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The promise of synthetic cells

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NIST researcher Elizabeth Strychalski's research group is helping to establish the measurements and standards needed for progress in engineering biology, also known as synthetic biology. Credit: J. Stoughton/NIST

For over a decade, scientists have made extraordinary progress on the long-held dream of fabricating an entire cell from nonliving molecules and materials.

Such synthetic (or "engineered") cells would behave similarly to the ones in our bodies, though they would also have built-in safeguards that ensure safety and ethics. By studying them, we could transform our understanding of the rules of life. They could also be used to manipulate living organisms and achieve astounding breakthroughs in medicine and science.

In 2010, the J. Craig Venter Institute announced it had created the first "self-replicating, synthetic bacterial cell" containing a genome synthesized outside the cell and then transplanted into it. It was then able to divide and reproduce according to instructions from its new DNA code.

Since then, researchers have only grown more ambitious, seeking to synthesize other cellular components and build a whole cell from scratch.

"We're closer than we've ever been before," said National Institute of Standards and Technology physicist Elizabeth A. Strychalski. The quest to create a synthetic cell from scratch "is a capability that is, if not on our doorstep, maybe, you know, at our mailbox."

Much of the recent progress rests on technological advances that have made it easier and cheaper to synthesize long strands of DNA in laboratories.

Scientists worldwide have also figured out ingenious methods for producing basic versions of membranes, mitochondria and other cellular components. And using new techniques that allow them to manipulate tiny amounts of fluid, they are beginning to coax these synthesized cell parts into interacting and communicating.

At NIST, Strychalski's research group is helping to establish the measurements and standards foundational to further progress in engineering biology (also called synthetic biology).

NIST is also collaborating with the J. Craig Venter Institute on the "minimal cell," a stripped-down synthetic cell. Instead of multiple synthetic parts and components, only its genome is synthesized. Strychalski said the minimal cell will help researchers achieve "the holy grail of understanding what every single gene in the human cell does."

We spoke with her about her work and a recent paper she co-authored in *ACS Synthetic Biology* that explores the state of research in her field.

Let's start with the most fundamental question. How will we know when we've built a synthetic cell from scratch?

It will likely have some important properties, like the ability to replicate, a metabolism, and some kind of internal organization or compartmentalization. Some properties emerge when you begin to assemble the components of a cell, such as the ability to respond to some kind of stimuli in your surroundings and the ability to move.

Now, will we require that our synthetic cell have all or just some of these properties? That's still an open question and will depend on its application. But certainly, these are all attributes of a synthetic cell built from scratch that we would eventually want to incorporate.

How could such synthetic cells be used to treat disease?

So much of what makes people sick can be traced back to cells not working properly.

So, let's say cells are taken as a capsule, and we've engineered them to sense when there's a certain disease state. It could be that some harmful bacteria is poisoning you, or your body is missing the ability to make a certain protein.

The synthetic cells could fix this by maybe killing those harmful bacteria or helping your body make all the molecules it's supposed to make so that you don't have that disease.

You write in your journal article about the role synthetic cells could play in space exploration.

One of the exciting things about building synthetic cells is that we get to think about making synthetic cells or cell-like systems that could be much better adapted to a space environment, whether that's in a spaceship or on the surface of another planet.

There's also so much opportunity to use cells as factories for making products, medicine, building materials, food or whatever you might need in these resource-limited settings. And what's nice about synthetic cells is you don't have to leave the earth's surface with very much of them to grow them in space, where you might want a whole lot of them.

Could we synthesize designer cells or cell-like systems that explore biological diversity beyond what currently exists in nature?

You know, we study cells as they evolved on Earth. We don't know how much of what we see now was because it had to happen that way and couldn't have happened any other way.

How can we go into the laboratory, roll back the clock, and look at other possibilities?

For example, the nucleic acids in DNA are made from four bases — adenine (A), thymine (T), guanine (G) and cytosine (C). It's possible to make additional bases in the laboratory that we don't find in nature that seem to work just as well.

How can we ensure ethics and safety?

It's essential that everyone has a say in how we develop these technologies, how we use them and who has access to them.

We now have the opportunity to build in safety instead of looking back and trying to put the safety back in. So, I'm a big fan of starting with a safety mindset.

For example, how do we ensure that synthetic cells cannot grow outside of where we want them to be? Can we build "kill switches" inside synthetic cells? When they exit your body, they might sense the temperature difference, triggering a stress response in the cells that causes them to die.

Another thing we need is robust screening measures to ensure that people who are ordering synthetic snippets of DNA code or synthetic cells aren't ordering ones that could be harmful.

Tell us about NIST's role in all of this.

I like to think of building synthetic cells from the perspective of control. Researchers are trying to control the function of these systems and do it safely.

To have this kind of control, we need to measure what the system is doing quantitatively with confidence. How else are we going to know it's achieved its intended function?

And we're thinking about ways that these synthetic cells can do the measuring. It's about building biomolecular circuits to make measurements and even perform computations inside living systems.

What motivates you in your research?

We are in the biotechnological revolution right now. We have real problems that we need to face as a society, and we need biotechnologies to help us solve those problems.

It's also about discovery. Once we understand how to build synthetic cells from scratch, we can better understand what it means to be human.

More information: Lynn J. Rothschild et al, Building Synthetic Cells—From the Technology Infrastructure to Cellular Entities, *ACS Synthetic Biology* (2024). DOI: 10.1021/acssynbio.3c00724

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