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INSIDE THE RACE TO BUILD LIFE FROM SCRATCH

The effort to leap-frog evolution and build new types of life turns out to be more complex than reading and writing DNA. Illustration by Daniel Zender

Synthetic biologists aim to transform the world with manmade organisms. What will it take to get there?

By Emily Sohn

In 2016, researchers at the J. Craig Venter Institute announced that they had created a brand-new life form: a bacterium with just 473 genes. Known as Syn 3.0, the cell had a genome smaller than that of any life form found in nature. It was celebrated as a landmark achievement, heralding a new era in which scientists would use the genetic code to create designer life forms. Synthetic life, proclaimed Venter, was a reality. “I was involved in building it,” he says.

Not everyone agreed—then, or now. To make Syn 3.0, the JCVI team synthesized replicas of genomes from natural bacteria and placed them into living cells whose genomes had been removed. Then they took away genes, one by one, until the cells could no longer function.

The JCVI's accomplishment was the culmination of "heroic work," says Drew Endy, a synthetic biologist at Stanford University. But it doesn't really count as artificial life.

The point of doing it this way was to systematically determine which genes are essential for life. The result, a sort of minimum viable life form, left many important questions unanswered. Among them: nobody knows what 149 of the 473 essential genes do. What Venter's team did in 2016, Endy and others suggest, was like copying a novel by hand. The process offers important clues into the structure of a narrative, but it's not the same as knowing how to write a completely new book.

In the minds of artificial-life purists, researchers will only be able to claim success when they have produced a fully functioning cell out of chemically synthesized molecules. That cell will need to reproduce, sustain its own metabolism, and adapt to the environment. And scientists will need to understand what all the cell's genes do.

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If your goal is to make novel life forms from scratch, in other words, you need to do more than just reproduce what already exists. That's basically just blind imitation, suggests Kate Adamala, a biochemist at the University of Minnesota, Twin Cities. By copying out all the words, she says, "I could say, 'I wrote *A Hundred Years of Solitude*,' and technically I did write it. But I didn't understand how."

Synthetic biology is a field of mind-blowing possibilities. By tweaking the genomes of microbes, bioengineers might produce virus-proof crops, biodegradable computers to be implanted in our brains, or cells that could add nutrients to Martian soil and make the Red Planet habitable. Those possibilities are so evocative that each new step forward sparks both hopes and concerns about a made-to-order world filled with engineered organisms that could cure diseases and save the environment, or unleash evolution with uncontrollable consequences.

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But the field has an identity problem, with an uncertain finish line muddled by a disparate set of motivations. And those conflicting visions reflect a fundamental problem with assessing the progress of synthetic biology: Even as research begins to bring new inventions into the world, nobody agrees on what the field's ultimate goal should be, which means there's no consensus about how to get there.

Because there are so many different definitions of success, estimates for when we'll have true artificial life range from five years, to 1,000, to never. "There is ambiguity in the

community regarding what is possible," Endy says. The search for artificial life is also hung up on the most basic question of all: what *is* life in the first place?

Their so-called life

For some scientists, synbio will have created artificial life if it can arrange DNA into new combinations on a large scale—adding or subtracting hundreds of genes at a time, rather than the single-gene edits now possible with genetic engineering. These manipulations will push the boundaries of what life can be, creating new forms and functions. That idea of artificial life—novel and functional organisms with gene combinations that have never existed before—is often motivated by practical engineering goals: to build things like cells that can clean up toxic waste, deliver medications, or combat antibiotic resistance.

For others, the ultimate goal is more elemental: to use the tools of synthetic biology to learn about life's origins or figure out what to look for in the search for life on other planets. This definition of artificial life requires that scientists make all the parts and assemble them with a much deeper understanding of how each component works and how they all interact.

Methods differ, too. The Venter team took a top-down approach, dismantling life forms to gain insight into how they work. In order to truly understand how each component works, other scientists are using a bottom-up strategy of putting pieces together in test tubes to spark a working cell. The ambitious Yeast 2.0 project, for instance, aims to synthesize all 16 chromosomes (and 12 million base pairs) of a yeast cell from scratch. So far, researchers have rebuilt six of the 16.

The technically challenging feat of synthesizing an entire yeast genome would offer new insights into evolution, with potential uses in agriculture and ethanol production. But projects like these require scientists to face down some of the deep unanswered questions in biology and genetics.

