LIFE'S BEGINNINGS

STUDYING HOW LIFE BLOOMED ON EARTH—AND MIGHT EMERGE ELSEWHERE

BY COURTNEY HUMPHRIES

ARE THE INHABITANTS OF EARTH the only life forms in the universe, or could life exist elsewhere? As astronomers rapidly identify exoplanets—those beyond our solar system—the question has been transformed from a science-fiction trope to one discussed in scientific journals and conferences.

And it quickly leads to another question: How did life start here on Earth? That question, says Dimitar Sasselov, professor of astronomy and director of the Origins of Life Initiative at Harvard, "is one of the big unsolved questions humanity has always asked." And yet for various reasons it has been difficult to answer. Biology has been very good at describing how living organisms work; it has been far less successful at answering what life is and how it could emerge from a non-living world.

"If you think of the two deepest and most challenging questions we could ask about life, I think they're 'How did it begin, and are we alone in the universe?'" says Andrew Knoll, Fisher professor of natural history. "And what I find remarkable when I think about it is that we are really the first generation in human history to ask those as scientific rather than philosophical questions."

The initiative (http://origins.harvard.edu), launched with seed money from the University in 2005, has brought together scientists from largely disconnected fields—astronomy, physics, chemistry, biology, earth and planetary sciences—to tackle these issues. Sasselov says such breadth of expertise is necessary because so many conditions influence life's emergence. How did the Earth aggregate from cosmic elements in such a way that it could support life? What environmental conditions does life require? How do inorganic molecules begin to behave like living organisms: replicating, organizing into cells, growing, evolving?

"In a certain sense our main question is really: what is the nature of life?" Sasselov explains. "That's why we call it the *Origins* of Life Initiative. The plural here is very intentional." If the only goal is to understand life on Earth, he says, it's a historical question. But if the goal is to understand how life emerges from particular environmental and chemical conditions, then the answer is much more fundamental. It raises the possibility that life could form in different ways on different planets. And ultimately, Sasselov believes, it could help us move beyond simply describing life to uncovering universal principles that govern it, akin to principles of planetary motion.

DISCOVERING OTHER WORLDS

THE FIRST EXOPLANETS discovered were hulking, puffy, Jupiter-like planets that would not be able to support life as we know it. While all exoplanets are interesting in their own right, to anyone looking for life outside Earth, the true prize is small planets that are dense and rocky like our own, and that exist in the so-called "habitable zone," where surface temperatures are consistent with liquid water, a requirement for familiar life forms. Scientists are making rapid progress in hunting this smaller prey; in fact, they now estimate that small planets far outnumber large ones.

The challenge, of course, is not just to identify planets but to know something about them and whether they could support life.

Dimitar Sasselov, director of the Origins of Life Initiative, searches for planets around red dwarf stars. Because they are dimmer and smaller than our sun, red dwarfs make ideal targets for taking images of the extrasolar planets that orbit them.

One of the initiative's most significant accomplishments to date is the development of a new resource, the HARPS (High Accuracy Radial velocity Planet Searcher) North instrument, which is designed to detect and characterize exoplanets similar to Earth in mass and structure. NASA's Kepler space telescope has detected thousands of potential candidate planets, but determining their mass, mean density, and composition requires a more precise instrument. HARPS is a spectrograph that can measure subtle wobbles in the stars the planets orbit, caused by the gravitational tugs the planets exert. The first HARPS instrument is located at the European Southern Observatory telescope at La Silla, Chile. The newer HARPS-N—created through an international partnership that included the Origins of Life Initiative, the Smithsonian Astrophysical Observatory and Harvard College Observatory, the University of Geneva, and other institutions—has been installed on the TNG (Telescopio Nazionale Galileo), a 3.6-meter telescope at the Roque de Los Muchachos observatory in the Canary Islands. This telescope is trained on the same skies as Kepler, which makes HARPS North a powerful partner in characterizing planets.

