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The very first living thing is still alive inside each one of us

A cellular machine so powerful that it gave rise to all of life and created our marble planet can tell us how it all began

Levente Szabo

By **Bob Holmes**

SOME 4 billion years ago, somewhere in the mass of inert minerals and molecules that made up our wet, rocky planet, dead became alive. This was the most important chemical transformation ever to happen on Earth. Not only did it give rise to all the living things that have ever existed, it also altered the chemistry of the oceans, the land and the atmosphere above. If it hadn't happened, there would be no blue marble.

That first chemical step towards life may be a lot closer than we thought. Buried within every cell of every organism on the planet, from bacteria to barnacles to Britons, is a living, working version of the earliest life on Earth – a time machine that allows us to peel away those 4 billion years of history and work out how it all began. "We can stop bullshitting about the origin of life," says Loren Williams, a biochemist at the Georgia Institute of Technology in Atlanta. "We can see it." What he and his colleagues are discovering is turning our view of life's origins on its head.

Until now, most efforts to understand how life began have attacked the problem from the bottom up. Broadly, they start with an experimental soup of primordial molecules and try to either recreate the building blocks of genes or get them to evolve key functions, like self-replication. Despite some promising results, these approaches can at best show a plausible path that life might have followed. They can never reveal what actually happened.

The new approach starts with modern life and works backwards. Formed of a tangle of proteins and a relative of DNA called RNA, ribosomes are molecular machines found inside every living cell. They do just one thing and do it well: they read the genetic code contained in DNA and use it to construct proteins. In essence, they are cellular robots that build the stuff that makes our cells tick.

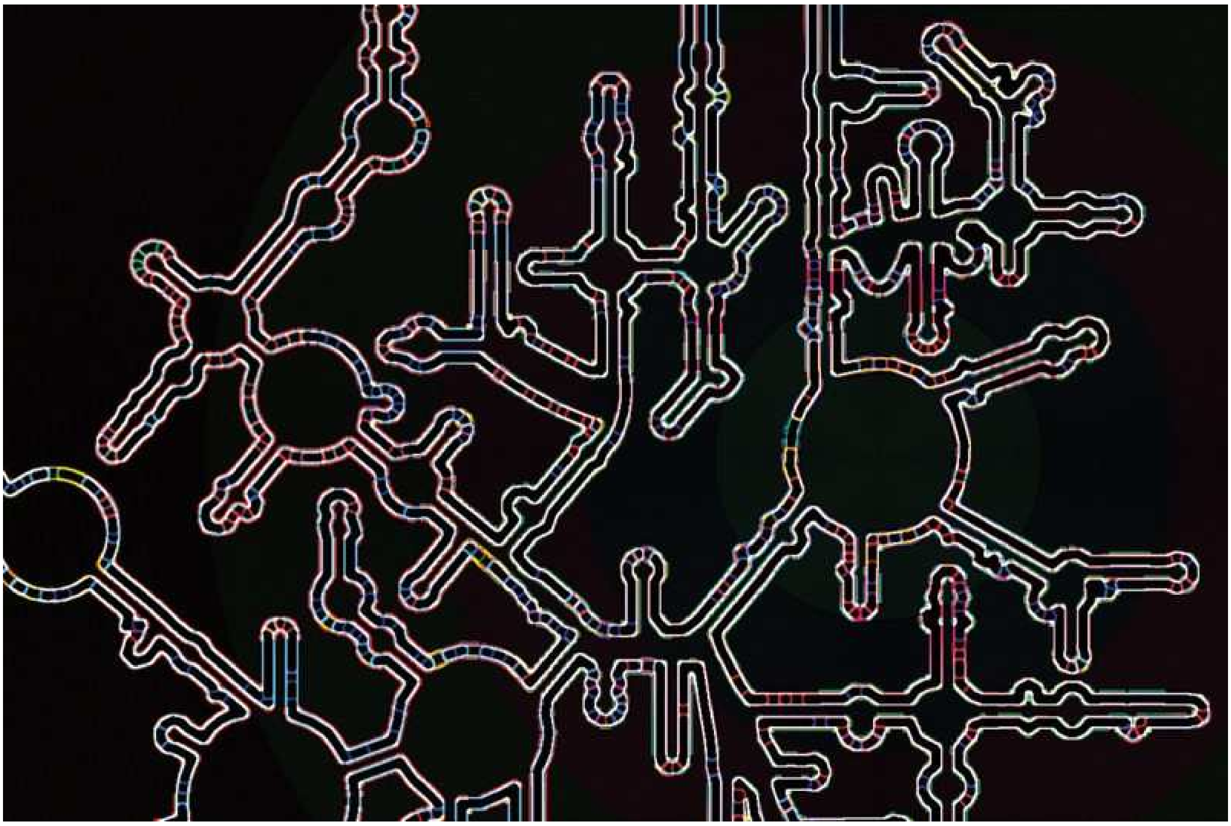
Their task is so crucial to life that it works the same way in all organisms: your ribosomes differ from those of a lowly bacterium only in the ornamentation on their outer surface. That kind of uniformity suggests they date back to when life began. As evolution progressed, new species tacked extra bits of RNA to their ribosomes. The additions left identifiable traces, much as a branch sprouting from a tree leaves a visible mark in the wood. “Even if the branch is gone, you can look at the wood and say something grew out here,” says Williams. Strip these sprouting branches off and you are left with a common core: the part of the ribosome that was functional at the time of the last universal common ancestor (LUCA) from which all known life is descended.

