Evolution Is Our Laboratory

Studying how evolution acts on all levels—molecular, cellular, organismic, ecological, social—investigators find thematic threads that draw the disciplines together.

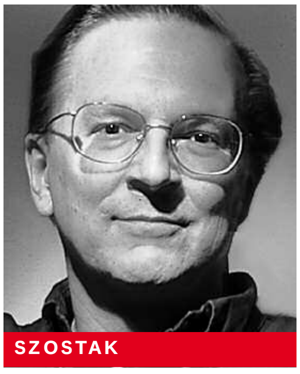
BY STEVE OLSON

ILLUSTRATION BY DAVID PLUNKERT


PLUNKERT

A great irony of the recent upsurge in creationist sentiment in the United States is that research in evolutionary biology has never been more dynamic or exciting. ¶ Biologists in many fields are discovering that they cannot answer critical questions without first understanding how living systems evolved. “Many biologists would now agree that a grounding in evolution is fundamental to biology,” says Sean B. Carroll, an HHMI investigator at the University of Wisconsin–Madison. “Before, I think they would have said that evolution is a branch of biology but not an integral foundation.” ¶ Several developments underlie this trend. Biologists have come to recognize the many ways in which evolution has forged commonalities among organisms. “There are much greater similarities at the genetic level than biologists had appreciated, profound similarities,” says Carroll. “That forced a rethinking. It meant that a generation of biologists had to learn not only about the connections among organisms but also about how those connections could be used as research tools.” ¶ New genomics data have highlighted these evolutionary links. Whereas biologists used to rely on similarities in shape or behavior to draw evolutionary connections, they now can reconstruct evolutionary lineages by analyzing DNA sequences. “You can document the dramatic genetic events that changed the nature of an organism over evolutionary time,” says HHMI investigator David Haussler at the University of California, Santa Cruz. ¶ In addition, biologists increasingly have realized that questions involving evolution have important connections to other scientific fields. And as they have forged multidisciplinary collaborations with chemists, geologists, computer scientists, and social scientists, new ideas and techniques have flooded into the biological sciences. ¶ The growing prominence of evolutionary biology is apparent in the work of many HHMI investigators. **Here are five examples.**

1 The Origins of Life



In principle, evolution is remarkably simple. Among assemblages of molecules able to reproduce themselves, some copies turn out slightly different from the original. When a variant appears that is better able to survive and reproduce, it will become more numerous. And as these entities continue to copy themselves and change, some will come to exploit existing resources in new ways or move into new environments.

Biologists may never know exactly which molecules came together to form the first living organisms, but HHMI investigator Jack W. Szostak, a geneticist at Massachusetts General Hospital and Harvard Medical School, is very close to demonstrating how the process could have occurred early in Earth’s history. In his laboratory at Massachusetts General Hospital, Szostak and colleagues synthesized chains of nucleic acids that can latch onto other nucleic acid chains (including copies of themselves) and partially copy those chains. On the early Earth, reproducing chains of nucleic acids could have formed within vesicles composed of fatty acids, which could have been plentiful in certain places. This compartmentalization is critical, Szostak points out, because otherwise, highly efficient replicators will make copies of all the nucleic acid chains around them. If they are isolated inside a vesicle, however, they will make more copies of themselves and thereby increase in number.

A major challenge for Szostak’s team has been devising a way of coordinating the growth and division of the vesicle with the replication of its contents. After examining several possible mechanisms, “we worked out an idea that was relatively simple,” he says. They found that putting nucleic acid chains inside a vesicle creates osmotic pressure inside the membrane. These highly pressurized vesicles are able to absorb fatty acids from less-pressurized vesicles and grow. If these growing cells divide randomly or at a certain size threshold, they reproduce faster than less rapidly growing cells. In this way, says Szostak, a highly efficient nucleic acid replicator could outcompete less efficient replicators.

The outcome is natural selection among membrane-encapsulated nucleic acid chains. “It’s a nice simplification of the whole process,” says Szostak. Different replicator-vesicle packages compete with each other to become more numerous, so Darwinian evolution can occur with relatively simple molecular systems. Once these simple cells start competing, Szostak believes, there is a “snowball effect. You start to get additional functions evolving, and that’s going to lead to changes in the membrane composition. The whole system is going to be under pressure to get a lot more complicated pretty quickly.”