David Charbonneau, professor of astronomy, says that after making first observations with the instrument last spring, the research team is now in the process of gathering and analyzing data, which takes time because of the slow cycles of planets around their stars. He says the instrument's precision makes it possible to begin studying the planets' atmospheric content. "The light from the star passes through the planet's atmosphere on the way to telescope," he explains, and the atmosphere's signature on that spectrum of light can be measured. Charbonneau's next task is to design experiments that can do just that: find signatures of molecules like oxygen within these spectra.

In the longer term, the Giant Magellan Telescope (GMT), now under development in Chile's Atacama Desert, will also be paired with a sensitive spectrograph, dubbed G-CLEF (GMT Consortium Large Earth Finder), to enable more direct observations of distant stars and their planets (see "Seeing Stars," May-June, page 32). "I can guarantee you that, 10 years from now, we will have spectra that will be extremely exciting and interesting," says Sas-

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Photographs by Stu Rosner

selov. Astronomers will join with colleagues in chemistry and biology to interpret those data, enabling scientists to know, for instance, if a planet has lots of oxygen or methane or carbon dioxide, or whether it has other molecules not abundant on the Earth. "That's the moment to which we are building," he says.

The first characterizations, he adds, will almost certainly be of planets that are not inhabited, "but they will teach us about some of the basics of geochemistry, and what the variety of different environmental conditions are beyond what's available in the solar system." That in itself might stimulate new ways of thinking about how life arises.

The conditions for life, on Earth and elsewhere

With technologies available soon that may enable scientists to identify the conditions conducive to life on other planets, the question of which planets to study becomes critical. Despite their best speculations, scientists have only one model to work from: Earth.

But Earth's surface is constantly turning over and weathering down, so any signs of sedimentary deposits from the planet *prior* to the appearance of life have been subsumed through plate tectonics or eroded. As Knoll says, "When the curtain goes up on the geologic record, life is already there. Every time you go by a road cut or a cliff, you are looking at a chapter in the history of life."

Earth's biological and physical history are intimately linked. The planetary conditions on Earth shaped the life that evolved, and life in turn dramatically altered the planet. The early Earth provided elements like carbon and nitrogen needed to create organic molecules, but as life evolved, photosynthetic bacteria filled the atmosphere with oxygen. Long before the fossil record of plants and animals begins, scientists see evidence of microbial activity throughout the planet: single-celled creatures that left behind physical structures like giant reefs as well as chemical byproducts of their metabolic activities. In recent years, Knoll and other scientists have enhanced their ability to "read" this history, finding chemical signatures of life buried deep within ancient rocks. They can use this information to understand better how the chemical environment of the planet drove evolution, and vice versa.

This knowledge can be applied to understanding the histories of other planets. "Our experience of the Earth, it doesn't exhaust the possibilities for life in environments elsewhere, but frankly it gives us our only mooring point," says Knoll. Just as the Earth has changed throughout its history, other planets are also dynamic systems. Knoll has been on the scientific team analyzing data from the Mars rover missions, which have provided the first chance to decipher in detail another planet's geologic history (and because Mars has no plate tectonics, its ancient history is better preserved than Earth's). Though Mars is devoid of water and hostile to life now, scientists have found evidence of a watery past and hope to encounter signs of microbial life. But Knoll says that it now appears that any narrow window of habitability on Mars had closed just as Earth's was opening, around four billion years ago.

With so many planets to choose from, scientists are discussing the best ways to winnow down candidates for life. In an article in *Science* this past May, Sara Seager, a planetary scientist at MIT, argues that scientists should adopt a broader understanding of which planets are habitable, given the diversity of characteristics of planets and their solar systems. In environments with different pressures, temperatures, and chemical compositions, habitability might look quite different from what we expect. Sasselov wants scientists to abandon the term "habitable zone" altogether, as it focuses on a particular region rather than specific planetary conditions conducive to life. He says the debate can be re-

Emergence of a Field

In its first few years, the origins initiative has forged new connections among faculty members in disparate departments and influenced similar programs at other universities. It has led the investment in new tools and fostered cross-disciplinary research with postdoctoral fellowships. But launching such an endeavor has been challenging.