“This system may not have been truly alive, but it was starting on the path to life”

In this way, by comparing the ribosomal RNA of living organisms, Williams and his team have been able to ride the ribosome back to LUCA’s time, and beyond. Then, once they knew how to recognise the “insertion fingerprints” in the ribosome’s modern decoration, the team looked at what RNA would already have been present in LUCA’s ribosome. They found similar traces of insertions, pointing to ancient additions that must have taken place even before LUCA. Every time they found an addition, they snipped it away, pruning branches further and further into the past to reconstruct ever earlier, more primitive versions of the ribosome, all the way back to its beginnings.

The most ancient part of the ribosome, Williams and his colleagues found, is a stretch of RNA that includes the cradle-resembling region that today links amino acids to form protein-like chains. Other teams have used different methods to identify the earliest parts of the ribosome, such as simply peeling away layers, like an onion, to reveal the core. They agree that this cradle is the most ancient bit. “This is probably the best model we have of the history of the ribosome,” says George Fox, an evolutionary biologist at the University of Houston, Texas.

Stripped of all its later refinements, this rudimentary ribosome had none of the precision it would achieve by the time of LUCA. It lacked the regions that read the genetic code, so it couldn’t have produced specific proteins. Instead, it must have linked amino acids, and probably whatever other molecules would fit into its cradle, willy-nilly into short, random chains through a simple chemical reaction that points to a terrestrial origin of life (see "A dry little pond"). As a result, early ribosomes would have made a mishmash of different molecules, says Williams. "We call them molecular sausage-makers." Other researchers have found supporting evidence: under the right conditions, even modern ribosomes can be tricked into linking molecules other than amino acids together.



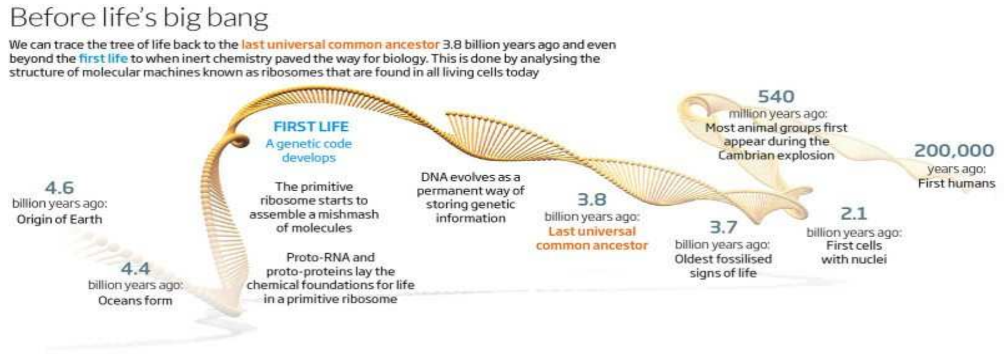
These most ancient parts of the ribosome can tell us about how all of life on Earth was booted up
Loren Williams

On primordial Earth, as random fragments churned out of the sausage-maker, a few would have happened to take a shape that helped them stick to the ribosomal RNA. This would have stabilised them a little. "Those sequences that form more stable structures are going to last longer, so we're going to have those building up," says Nicholas Hud, a biochemist at Georgia Tech who collaborates with Williams. Gradually, these accretions built the ribosome into a larger and larger structure. "That's a form of evolution, and I haven't said anything about genes or information. I would call it chemical evolution," says Hud.