Szostak, well-known in biology for his work on chromosomal recombination, notes that his interest in evolution has caused him to establish strong collaborations with chemists: “I have people in my lab who are doing synthetic chemistry, and because we have to make molecules to build these systems, we collaborate with a number of other chemists, too.” This connection between disciplines is being further strength-

MARK WILSON

A RELATIVELY SMALL CHANGE IN A REGULATORY REGION CAN HAVE A DRAMATIC EFFECT ON THE BODY PLAN OF AN ORGANISM.

ened by the creation of a new center at Harvard to study the origins of life. "Both in chemistry and biology," he says, "the origin of life is a fundamental issue."

2. The Coevolution of Life and Earth

NEWMAN

For more than a billion years, single-celled organisms were Earth's only inhabitants. But these cells were evolving and diversifying, and in so doing they began to change their environment. As California Institute of Technology geomicrobiologist and HHMI investigator Dianne K. Newman puts it, "Life and Earth have coevolved."

The earliest organisms lived in a forbidding world. Earth's atmosphere contained virtually no oxygen and would have killed many of the organisms that live on the planet today. Instead, scientists believe, the atmosphere contained substances such as nitrogen, carbon dioxide, and water vapor. As a result, our ancient predecessors had to rely on these atmospheric components, not the oxygen that now sustains us.

Newman studies modern-day organisms that essentially breathe metals—they transfer electrons from one metal ion to another to produce metabolic energy. The distant ancestors of these metal-breathing bacteria ruled Earth early in its history, but bacteria evolved that released oxygen into the atmosphere. For many millions of years this oxygen was sequestered in rocks, producing the ore deposits now known as banded iron formations. Eventually, oxygen began to build up in the atmosphere, triggering an environmental and biological "crisis" by changing the composition of rainwater, streams, and oceans.

Newman's work on metal-breathing bacteria has led her to consider the broader question of how bacteria have changed Earth's environment over evolutionary time. For instance, she and a group of colleagues recently proposed that a particular kind of bacterium played a key role in deposition of the banded iron formations. "I'm not an evolutionary biologist," says Newman, who studied German as an undergraduate at Stanford before receiving a Ph.D. in civil and environmental engineering from the Massachusetts Institute of Technology. "What I hope to contribute is an understanding of the mechanisms whereby these putatively ancient bacteria do what they do, and then make connections back to the rock record."

Like Szostak, she stresses the importance of interdisciplinary collaboration. "It's imperative for someone like me to have good colleagues who are experts at looking at ancient rocks," she says. "We're also beginning to design experiments with bacteria in the lab to help geologists interpret certain structures they see." To that end, she recently visited South Africa with a team of geologists and biologists to investigate the banded iron formations there.

Newman's work has many practical applications. For example, because some metal-breathing bacteria can convert toxic metals into less toxic compounds, these descendants of Earth's first occupants may someday be hard at work cleaning up pollution produced by humans.

3. Experimenting with Body Plans

CARROLL

PATEL

KINGSLEY

About 2.4 billion years ago, the atmosphere began to harbor appreciable amounts of oxygen. A few hundred million years later, according to the fossil record, new kinds of cells appeared. They were larger and more complex, possibly because they had evolved ways of using oxygen to support metabolic processes. Shortly thereafter, organisms appeared that were large enough to be seen without a microscope (had one existed)—algae consisting of cells in spiral chains.

For more than a billion years, these simple multicellular organisms evolved internally without great changes in external form. But beginning about 545 million years ago, during a period known as the Cambrian, evolution headed down a different path. A wealth of new organisms suddenly appears in the fossil record; they have hard shells, segmented bodies, and wildly different kinds of legs, antennae, spines, and claws. All the major types of animal lines—including organisms that would evolve into the vertebrates—appear during the Cambrian period, along with many bizarre biological experiments that proved unsuccessful.

The sudden appearance of these different body plans

NEWMAN: JOHN HAYES/AP; *CARROLL*: MICHAEL KIENITZ; *PATEL*: TODD BUCHANAN; *KINGSLEY*: KAY CHERNUSH

HUMANS EVOLVED IN THE MOST RECENT FEW MOMENTS OF EVOLUTION'S GRAND PAGEANT—APPEARING JUST 150,000 YEARS AGO.

has always puzzled biologists. How did all these animals evolve so quickly? Was it the result of abrupt and dramatic genetic changes?

