

Call of the Wild

Could quirky, new
animal models
help scientists
learn how to
regenerate human
limbs or avert the
debilitating effects
of a stroke? » » »

By Kathryn Brown

BAT EMBRYO

Differences in when and how identical genes are expressed mean humans have fingers and bats have wings.



SCOTT WEATHERBEE, NISWANDER LAB

Humans bear little resemblance to squirrels and even less to a bacterium that thrives in tins of irradiated horsemeat. But these and other far-flung creatures are offering new insights into the human condition. Although only a handful of organisms—notably fruit flies, nematodes and mice—have dominated comparative biology, scientists are casting a wider net for the biological lessons they say are lurking undiscovered in the wild.

HHMI investigator Sandra L. Wolin, at Yale University School of Medicine, and colleagues came across the bacterium *Deinococcus radiodurans*—the most radiation-resistant organism known—while studying proteins involved in two autoimmune diseases: systemic lupus erythematosus and Sjögren’s syndrome. Researchers have marveled at *D. radiodurans* since the 1950s, when they discovered it flourishing inside tins of meat that had been heavily irradiated during food-sterilization experiments.

A computer specialist working with Wolin, Anne Marie Quinn, was scanning a microbial genome database when she realized that *D. radiodurans* produces a protein

One Tough Bug To learn about photosensitivity, HHMI’s Sandra Wolin and postdoc Xinguo Chen study a bacterium that thrives in cans of irradiated horse meat.

ARCTIC SQUIRREL

Hibernating squirrels have remarkable defenses against brain injury.



COURTESY OF KELLY DREW

strikingly similar to an RNA-binding protein found in humans, called Ro. People with lupus often make antibodies against their own Ro protein, though no one knows just how Ro functions.

To learn more about Ro’s role, a postdoctoral fellow in Wolin’s lab, Xinguo Chen, created a strain of *D. radiodurans* that lacked the protein. The resulting bacteria were no longer so hardy; they died when exposed to ultraviolet (UV) radiation.

“One fascinating thing is that lupus patients with antibodies against Ro often have serious sensitivity to sunlight,” Wolin says. Perhaps, she suggests, a lupus patient’s antibodies interfere with Ro in skin cells, leaving the patient sensitive to sunlight. Her team now hopes to unravel Ro’s precise role. Wolin suspects Ro binds RNAs damaged by UV radiation and targets them for destruction.

Hints from Hibernation

For some 50 years, a small group of researchers has studied hibernating animals such as the woodchuck and ground squirrel for clues to treating stroke. During a stroke, a person’s blood flow and oxygen in the brain plummet. Much the same occurs as animals begin hibernating, though these sleepers stay safe until spring, when they awaken unscathed. “Hibernation is nature’s solution to enduring in the face of very low oxygen and blood flow,” says John M. Hallenbeck, a senior investigator at the National Institute of Neurological Disorders and Stroke in Bethesda, Maryland.

How do hibernators do it? Over the past decade, researchers have shown that hibernating squirrels basically shift biochemical gears, suppressing metabolism and immune response while boosting antioxidant defenses, among other adjustments. “The key is that all these things happen at once,” Hallenbeck says, and this convergence yields potent results. “These ground squirrels have pretty dramatic protection against brain injury,” notes neurochemist Kelly Drew of the University of Alaska in Fairbanks.

More recently, Drew decided to see just how well hiber-

AMY ETRA



nation helps an animal resist brain injury. She and her colleagues inserted microdialysis probes into the brains of five Arctic ground squirrels, two hibernating and the others awake as usual. Several days later, the team compared the squirrels' brains. Those that were hibernating at the time of the probe-induced injury fared well, with very little tissue damage. By contrast, the active squirrels showed clear signs of injury—significant cell damage and inflammation of the surrounding brain tissue. “These strikingly different responses do support the idea that hibernation is a good model of neuroprotection,” says Drew, whose team published the study in the June 2001 issue of the *American Journal of Pathology*.

If researchers can identify hibernation's key biochemical steps, Hallenbeck suggests, it may be possible to induce a similar process in stroke patients. Emergency paramedics, for instance, could deliver drugs that minimize brain damage during, or immediately after, a stroke. “In a clinical setting, you'd want a patient's metabolism to drop to some minimal level, while generating molecules that suppress inflammation and fight free radicals,” Hallenbeck says. Scientists still have much to learn about hibernation, and no one knows whether nature's long winter nap will inspire realistic stroke therapies. Drew, for one, is optimistic.

Reviving Old Models

Some of the new creatures being studied are merely rediscoveries of some of science's old models—such as the bat (see page 32)—that fell out of favor when biologists began training their microscopes on fewer organisms. “If you go back to the 1800s or earlier, you'll find scientific sketches of bat embryos,” remarks Richard R. Behringer, a molecular geneticist at the M.D. Anderson Cancer Center in Houston. “In fact, there's a heritage of reproductive biology in diverse organisms, with a wealth of knowledge to be gained by doing comparative studies.”

About five years ago, Behringer decided to combine embryological studies of mice with research on bats. “We all say we're studying this or that animal to learn more about human biology and disease,” says Behringer. “If that's true, we should start questioning the relevance of our models. At some stages of development, human embryos are very different from mouse embryos. So you start thinking, why am I studying the mouse? How does it relate to humans?”

Bats may look like flying mice—but in

many other ways, they distinctly differ. As the embryos develop, for instance, bats grow wings, with cape-like webbing between their digits. But mice, like chicks and humans, lose these “interdigital cells,” and their digits or fingers form with no webbing in between. All four creatures probably share the same limb-development genes—they just express those genes during different developmental windows, says molecular biologist Lee Niswander, an HHMI investigator at the Sloan-Kettering Institute in New York. “How do changes in gene expression give rise to these evolutionarily important differences in animals?” Niswander asks. “If we can understand how these limbs develop in bats, we'll gain insight into the process in the chick, mouse and human.”

