B·DEBATE International Center for Scientific Debate BARCELONA

upf. Universitat Pompeu Fabra Barcelona — Department of Experimental and Health Sciences

Synopsis

# SYNTHETIC BIOLOGY

## FROM STANDARD BIOLOGICAL PARTS TO ARTIFICIAL LIFE

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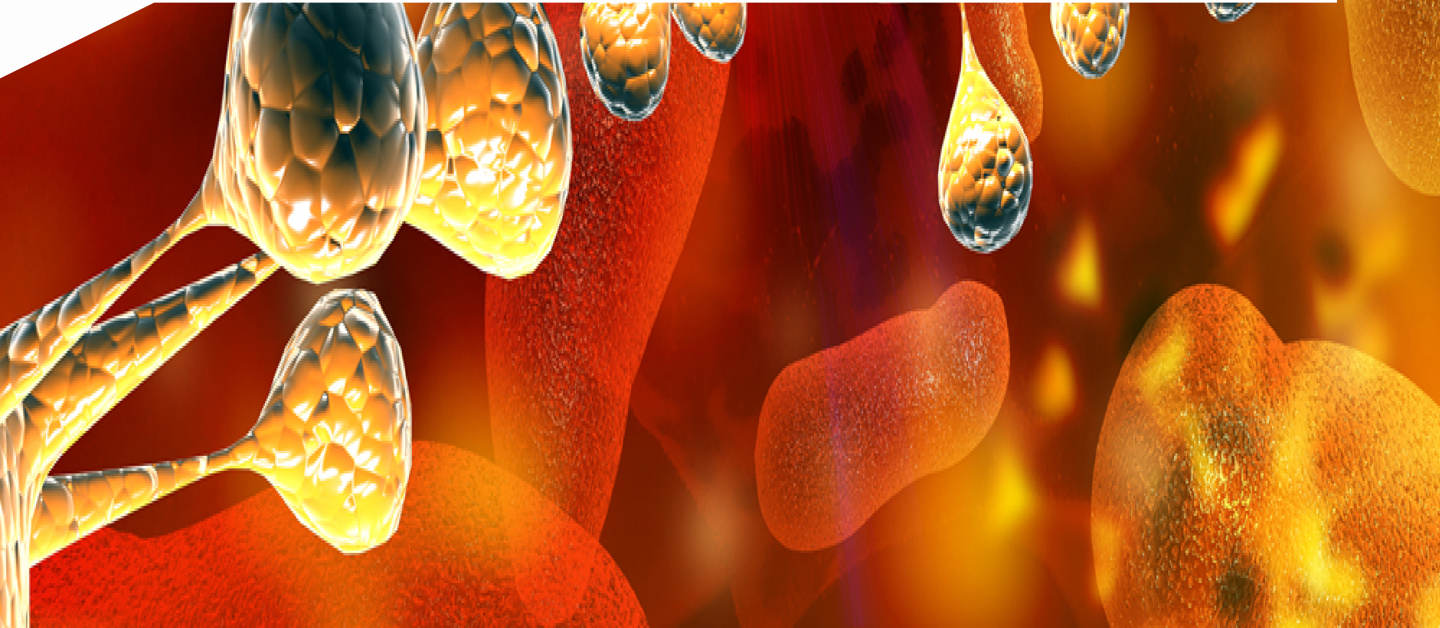

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UNA INICIATIVA DE: biocat Obra Social "la Caixa"

# SYNTHETIC BIOLOGY : BUILDING LIFE TO IMPROVE (AND UNDERSTAND) IT

**Synthetic biology is the field of science that deals with designing (or redesigning) living organisms in order to understand how they work and attempt to adapt them. The goal: to create what nature hasn't yet on its own.**

**To "improve" an existing living organism, scientists use a growing arsenal of techniques to modify the genome. These techniques, among other things, allow modified bacteria to manufacture malaria drugs, break down certain types of plastic or rearm the lymphocytes in our defense system to detect and fight certain types of tumors.**

**Some of the top international experts discussed the latest advances in this field at B·Debate, an initiative of Biocat and the "la Caixa" Foundation to promote scientific debate.**

## CONCLUSIONS:

- ✓ Synthetic biology seeks to design or redesign living organisms to carry out functions beyond those assigned to them by nature. It is a developing field in which advances in disciplines like biology, engineering, physics and mathematics interact.
- ✓ There are two approaches to synthetic biology: top-down, copying and modifying existing genomes, or bottom-up, designing artificial life from scratch.
- ✓ Modifying the genome of microorganisms has already allowed scientist to produce insulin in bacteria and use yeasts to synthesize malaria drugs. Some of the applications currently being developed include modifying cells in the immune system to attack tumors and using microorganisms to produce new antibiotics and recycle plastics.
- ✓ Synthetic biology allows us to expand the genetic code, creating proteins that don't exist naturally. This expansion will allow us to discover new functions and develop safer modified organisms that are unable to live outside the laboratory.

