laboratory there offered a bounty of biological diversity to explore. Morgan investigated regeneration in hermit crabs, cell division in sea urchins, embryonic development in frogs, and sex determination in aphids. He moved from animal to animal with a dizzying agility unheard of in contemporary biologists, uncovering major insights into basic biology with each foray.

Then in the early 1900s, Morgan was looking for an organism to test some of Charles Darwin’s theories. He heard about an insect that was easy to raise in the lab and produced hundreds of progeny every few weeks. This insect — the fruit fly — sounded like just the right animal for the job.

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It was. Morgan used fruit flies to show that chromosomes are the basis of inheritance, a discovery that set the stage for modern genetics and earned him the 1936 Nobel Prize in Physiology or Medicine.

Morgan became one of the most revered biologists of the 20th century, but his scientific fame would never compete with that of his subject, which has become nearly synonymous with biological research. The fly, *Drosophila melanogaster*, has morphed into a test system to study the inner workings of biology — a model organism. Scientists study model organisms with the aim of understanding biology more broadly, including issues applicable to human health.

In the decades since Morgan began breeding his flies, the model organism approach has blossomed. The lion’s share of biological research today is centered on a select group of species — fruit flies, the roundworm *C. elegans*, zebrafish, mice and a few others. These animals are easy to grow in the lab, and researchers have developed an arsenal of tools for analyzing and modifying their genomes. The animals have had an enormous impact on our understanding of both basic biology and disease, earning scientists dozens of Nobel Prizes.

But some scientists argue that biology needs a taste of Morgan’s pre-fly days, when scientists studied a panoply of organisms. They argue that by focusing on roughly seven animals out of the estimated 9 million species on Earth, we are missing a huge chunk of interesting biology. “We are due for a renaissance,” said Alejandro Sánchez Alvarado, a biologist at the Stowers Institute for Medical Research in Kansas City, Missouri. “We have narrowed our focus to a handful of organisms that statistically are highly unlikely to encompass the gamut of biological activity on the planet.”

In June, Sánchez Alvarado and a few other scientists convened a panel of experts at Woods Hole’s Marine Biological Laboratory to discuss the development of new model species. The researchers want to combine the best of both worlds — narrow and broad — taking advantage of both nature’s diversity and the wealth of tools and knowledge that amass from focusing on specific species. “Most of the biological world lies before us unexplored and unknown,” said Jonathan Gitlin, MBL’s director of research. “If most of what we know comes from seven organisms, imagine what we would know if we had 700.”
The candidate model organism *Paryhyale hawaiensis* is a crustacean used to study the evolution and design of body plans. Scientists have successfully used CRISPR in this species.

**The Making of a Model**

The squid *Doryteuthis pealeii* is smaller than a house cat, but it possesses a nerve fiber hundreds of times larger than the typical human version. In the 1940s and ‘50s, the squid was a favorite among neuroscientists in Woods Hole because they could stick an electrode into the giant fiber and measure the electrical activity that propagated along it. That unprecedented access revealed the basics of nerve cell communication and earned its discoverers a Nobel Prize in 1963.

“The Woods Hole squid,” as it came to be known, embodied the approach of biologists at the time — find creatures that were best suited to the particular problem of interest. “Up until the 1970s and ‘80s, people chose organisms to answer certain questions based on the individual attributes of those organisms,” said Joshua Rosenthal, a biologist at MBL who convened the panel with Sánchez Alvarado and Gitlin.

The field began to close in on a handful of species in the 1980s, driven in part by the emergence of new genetic tools. These tools were laborious and expensive, so researchers focused their efforts on making them work in a few species. Like Morgan, they chose organisms that were easy to breed and had a relatively short generation time, such as worms and mice. That’s particularly important for genetics experiments, where scientists tinker with an organism’s genome and then have to wait for the subsequent generations to see the fruits of their labor.

“Many organisms are hard to grow and breed in the lab, so when someone comes up with one that has lots of convenient characteristics, it’s liable to be picked up quite quickly,” said Garland Allen, a historian of science at Washington University in St. Louis.

As more and more scientists studied a particular organism, they invented tools specific to that
species that gave them a deeper understanding of its biology. That in turn drew in even more scientists, who built on the technology and findings of the previous generation, sparking a positive feedback loop. The most commonly studied organisms were among the first to have their genomes sequenced, further enhancing the arsenal of molecular tools that scientists had to work with. “Research got funneled into a small number of organisms,” Rosenthal said. “That list of species has dominated everything for decades now.”