As shown by the JCVI experiment, for instance, more than 100 of the genes that are clearly necessary for life are enigmas, their function and purpose still unknown. In addition, the way genes are managed is still largely a mystery. A simple metabolic process might require five steps to process a protein necessary for life, and scientists may discover in precise detail which genes and enzymes are involved in each step. But without knowing what triggers, regulates, controls, or inhibits each step of the pathway, they'll never understand how to take control of the process and keep an organism alive. Despite many breakthroughs that have produced precise tools for repairing and editing DNA, scientists still can't explain how genes interact with each other or what makes them turn on or off. "Reading the genetic code is very simple now," says Venter. "Writing all the genetic code—it's a different level."

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To this end, the JCVI team has been sleuthing the biology of essential genes and how they depend on each other. One gene that didn't seem necessary at first turned out to be essential for the function of another gene, says Venter, adding that there is a paper about this co-dependency that is now in the works. "We haven't solved it completely, but we've gone a very long way," he says.

In one sense, though, this progress has backfired. Instead of clarifying what life is and how to make it, the new era of bioengineering has bred confusion about what qualifies as living and what the difference is between real and artificial. "We have not only not answered the previous questions, we have generated a whole set of new questions we never even imagined before," says Robert Dorit, an evolutionary biologist at Smith College in Northampton, Massachusetts. "We're not mopping up the edges here. We're right in the belly of the beast."

Is this real life, or just a forgery?

The idea that people might someday be able to create life from scratch dates back at least to the early 1910s, when French biophysicist Stéphane-Armand Nicolas Leduc supposedly was the first to use the words "synthetic biology." Leduc was inspired by a colleague who had used inorganic materials to synthesize urea, an organic molecule found in the urine of mammals. Today, synthesizing urea is an undergraduate-level chemistry exercise. Back then, it was a dramatic achievement. At the time, it seemed beyond the realm of possibility to create manmade versions of the molecules produced by living cells, says Floyd Romesberg, a chemical biologist at the Scripps Research Institute in La Jolla, California. "Some people believed they required a spark of life, a god, or some kind of vital force. Then a chemist made one," Romesberg says. "That sort of shattered the boundary between inanimate and animate."

Modern synthetic biology was born about 15 years ago with a fusion of ideas and techniques in engineering, molecular biology, biotechnology, and other fields. As the ability to sequence genomes became quicker and cheaper, it started to seem like only a matter of time before scientists would be able to not just read the code but use DNA to reprogram cells as they chose, just as biologists and chemists in prior generations eventually learned to synthesize organic molecules not found in nature.

Some of that reprogramming is already happening in Venter's lab and elsewhere. In 2014, Romesberg and colleagues synthesized two new nucleotide "letters" that could be integrated with the A, T, G, and C bases of DNA. New nucleotides open up the possibility that DNA can code for all-new proteins with novel shapes that allow them to perform new functions.

In 2017, by strategically placing those unnatural letters within an otherwise natural genome, Romesberg's group created new amino acids and new proteins with potential medical applications. A synthetic variation of the protein interleukin-2, for example, is

showing promise as a cancer drug with fewer side effects, says Romesberg, whose startup company Synthorx recently filed an IPO seeking $100 million to make the drug.

In general, semi-synthetic genomes like these that incorporate a couple hundred unnatural nucleotides into a basically natural genome are more feasible than fully synthetic organisms, says Romesberg. Other practical applications could include laundry-detergent enzymes that withstand high heat or manmade replacements for fossil fuels.

In a decade or more, Church predicts, we'll have "mirror life," organisms whose proteins fold in opposite configurations, making them immune to viruses, predators, and enzymes.

But other groups are diving right into the intensive (and potentially futile) challenge of trying to build life from scratch. An open-source collaborative effort called Build-A-Cell aims to construct an entirely new cell capable of reproducing itself, that scientists can understand to the point of explaining exactly what each gene does. That cell will probably be a simple prokaryote like a bacterium at first, but there are no limits to what scientists can attempt. “The stated goal of Build-A-Cell is that we don’t have a goal,” says Adamala, one of six steering-group members. “Everyone who thinks they want to build an artificial cell is welcome.”

Endy describes Build-A-Cell, which includes dozens of research groups around the world, as a “community of love,” not a race or competition. The effort, which incorporates both bottom-up and top-down strategies (including Venter’s group), runs off of Slack groups, Google documents, and a policy of no secrets. Parallel efforts in Europe include Fabricell and BaSyC, or Building a Synthetic Cell. So far, researchers have made progress toward synthesizing individual components of cells, including ribosomes and membranes—early steps toward the group’s end goal of making life from nonliving matter. What’s still missing, Adamala says, is a way to combine all of those sub-systems into a whole.