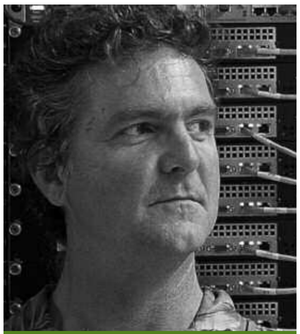
HHMI investigators Sean Carroll, David M. Kingsley at Stanford University School of Medicine, and Nipam H. Patel at the University of California, Berkeley, have been investigating these questions from a relatively new perspective. They are leaders in the new field of evolutionary developmental biology—evo devo, for short—which relates the development of organisms to the regulation of genes. According to these investigators, evolutionary changes in body plan do not necessarily require changes in the number of genes or in the protein products of genes. Instead, evolution can create new kinds of organisms simply by experimenting with how genes are turned on and off as an organism develops from a single fertilized cell to its mature form. "If you want to tinker with body patterns, you tinker with genetic switches," says Carroll.

Besides containing the genetic sequences that dictate the order of amino acids in proteins, DNA contains noncoding sequences that tell cells when and where specific proteins should be expressed during development. These regulatory regions undergo evolutionary changes just as the coding regions of DNA do. But a relatively small change in a regulatory region can have a dramatic effect on the body plan of an organism. It can change the number of segments of an organism, and it can alter the appendages—themselves often segmented—that emerge from a body segment.

Patel, for example, studies this process in crustaceans, the segmented organisms that first appeared in the Cambrian period. "The particular animal we work on [the crustacean *Parhyale hawaiensis*] is remarkable because each segment comes from an individual row of cells in the embryo, so it's very easy to keep track of what goes on," he says. Patel and his colleagues have identified a number of genes that play a role in the segmentation process, and they have begun modifying the regulation of these genes to gauge the effects on development. They also have been relating changes in expression of the genes to changes in the segmentation of fossilized crustaceans. "In different species, different appendages have become specialized to do different things, and we're trying to develop a molecular understanding of how that occurs."

Patel, Kingsley, and Carroll all emphasize the importance of understanding how ecological forces have shaped an organism's evolution. Kingsley, for example, studies the evolutionary genetics of the stickleback—a small bony fish that lives in lakes, oceans, and coastal habitats throughout the Northern Hemisphere. He chose the stickleback as a model organism, he says, because different forms can be crossed and because thousands of papers have been written about the fish and its adaptation to different environments. "We were able to leverage a rich history of biological work to develop a full picture of this organism, from its DNA to its ecology," he says.

4. Diversification of Life on Land



HAUSSLER

After the Cambrian period, animals moved from oceans onto land and evolved into insects, amphibians, and reptiles. The dinosaurs that came to dominate suddenly went extinct, quite likely because a giant asteroid hit Earth. In the absence of dinosaurs, early mammals diversified and spread, eventually producing many of the creatures familiar to us today.

Until recently, biologists studied this grand saga largely through the fossil record. But in the past few years they have gained access to an entirely new way of studying evolution. As genome sequencers have derived the complete or partial DNA sequences of different organisms, evolutionary biologists have been able to track how these organisms diverged genetically from a common ancestral species. In so doing, "you can feel the DNA evolving," says HHMI investigator David Haussler.

Haussler leads several teams that have been developing mathematical algorithms and software to analyze and display the genetic differences among organisms. Using these bioinformatic techniques, one team has reconstructed with an estimated 98 percent accuracy part of the genome of the common ancestor of most placental mammals—a small, shrewlike creature that lived about 100 million years ago. "It sounds implausible," Haussler admits, "but there's enough information to reconstruct quite a good approximation to the ancestral genome on the basis of mammals alive today."

Building on this reconstruction, Haussler and his colleagues have been putting together a database that can trace the changes in any given nucleotide from the common placental ancestor to humans or other living mammals. "We hope to literally show you evolution working," he says. In turn, Haussler's group has been using this tool to study the functional significance of various parts of our genome. Only 1.5 percent of the human genome actually codes for proteins. But by comparing genomes across organisms, Haussler and his colleagues have estimated that an additional 3 to 4 percent of the human genome is constrained in its changes—presumably because it regulates the expression of genes or helps organize other functions of our DNA. "There's a huge amount

TIMOTHY ARCHIBALD

of uncertainty and discussion right now about what these areas are doing," he says. "We're mapping them out to try to understand how they have changed over time and beginning to explore their function in the lab."