Ironically, genome sequencing is one of two major technical advances that has begun to break biology’s reliance on just a few model organisms. The cost of genome sequencing has dropped precipitously, so it’s easy to decode the DNA of almost any species. “We can start generating genomes for basically any organism you want,” Rosenthal said.

Even more importantly, new techniques for editing DNA, such as CRISPR, dramatically expand the number of species that can be genetically engineered. That means that scientists can tinker with genes in an array of organisms, figuring out which are crucial for regeneration or camouflage or memory. “That would have been a pipe dream 20 years ago because the tools were not there,” Sánchez Alvarado said. “But that’s changed in the last five years — all of a sudden, we can peer into the darkness much further than before.”

Indeed, CRISPR highlights a potential benefit of exploring the outer reaches of biology. The gene-editing technology, hailed as one of the most significant biological discoveries of the century, was uncovered by scientists studying microbes’ immune systems. “Who would think that something characterized in the backwater of biology would present itself as remarkable tool for understanding
the mechanisms of biology,” Sánchez Alvarado said.

A broader approach could also help fill in the biological gaps not covered by worms, flies and mice. None of these organisms can regenerate body parts, for example, nor are they particularly long-lived, two traits that could be of great interest for human health.

The ocean, however, is littered with creatures capable of complex reconstruction. Chop the freshwater flatworm *Schmidtea mediterranea* into tiny parts, and those parts can regenerate complete individuals. Sponges are similarly able to regenerate from fragments or even single cells. They possess striking cellular flexibility — even adult cells can develop into any kind of cell. And they can live incredibly long. In May, scientists discovered a 2,000-year-old sponge the size of a minivan living off the coast of Hawaii.

A decapitated planarian worm *Schmidtea mediterranea* regenerates its head over the course of a week.

Unlike sponges, our own cells are mostly stuck once they acquire a specific identity, limiting our ability to repair damage to the heart, brain and other tissues. But we share many of the same genes with sponges and flatworms, so deciphering their regenerative powers might inspire new approaches to healing. “It would be a fantastic boon to our understanding of stem cell regulation and tissue repair,” Sánchez Alvarado said. “It’s very likely that whatever we study will have profound implications for our understanding of ourselves and the ecosystems in which we live.”

**Inky’s Great Escape**

When Carrie Albertin was choosing a lab for her doctoral research, a professor at the University of Chicago took her to see the octopus tanks. One lone egg the size of a pinky nail floated in the 240-gallon tank. “Within five minutes, it hatched, looked at us, changed colors, inked and swam away,” Albertin said. “I was sold.”

Albertin isn’t alone. Many biologists are fascinated by cephalopods, the group that includes octopus, squid and cuttlefish. Octopus and squid, for example, have amazing powers of regeneration; in some cases, they are capable of growing new tentacles from scratch. They have a sophisticated means of communication and disguise, accomplished by an LED-like skin. And despite the fact that they are invertebrates, like flies and worms, with a nervous system much different from our own, they are capable of strikingly complex behaviors. YouTube is replete with cephalopod feats, from octopuses that can open jars to those that carry around a coconut shell to shelter themselves from predators. An octopus named Inky at a New Zealand aquarium made global headlines in April after he slipped through a small gap in the top of his tank, scampered across the floor, and slithered down a 164-foot-long drainpipe into the sea.

The cephalopod brain — the largest of any invertebrate — is still something of a mystery to scientists. But they know it’s organized much differently than our own. In addition to a central nervous system, an octopus has a distributed system of intelligence, with many of its neurons apportioned to each of its eight arms. Indeed, some species of octopus can remove an arm when
attacked by a predator, leaving the detached but active limb to struggle with the predator while the animal escapes. “They are interesting because they evolved complexity through a completely different avenue,” Rosenthal said.

The California two-spot octopus is a promising model organism because it can be raised in the lab and has had its genome sequenced. One of the top candidates for an octopus model species is the California two-spot octopus, the first cephalopod to have its genome sequenced. Its genome, published last summer, is nearly as big as our own — 2.7 billion bases compared with 3 billion — and it has more genes than we do: roughly 33,000, compared with 20,000 to 25,000 in humans.

The genome hints at the molecular innovations that might drive complex behavior. One of the most surprising findings of the genome study is a large family of proteins called protocadherins, which help determine how different neurons are connected. Before sequencing the octopus, scientists thought that only vertebrates had large numbers of these proteins. But the octopus has 168 different kinds of protocadherins, compared with our 58.