In a parallel effort, George Church, a geneticist at Harvard and the Massachusetts Institute of Technology, cofounded Genome Project-Write (GP-Write), an international collaboration to synthesize large genomes, including those for plants and humans. Putting new genomes into existing cells and organisms, they think, will revolutionize medicine and agriculture—creating cell lines with immunity to cancer and viruses, or crops that are resistant to pests. At a meeting in May, GP-Write collaborators discussed ongoing projects such as an effort to create these resilient cells by recoding stretches of DNA that viruses rely on to replicate in cells.

By replacing about one percent of the genome in a human cell line, Church and colleague Jef Boeke of NYU Langone Health think they can make a platform for producing vaccines and medications that would be resistant to contamination by viruses and prions, those mysterious infectious proteins. They also want to engineer pigs to

make them immune to diseases and grow virus-resistant organs that are ultra-safe for transplant into humans. Engineered pig transplant trials in primates have already begun, but Church estimates that virus-resistant pig cells are three to 10 years away. Already, he and colleagues have constructed a strain of *E. coli*, making 321 changes in the bacteria that help it resist viruses. Still, it's a big leap from there to the thousands of changes that would be required to virus-proof a human cell.

Down the line, Church has far grander ideas. In a decade or more, he predicts, we'll have "mirror life," organisms whose proteins fold in opposite configurations, making them immune to viruses, predators, and enzymes, which would be unable to recognize them. Applications might eventually include biodegradation-resistant cotton, silk, wood, and ropes, which would render ineffective the digestive enzymes of fungi, worms, insects, and bacteria. Perhaps someday, we'll have mirror-image plant or animal cells which would be completely resistant to all known pathogens.

"It's kind of funny. We're in the business of supposedly making life, and we don't know what life is."

For Church and others like him, these marvels of bioengineering are the real payoff of synthetic biology and the quest for artificial life. And once the benefits of synthetic life become apparent, Church suspects that people will stop worrying that scientists are "playing God," a common criticism. "Most of the things that people were worried about at one point or another—like railroads and refrigeration and in-vitro fertilization—go through a very brief period of time during which they're unacceptable, usually when they are technically infeasible. It's easy to be opposed to something that doesn't work," Church says. "The instant that it works and is shown to be safe and effective, suddenly it is hard to resist."

But even the most marvelous creations would leave open questions, says Adamala. By working together, she predicts, scientists will soon figure out how to synthesize self-replicating, evolving biochemical systems that are capable of maintaining their own metabolisms. But the community is unlikely to agree any time soon on whether that qualifies as life—or even what it means to be alive. If a cell has no metabolism but can replicate itself, does it make the grade? If it adapts to the environment but cannot reproduce, is it life, or something else? "We have these discussions all the time," she says. "It's kind of funny. We're in the business of supposedly making life, and we don't know what life is."

On top of the profound issues, there are also practical ones, such as the high price tag. Synthesizing DNA still costs about a dollar per base pair, Venter says. That adds up to more than half a million dollars just for the 531,560 nucleotide pairs in his team's 473-gene bacterium. "The cost of synthesis simply has to come down another order of magnitude for people to be able to do the experiments," Venter says. "Instead of designing one, building it, testing it and trying to work out what went wrong, we need to be able to multiplex it."

Declaring success might eventually depend on toning down expectations, Venter adds. Just like bakers use off-the-shelf ingredients like flour and sugar when they bake "from

scratch," some synthetic biologists will probably always rely on existing cell parts and biological molecules, like membranes and nucleotides, as they build new cells. Even those going for the next level will use existing molecules—by, say, chemically modifying existing amino acids. "All of this stuff has a certain level of artificiality to it," Venter says. "Everything is cheating to some extent."

For now, suggests Dorit, the pursuit of artificial life—to even begin to imagine that it's possible—requires a healthy dose of arrogance, along with an equal dose of modesty. "There are lots and lots of things we still don't understand about how organisms manage survival," he says. This quest has brought essential mysteries into sharp focus: How does a string of DNA coordinate the reproduction, evolution, and death of a living cell? And what are the limits of biology for understanding the meaning of it all? Answers are unlikely to emerge any time soon. And in a way, Dorit says, he's glad. It would be a little disappointing if creating artificial life turned out to be easy.