5. The Evolution of Humans

WALSH

LAHN

Humans evolved in the most recent few moments of evolution's grand pageant. The evolutionary lineage leading to humans split off from the lineage leading to chimpanzees some 6 to 8 million years ago. But anatomically modern humans—people who looked as we do today—appeared only about 150,000 years ago (less than one three-thousandth of the time between us and the Cambrian period).

The lineage leading to humans obviously underwent profound changes since the time of our common ancestor with chimps. HHMI investigators Christopher A. Walsh at Harvard Medical School and Bruce T. Lahn at the University of Chicago have been studying those changes in the brain. The human brain is much larger in relation to our body size than the brain of any other animal, and it "has a more complex organization," says Lahn, "particularly in terms of the subdivision of regions for specific tasks."

Walsh points out that three genetic mechanisms could have caused the human brain to diverge from the chimpanzee brain. New genes may have been added to the human genome that are not present in the chimpanzee genome. Some of the genes that the two organisms share could encode subtly different proteins. Or the regulation of genes could vary—shared genes might be more or less active in the two organisms during different periods of development and in different tissues.

"We have some evidence for the action of all three of those mechanisms, and we're sorting out which of them is likely to be most important," says Walsh. Publication of the chimp genome a few months ago revealed that a number of genes in humans have been duplicated and then altered since the days of our common ancestor, and some of those genes may influence the development of human brains. Similarly, many of our genes are slightly different from the corresponding genes of the chimp, although that animal's genome reveals a striking similarity in coding sequences across the two species.

But Walsh thinks that regulatory changes eventually will prove to be the most important distinguishing factor. Small changes in the expression of a gene can have dramatic effects on an organism. Researchers also have shown that levels of gene expression have changed more over time in the human lineage than in the chimpanzee lineage. Unfortunately, says Walsh, "Our tools for studying changes in noncoding DNA are very poor."

To understand the complex development of the human brain, Walsh and Lahn both stress the importance of studying genetically transmitted neurological disorders. With a human genetic disease, says Walsh, "You can really learn something about why a gene is essential in our brains, and you can learn that only in humans." For example, Walsh and Lahn have been studying inactivating mutations in a gene called *ASPM* (for "abnormal spindle-like microcephaly associated") that can produce brains much smaller than normal. Both their labs have demonstrated that the protein product of the gene has undergone significant evolutionary changes since the time of our common ancestor with chimpanzees, implicating the gene in our ancestors' dramatic brain expansion.

In fact, Lahn believes the gene is still under significant positive selective pressure in human populations. He and his colleagues have identified variants of the *ASPM* gene that have arisen relatively recently, and they have found one variant that appears to be spreading through the population. Lahn thinks that people with the variant *ASPM* gene have some sort of selective advantage, enabling them to have more children and thereby producing more copies of the gene. "This [work] is very relevant to behavioral evolution studies," says Lahn. "We have to start thinking about how social structures and cultural behaviors in the lineage leading to humans differed from that in other lineages."

We tend to think of ourselves as distinct from the rest of the biological world, as if our appearance marked the end of evolutionary history. That's clearly not true. We are the products of a vast evolutionary process that will continue indefinitely, whether we are here to influence it or not.

As Sean Carroll says in his 2005 book *Endless Forms Most Beautiful: The New Science of Evo Devo and the Making of the Animal Kingdom*, humans are "ensemble players working from a shared evolutionary script."

And, just as studies of evolution have revealed a profound unity among biological organisms, so have they fostered an appreciation of the unity among biological disciplines. In the past, different fields of biology were relatively isolated, Carroll points out. "Paleontologists and molecular biologists never used to meet," he says. "People published in different journals and ran in different circles. There was a pronounced split in the biological community."

In recent years, the study of evolution has been drawing the disciplines together. Researchers are increasingly appreciating that evolution acts on all levels—from the molecular to the cellular to the organismic to the ecological to the social—and that all aspects of biology reflect the workings of natural selection. Thus, a major challenge facing biology today, says Patel, is to "integrate all of the various fields of biology and get a more holistic view of how evolution works." ■

WALSH: ASIA KEPKA; *LAHN*: MARK SEGAL