Cliff Ragsdale, a neurobiologist at the University of Chicago who led the sequencing project (and who first brought Carrie Albertin to the octopus tanks), said they are now starting to look at octopus neurocircuitry, which they hope will explain why the octopus has so many of these proteins. They suspect a diverse array of protocadherins enables a more diverse set of neuronal connections. “Protocadherins make a code for how to connect nerve cells — the more elements to the code, the more complex the code,” Rosenthal said. But no one has yet been able to test this in a hypothesis-driven way, he said.
If the two-spot octopus attains model-species status, Ragsdale and others will have a larger armory of molecular tools to tackle these questions. They can then begin to do more controlled experiments, eliminating the genes for certain protocadherins and analyzing what happens to the neural circuitry.

**Raising Octopus**

When Sánchez Alvarado, Rosenthal and Gitlin were planning their model organism workshop, they invited scientists studying an array of species, from freshwater flatworms to crustaceans, squid and coral. Individual researchers touted the benefits of their pet organisms and how they might reveal new biological secrets. Corals could help us track global warming’s impact on the ocean. Squid might provide insight into the tight relationship between hosts and their resident microbes. Crustaceans, which have a broad diversity of body plans, could illuminate how limbs develop. “Let’s pretend that we don’t have to stick with the traditional models,” Sánchez Alvarado said. “We can start using organisms again for their biological attributes. What are the big questions we want to ask? What organisms can we use to answer those questions?”

Scientists are also employing model organisms to study environmental questions such as the potential impacts of global warming. Coral reefs, for example, are dying at a disturbing rate. Scientists have had some success unpacking the process, but it’s been difficult to study coral in their natural habitat. “Model systems give you a handle on exploring the basic science around these questions,” said Virginia Weis, a biologist at Oregon State University. Weis studies an anemone called *Aiptasia* as a model for difficult-to-grow corals. (The anemones are so easy to grow in tanks that they’re considered a pest in saltwater aquariums.) Weis and others are using *Aiptasia* to examine the mechanisms behind coral bleaching, which happens when corals shed their microbes in response to warming ocean temperatures. This process makes the organisms susceptible to disease. “Model systems are a playground that biologists use to fiddle with a system in an artificial manner,” Weis said. “They can generate foundational information that we could never generate in an environmental setting.”

Some of these organisms have already attained the status of minor models, studied in five to 10 labs rather than the hundreds or thousands of labs focused on flies, mice and worms. Sánchez Alvarado and a handful of others, for example, study the planarian flatworm *S. mediterranea* as a model of regeneration. But it’s difficult for individual labs to develop new model organisms. The process is risky and requires time and groundwork, which may interfere with scientists’ ability to get grants and publish new papers.

MBL leadership aims to make the process more systematic. MBL wants to become a hub for producing new model organisms, taking on some of the foundational work. The goal of the June
workshop was to begin to select their top candidates. Like Morgan, they want organisms that reproduce quickly and can grow easily in the lab. (The lab’s namesake cephalopod, the Woods Hole squid, has been an important workhorse for neuroscientists. But it’s an unlikely candidate because it’s extremely difficult to breed in the lab.)

The researchers will walk a fine line as they focus the candidate list. Experts at the workshop urged the MBL team to keep the pool broad enough to expose the wild world of biology that remains hidden to science. But they must narrow in on a few species, both because of resource constraints and the power of collaboration. A model organism is most powerful when a number of experts approach it from different angles. Their target number isn’t set in stone, but Sánchez Alvarado estimates that a half dozen new species would be useful. “Given how much we’ve learned from the seven or so model systems we have, I can imagine that developing a few, well-chosen organisms could prove transformative,” he said.

Scientists will run candidates through a gamut of tests, analyzing how they reproduce, how they develop as embryos and how they grow into adults. They’ll map the organisms’ chromosome structure and sequence their genomes. They’ll test the ease of gene editing, targeting specific genes of interest. “We’ve seen a burst in technology and used it in model systems we’re comfortable with,” Sánchez Alvarado said. “Now let’s test it on new biological frontiers.”

Sánchez Alvarado estimates the process will take five to 10 years, perhaps less if more scientists participate. “The fallacy is that developing new systems will take a long time, but things aren’t the same as they were 10 years ago,” he said. “I think it will be quick to determine which systems to focus on because of advances in microscopy, genetics, evolutionary biology and cell biology.”

It’s impossible to know what Morgan would think of MBL’s efforts were he alive today, but given Morgan’s diverse interests as a scientist, Sánchez Alvarado and others speculate he would support the plan. “He would have been tickled that Drosophila was being used to answer so many different questions in biology — genetics, ecology, behavior,” said Allen, who wrote a biography of Morgan. But he likely would have considered focusing on a small group of model organisms to be misguided, Allen said. “If you’re trying to base all of biology on seven or eight model organisms, you will be led quite far astray.”