This mess of co-evolving RNA and protein fragments falls well short of what most researchers would call truly alive. The molecules may not even have been recognisably RNA or protein, but a range of similar proto-molecules that self-assembled more easily. But the whole system was starting down a path to life, as chemical evolution winnowed through the randomness and selected the components that clung most to one another.

Although some details remain murky, Williams has no doubt about one feature of this early stage: there was no genetic code and no precise replication of a genome until just before true life evolved. In modern cells, instructions from the central DNA library in the nucleus are shipped out to the ribosomes via messenger RNA. The ribosome binds these mRNA transcripts and reads them three letters at a time, with each triplet coding for one amino acid. The specified amino acid, in turn, is escorted to the ribosome by a transfer RNA, which has a matching sequence to the triplet.

Transfer RNA and mRNA are essential executors of the genetic code. Yet in all the reconstructions of pre-LUCA history, the parts of the ribosome that are responsible for binding them appear relatively late. Even then, Williams conjectures, the initial function of mRNA and tRNA was unlikely to be anything as sophisticated as triplet coding. Instead, they probably arose as little snippets of RNA that happened to help position random amino acids in the right orientation to attach to the growing protein molecule.



Today, the blueprint contained in the genetic code allows the ribosome to make exact copies of the same protein over and over again. But at this point in life's prehistory, the proto-ribosome had no way to read a genome and, thus, no use for one. Instead of exact copies, it would have made a range of new molecules, with the ones that helped stabilise the system sticking around.

Gradually, this process would have selected mRNA and tRNA that were better and more precise at their jobs, eventually leading to molecules that introduced specific amino acids at specific times – the genetic code that today is found in all living things. At last, Darwinian evolution had arrived, and the system finally reached the point at which it can truly be called alive. Most evolutionary biologists agree that RNA would have carried the genetic code first. DNA, a more stable molecule, came later (see "Before life's big bang").

Molecular snuggling

One of the key processes that RNA and proteins had to evolve as they became more refined was folding: modern proteins all contort into intricate three-dimensional shapes without which they do not function. How this arose is a bit of a mystery. Folding is an extremely rare property, and there are more potential protein chains than there are atoms in the universe. So it is inconceivable that evolution could have explored all possible proteins to find the few that fold, says Andrei Lupas of the Max Planck Institute for Developmental Biology in Germany.

Chemical evolution offers a solution to this problem. For a protein to fold well, one part of it has to snuggle tightly against another without intervening water molecules. That is also the feature that would have helped bits of proto-protein bind and stabilise proto-RNA. As these molecules co-evolved, they would have selected protein fragments that were predisposed to fold well, says Lupas.

The ribosome still preserves a record of this process. The proteins associated with the oldest part of the ribosome show little or no complex folding. Moving to successively more recent parts of the ribosome, researchers observed proteins folding first into simple sheets and then into more and more precise and intricate shapes. At the same time, the RNA portions of the ribosome were also developing tighter and more stable folding. "The idea that protein and RNA co-evolved is mapped right there. We can see it," says Williams. His scenario offers a second way out of early life's "chicken and egg" paradox. It also represents a major departure from the dominant "RNA world" hypothesis (see "Cracked: the life and the egg").

Even Williams's critics welcome his ideas. "I think that Loren is championing a radical revision of the way we look at early life," says Niles Lehman at Portland State University in Oregon. "Even if you don't agree with all the details, it does help us rethink models of how life started, and that's a valuable contribution."

Williams says he's just getting started. His team is trying to recreate the stages of ribosomal evolution in the lab, so that they can test what each can do. So far, they have built the earliest proto-ribosomal core and are beginning to put it through its paces.