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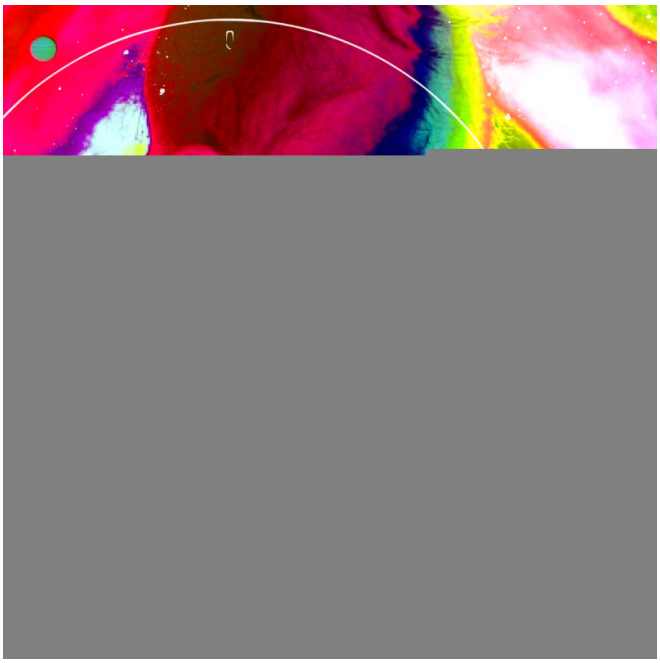
By **Emily Sohn** on Dec 13, 2018

Journalist covering science, health, environment, adventure and more. @tidepoolsinc



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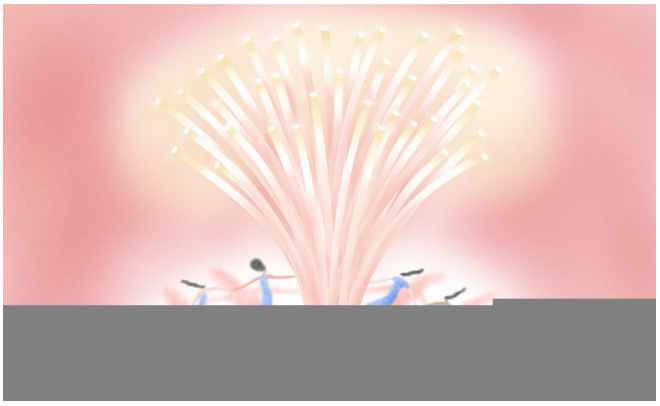

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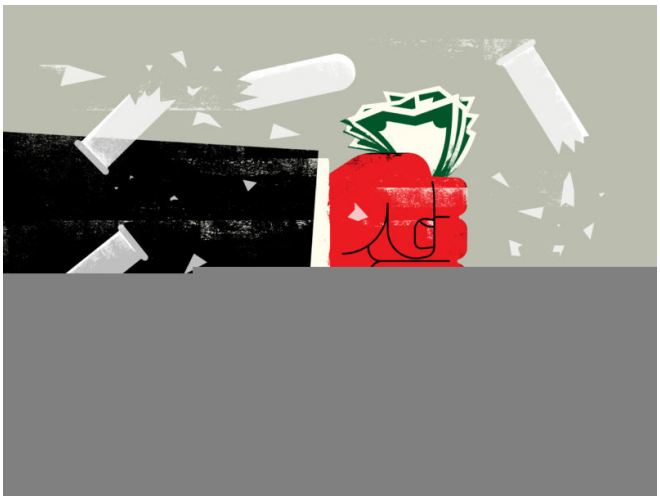

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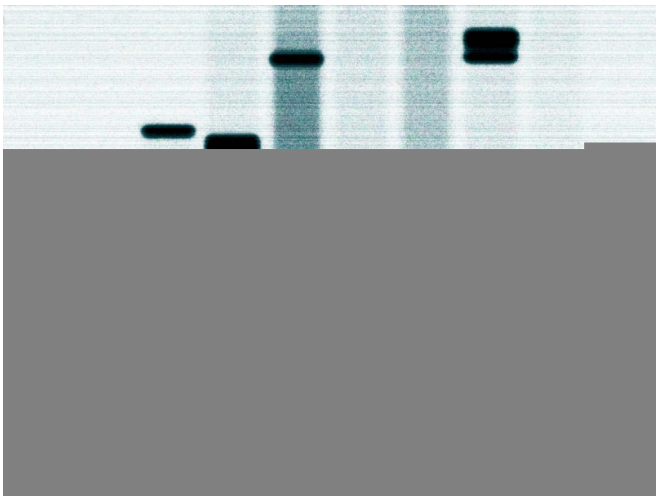

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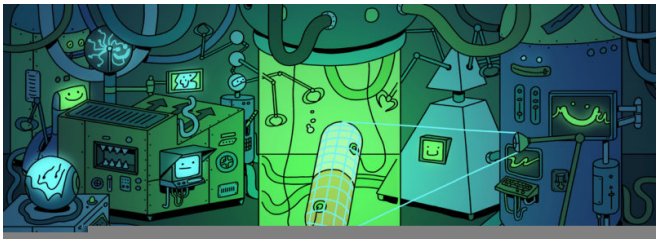

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