Sasselov has served as the effort's ambassador. "We're trying to answer a scientific question that may have few practical applications—it's a very big question," he says. "The reason why we're bothering is because there's such big, exciting science to be done." But calling the science interdisciplinary is an understatement, he adds. There is simply no way to address it without broadening the typical scope of disciplines.

The initiative's regular meetings have helped the nearly 30 associated faculty members explore connections within their research, and faculty are beginning to work collaboratively on papers. But the team has wanted more sustained funding for students and fellows to do research between labs, which would help make theoretical connections reality.

Despite a growing interest in interdisciplinary collaborations in science, the system of training, funding, and recognition still follows departmental distinctions. Sasselov's larger goal is to ensure that when young chemists come to the program to do cross-disciplinary research with astronomers, they will go on to find positions that value that training, and fellow scholars able to evaluate grant proposals and papers that require peer review. "What we're trying to do is create a worldwide community of scholars…who are truly representative of this new field," he says. Beginning this May, the Simons Foundation has made an eight-year commitment to fund the Simons Collaboration on the Origins of Life, directed by Sasselov and Szostak, to connect investigators from several institutions in support of faculty research and postdoctoral fellowships in the area.

Sasselov's hope is that the current resurgence of interest in life's beginnings won't get stymied again as it did in the middle of the last century, but will lead to a new way of understanding life in the universe.

solved only with substantive research that defines exactly what these conditions are—the initiative's goal.

Biology begins: a multitasking molecule and simple cells

In the 1950s, Stanley Miller and Harold Urey of the University of Chicago published the results of a now-famous experiment to test the possibility of creating organic compounds from the inorganic milieu of a primitive Earth. By adding an electric spark to an apparatus that contained methane, ammonia, hydrogen gas, and water, they were able to transform the carbon in the methane into simple organic compounds, including amino acids that are the basis for proteins in living cells. The Miller-Urey experiment dazzled scientists and laypeople alike with the idea that life could form spontaneously from a "primitive soup" of chemicals, and the right conditions (like a lightning strike to supply the energy).

But Sasselov says that the initial excitement faded when the complexity of DNA's structure—solved by Francis Crick and James Watson at about the same time—was fully appreciated. It seemed impossible that the elegant helix could arise from a primitive chemical soup. "Suddenly the difference between the Miller-Urey experiment and the biomolecules of today, which are DNA and RNA, became a huge gap, an unfathomable gap," Sasselov says. "And the initial excitement actually led to a serious depression where people left the field altogether."

Fisher professor of natural history Andrew Knoll, curator of the Harvard University Herbaria's paleobotanical collections. Behind him is an outcropping of ancient sedimentary Martian rock, which he's studied for NASA's Mars Exploration Rover Mission.

But in recent years, stalwart scientists have continued to experiment with the chemistries of early Earth, and have made progress in understanding how life could have emerged. One of them is Jack Szostak, professor of chemistry and chemical biology and of genetics at Harvard; two decades ago, he shifted the focus of his research from yeast genetics (for which he shared the 2009 Nobel Prize in Physiology or Medicine) to studying RNA molecules, which he thought could shed light on the next steps of life's emergence. "Once you have the right kinds of molecules," he asks, "how do they get together to assemble into cells that can grow and divide and evolve?" Scientists studying the origin of life today face a chicken-and-egg problem: in modern cells, the genetic instructions of DNA are translated and carried out by RNA and proteins, which perform cellular functions—including building DNA. So