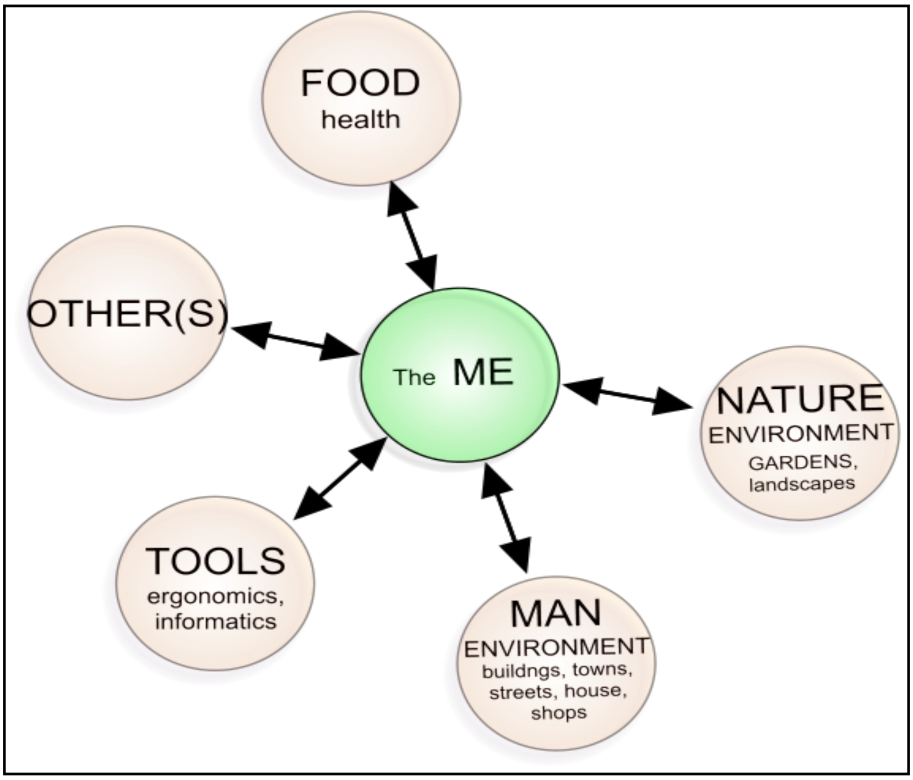
"The ribosome is nature's gift to us," he says. "It's a little time capsule, and we've just opened it up and are starting to look inside."

A dry little pond

Researchers have long debated whether life originated in a warm little pond, as Darwin speculated, or in some other habitat like undersea hydrothermal vents, terrestrial hot springs or even clay sediments.

The ribosome may offer a clue to this puzzle. Its oldest part does a rough job of linking small molecules into longer chains. It achieves this through a dehydration reaction, in which the link is sealed through the release of a water molecule. Because this happens more easily under dry conditions, it suggests the early ribosome didn't ply its trade in the ocean, says Nicholas Hud at the Georgia Institute of Technology.

The most likely spot would be around the fringes of a temporary pond, where conditions would alternate between moist – favouring the mixing of ingredients – and dry, which would favour longer chains.



Cracked: the chicken and the egg

Life as we know it today poses a chicken-and-egg problem: DNA can't replicate without proteins to do the work, but proteins can't exist without DNA to spell out their structure.

That dilemma is a big reason why researchers favour the idea that life began not with DNA but RNA, which can not only store information, but also fold into complex shapes that help it act as a catalyst. An RNA molecule that can catalyse its own replication would neatly solve the chicken-and-egg problem by combining both information and catalysis into one molecule. In this "RNA world" scenario, self-replicating RNA later outsourced its catalytic role to proteins, which are more versatile, and passed on its information-storage job to DNA, which is more stable.

Loren Williams and his colleagues at Georgia Tech offer a different solution. Neither proteins nor nucleic acids came first, they say. Instead, both evolved together from the very beginning.

The whole notion of an RNA world rings false to Williams because it requires life to abandon a working RNA-based system and reinvent itself in DNA and proteins, instead of tinkering to refine existing processes. "I just don't think evolution does those kinds of things," he says. "It would mean evolution is not a tinkerer, it's an engineer." The alternative – that RNA and proteins co-evolved – is more plausible, he says.

Not everyone agrees. "That is the minority report," says Niles Lehman, an evolutionary biochemist at Portland State University in Oregon. "But I think it is a growing minority."

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Before life's big bang

We can trace the tree of life back to the last universal common ancestor 3.8 billion years ago and even beyond the first life to when inert chemistry paved the way for biology. This is done by analysing the structure of molecular machines known as ribosomes that are found in all living cells today