The flatworm is another old model with a new twist. At the University of Utah in Salt Lake City, biologist Alejandro Sánchez Alvarado decapitates freshwater planarians—only to watch those fragments regenerate into

A Living Biology Lesson

It's a velvety green caterpillar. It's a tough brown pupa. It's a large, mottled gray moth.

Manduca sexta, or the tobacco hornworm, is all of the above, which is one reason (or three reasons) why the popular biology-lab animal has become a pet and living science lesson in the primary grade classrooms of Tucson, Arizona. The Manduca Project, run by the University of Arizona's department of biochemistry and molecular biophysics with a grant from HHMI, helps teachers exploit the 40-day life cycle of the hornworm to capture the attention of first, second and third graders.

Although the young *Manduca* breeders don't realize it, they're also honing their powers of observation and expanding their knowledge of biological systems, diversity, metamorphosis and the relationship between structure and function—all elements of Arizona's state science education standards. The project also addresses math standards as the children measure and graph the growth of their hornworms. Some classes have composed songs and poems about their multilegged pets.



Inspires Poetry Eduardo Hernandez plays with a tobacco hornworm in its caterpillar phase.

More than 3,500 first, second and third graders so far have raised tobacco hornworms from egg to moth. University of Arizona undergraduates, who work with the teachers and children to study these insects, take what they learn back to their own labs for further exploration. Kim Keene, for example, did her senior research project on a digestive enzyme that helps *Manduca sexta* move through its many molts and rapid growth.

—JENNIFER BOETH DONOVAN

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fully formed worms. “Flatworms have figured out how to access all their developmental processes at any given point during their lifetimes,” he says. “In this day of genome sequencing and developmental insight, it’s possible that we could learn a great deal about regeneration and stem cell biology from planarians.” For example, if scientists discovered the basis of nature’s regenerative talents, people who lost limbs to accidents or illness might ultimately be able to grow replacements.

When Sánchez Alvarado began working with flatworms six years ago, many of his colleagues derided his choice as “career suicide.” In developmental biology, after all, *Caenorhabditis elegans* was the worm to watch. But soon his lab began documenting genes found in planarians and humans, but not in *C. elegans* or fruit flies. “These may be missing pieces of evolution,” he says, “and it’s definitely a viable scientific endeavor.”

In fact, while some researchers debate whether adult-

FLATWORM

Alejandro Sánchez Alvarado is betting on *Schmidtea mediterranea*'s regenerative talents to help with limb regeneration in humans.



COURTESY OF ALEJANDRO SÁNCHEZ ALVARADO

mouse stem cells can reliably turn into different tissues, others are uncovering the molecular-mechanics systems of naturally regenerating animals. These animal architects include hydra polyps, tadpoles, zebrafish, newts and planarians. So far, Sánchez Alvarado’s lab has found about 5,000 independent markers of gene expression, called expressed sequence tags (ESTs), in the flatworm *Schmidtea mediterranea*. His group and others are now crafting assays to profile gene expression during regeneration. The big task will be to pinpoint responsible genes—and their human homologs, if any, adds Sánchez Alvarado. “We don’t know whether regeneration is the same, molecularly, across organisms,” he concedes. “But the genetics could tell us.”

Even nature’s farthest corners—and tiniest creatures—may hold hints for humans. “Biology often makes progress by looking at extreme cases,” says HHMI President Thomas R. Cech. Because all life is related through evolution, he says, scientists trust that biology’s extremes apply in more mundane settings as well. Cech speaks from experience. In the 1980s, his team at the University of Colorado, Boulder, discovered self-splicing RNA, or ribozymes, in a lowly pond organism, the ciliated protozoan *Tetrahymena thermophila*. Since then, scientists have recorded and sequenced 1,800 examples of this type of RNA spread across much of biological life.

While Cech advocates making the most of known animal models and their advanced tools, he also sounds the call for creative comparisons. “The best insights often come when you stop to compare vastly different species,” he says. **II**

JASON TANAKA-BLANEY

Where the Bats Are

When Lee Niswander goes to work, she gets a squeaky and high-pitched welcome, complete with a flutter of wings and a twitching of ears. This unusual greeting is from a colony of tropical fruit bats. When not in her lab at the Sloan-Kettering Institute, Niswander, an HHMI investigator, often works at one of the few bat research facilities in the country. Here, about 100 furry fliers spend their days snoozing and nights exploring. And when Niswander or

her colleagues intervene, the bats mate.

In fact, mating is what makes the bat facility so important. “The biggest reason for having a colony is the ability to do timed matings,” Niswander explains. “We want to study bat embryos at precise developmental stages.” That’s possible, she adds, only when she and colleagues can catch a developmental moment in action. (Ever try to lure a pregnant bat from the sky?)

While at Cornell University’s Medical College, bat researcher John J. Rasweiler IV, now at the State University of New York Downstate Medical Center in Brooklyn, founded the colony with bats collected in Trinidad almost a decade ago. When Rasweiler left Cornell, the facility’s funding was in question. But last year, Niswander appealed to HHMI Vice President Gerald M. Rubin for support. For roughly \$20,000 per year, HHMI has kept the facility open—allowing Niswander, as well as molecular geneticist Richard Behringer of M.D. Anderson Cancer Center in Houston, to conduct developmental studies of bats that also promise insights into human biology. Niswander estimates that housing each bat costs about 65 cents per day.

“We ultimately hope to make this colony available to the broader scientific community,” Niswander says. “Researchers are growing more aware of our developmental research on bats, and this is a valuable resource.” —K. B.

Out of the Night Lee Niswander says nocturnal bats are a valuable resource for developmental biology.