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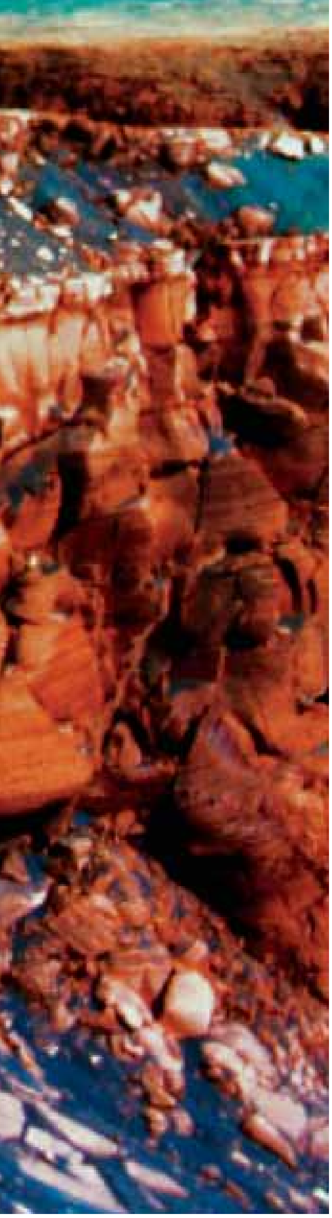

SCIENTISTS STUDYING THE ORIGIN OF LIFE TODAY FACE A CHICKEN-AND-EGG PROBLEM: HOW COULD ANY COMPLEX MOLECULE HAVE ARISEN WITHOUT THE AID OF OTHERS?

how could any of these complex molecules have arisen without the aid of the others? Szostak, like many other scientists, has focused on RNA as the primary genetic molecule of early life. RNA is a less stable molecule than DNA, but its instability comes with added versatility, allowing it to perform multiple tasks, including some now performed by proteins. Szostak and others hypothesize that in primordial times, RNA served as a quick and dirty multitasking genetic molecule, able both to store biological instructions and catalyze its own reproduction; in later, more stable times, DNA and proteins could have evolved and taken over these functions with greater precision. But how did an RNA-based biology emerge from the early Earth's chemistry?

Szostak has used a technique called in vitro selection to screen large numbers of molecules for forms that have a particular function. His lab has applied the technique to generate different kinds of RNA molecules, particularly "ribozymes"—RNA molecules that can catalyze chemical reactions the way protein enzymes do—in the hope of creating an RNA molecule that catalyzes its own replication, because an RNA molecule able to catalyze its own replication would be a prime early candidate for life. In the process, they have created diverse molecules that look much like RNA or DNA but don't exist in nature. "All these related molecules aren't used in biology, why is that?" he asks. "Is it because it's actually easier to get to RNA, or a historical accident?"

More recently, Szostak's work has focused on how the genetic material spelled out in RNA or DNA came to be bundled inside cells, which form the basis of all living organisms. The most essential feature of a cell is its membrane: a thin layer of fats that draws a critical boundary between inside and outside, self and the rest of the world. With this physical isolation, Szostak says, potentially useful genetic sequences could begin to gain advantage for themselves. His lab has managed to coax interesting behavior out of simple "protocells" (membrane-bound vesicles): getting them to grow and divide under various conditions.

"We actually can have an environmentally driven 'cell cycle' in which the membrane grows and divides repeatedly," he says. "What's missing from that picture is the genetic material, and that, at the moment, looks like a harder problem." He says there is still a laundry list of problems that must be solved to create a plausible scenario for RNA formation, and several labs around the world are painstakingly working on each one. "I'm fairly optimistic that we'll figure out a way to get the chemistry working in a few years," he says.

What it was like when life began

Research focused on studying molecules in test tubes increasingly points to questions about what the early Earth was like. "We're starting to deduce what kinds of environments you'd have to have to be compatible with the systems that we're building," Szostak says—making it productive to collaborate with planetary scientists to understand these scenarios better. One possibility is that geothermal vents, like the kind found in Yellowstone lakes, could have driven chemical reactions by creating drastic fluctuations of temperature in the water. Certain kinds of chemically active clays could help draw together molecules that would be unlikely to meet if circulating freely in water.

There is also evidence that the amount and type of light was important in the early Earth environment. In 2009, John Sutherland's lab at the University of Manchester made a major breakthrough in origins of life research when it discovered a way that ribonucleotides (building blocks of RNA) could form from a mix of chemicals. But Sasselov points out that one of the steps required to make one kind of ribonucleotide was the addition of ultraviolet light. The spectra of UV light available on the early Earth were different. Stars paradoxically become brighter as they age and deplete their hydrogen cores, so the early Sun was 30 percent fainter, but it was spinning faster, creating a more powerful magnetic field that barraged the Earth's surface with UV radiation that was 200 times stronger than it is today. Sasselov is an expert in analyzing starlight; rather than simply shining a UV bulb on chemicals in these experiments, he wants to recreate the spectra of the early Earth more faithfully in experiments involving prebiotic chemistry.

Research on microbes that live in unusual environments on Earth has shown that life can survive extremes in temperatures, acidity, pressure, dryness, or radiation levels, and thrive on nutrients like iron and hydrogen sulfide. For the purposes of the origins initiative, it's also important to consider that life could have evolved differently than it has on the Earth. Researchers have speculated, for instance, about life forms based on silicon rather than carbon. Another difference might simply be the orientation of biological molecules; many molecules are asymmetrical and can exist in two forms that are mirror images of one another, like right and left hands. But for reasons not entirely understood, life generally prefers to use only one of these mirror images (sugars in biological organisms are always "right-handed" while proteins are always "left-handed").

George Church, Winthrop professor of genetics, has been investigating this question of handedness, or chirality, in his quest to synthesize functioning parts of cells from scratch. Sasselov says the initiative is supporting work in Church's lab to build a mirror-image version of a synthetic cell, to see if it's possible to create functioning biological systems that have a different chirality than those on Earth. This is just one of the *(please turn to page 74)*

(continued from page 33)

ways that synthetic biology—an emerging field that tries to redesign or construct biological parts and systems for useful purposes—can inform origins of life research.

"Is there a single biochemistry underlying any form of life anywhere, or are there alternatives?" Sasselov asks. "And if there are alternatives, do they depend on the initial conditions of the planetary environments, so one planet will have one, another planet will have another?" As scientists start to explore exoplanets, this question will become increasingly practical rather than theoretical.

The evolutionary engine

Life requires more than just getting the right molecules together—it's an engine propelled by evolution. Martin Nowak, professor of mathematics and of biology and a member of the initiative, says that most biologists think of evolution as a process that takes place among *organisms* that reproduce; evolution at the level of *molecules* is unfamiliar. But Nowak looks at the problem from a mathematical perspective; to him, evolution "is a well defined process that can be described as precise mathematical equations." Accordingly, he believes that the same principles governing complex life forms must have been present at the simplest levels—otherwise scenarios for the origins of life depend on a collection of random events.

Nowak argues that evolution is the driver of life, not an added feature. His research on humans and other organisms has focused on cooperation, which he says is a fundamental aspect of evolution. By the same token, he adds, "I believe that cooperation among molecules is essential." What he calls "prelife" was not a primordial soup of chemicals but an active, generative phenomenon in which mutation and selection were already acting on molecules. Only when some of them began reproducing, out-competing the others, did life truly begin. Nowak hopes to carry this line of thinking forward with the initiative, bringing his theoretical perspective to the chemistry research already under way.

For Szostak, the question of when life began isn't necessary to answer right now. "If we really want to understand the origin of life, what we want to understand is the process. It's a whole pathway of steps," he says. "Where do you draw the line between life and not-life? Well, different people might have different places where they like to draw the line. It doesn't really matter—what matters is getting some insight into the overall process."

Understanding that process might make the definition of life a little less mysterious. "We want to understand exactly what it takes," says Sasselov, "not just say, 'Something magic happens.'"

Contributing editor Courtney Humphries is a freelance science writer in Boston.

Jack Szostak, professor of chemistry and chemical biology and professor of genetics. Behind him is an illustration of a protocell, a vesicle containing fragments of RNA.

BACKGROUND IMAGE: COURTESY OF JACK SZOSTAK