# WHAT IS SYNTHETIC BIOLOGY

***What I cannot create,***

***I do not understand.***

Richard Feynman, physicist.

"The goal of synthetic biology is to design and redesign living organisms with precision," sums up Jordi García-Ojalvo, director of the Dynamical Systems Biology Laboratory at Pompeu Fabra University and scientific leader of this B·Debate. "It's genetic engineering 2.0 because it isn't just putting parts together: it uses the tools of physics, engineering and mathematics taking into account how they all interact. This way, it **seeks to reprogram organisms to do things they don't naturally do, which could be beneficial to humans."**

For Ricard Solé, director of the Complex Systems Laboratory at Pompeu Fabra University, "synthetic biology is still in its adolescence, but is picking up speed. We can now engineer life."

However synthetic biology isn't free of controversy among scientists, especially engineers and biologists In the words of Wendell Lim, professor of Cellular and Molecular Pharmacology at the University of California, "**for biologists, genetic modifications are a way to understand nature**, not an end in and of themselves, and they wonder why engineers don't appreciate nature's complex, precise designs. Engineers are also perplexed: why don't biologists appreciate it when we replace such a complex system with a much simpler, more predictable alternative?".

In general, engineers look for "standards", parts that carry out a function and can do so when introduced into any organism. Biologists disagree, as they believe life is too complex to be simplified and that the genetic background of any organism will always affect how the parts behave. This is the opinion of Manel Porcar, director of the Biotechnology and Synthetic Biology laboratory at the University of Valencia: "In biology, the number of components is relatively small, but the number of interactions is huge. Just he opposite of what happens in traditional engineering," he explains.

There are two other broad traits that separate biology from pure engineering. One is noise: cells change their behavior over time and no cell is ever exactly the same as its neighbor. This makes it complicated to find the precision and clarity engineers seek. Another is evolution. Living beings are the product of millions of years of trial and error. For García-Ojalvo, synthetic biology mustn't lose sight of this, it has to "use what we know to improve design and remember that any organism we design will also tend towards evolution."

# TOWARDS THE CREATION OF ARTIFICIAL LIFE

In 2010, a study conducted at the J. Craig Venter Institute made its way around the world: they had synthesized a living being for the first time. According to J. Craig Venter, it was "the first cell whose mother was a computer." However, for Jane Calvert, reader in Science, Technology and Innovation Studies at the University of Edinburgh, "what Venter proposed was copying, not designing an organism." They copied the DNA of the *Mycoplasma mycoides* bacteria letter by letter (approximately one million) and then put it into another, very similar one.

## FIRST ARTIFICIAL LIFE?

After the study conducted at the J. Craig Venter Institute that synthesized a living being in 2010, the media heralded the discovery as the first time artificial life had been created. But the idea wasn't new: according to Juli Peretó, researcher at the Evolutionary Biology Institute at the University of Valencia, the first one goes back to 1899, when Jacques Loeb proposed what is called artificial parthenogenesis.

A new project proposes going further, synthesizing a more complex genome: that of a yeast (used to make bread or even beer). Plus, scientists are also modifying the genome as they manufacture it: adding, for example, sequences to cut and paste DNA when the estradiol hormone is present, which would allow them to study new combinations. "It isn't exactly a yeast," explains Calvert, "It will be a *yeast-like* organism."

Both of these projects require a mold: an organism to house the DNA. Plus, particularly the second, they have a top-down approach: they take the full information and *play* with it to understand and take advantage. But there is another possible approach, making life forms without any pattern: from the bottom up. There is no clear consensus about what constitutes life. Not even "minimum life". For Steen Rasmussen, director of the Center for Fundamental Living Technology in Denmark, this implies a system that is able to transform resources from its environment in order to form, grow and divide, and that can evolve. In his laboratory, they have "created" some of these conditions. His idea consists in synthetic DNA molecules and a series of light-sensitive compounds "stuck" to oil droplets. When they are exposed to light, these "protocells" can interact with their environment and, through rudimentary metabolism, produce small products that join onto the droplets to make them grow. Later, they divide as they get bigger, creating similar "daughter cells".

"It's a conceptual approximation," says García-Ojalvo, "in which the cell acts not as a container, but as a substrate for life. Although it doesn't have a direct application, studies like these are very interesting, among other reasons, because we don't know what life could be like in other places."

# TOWARDS A WORLD OF APPLICATIONS

Although the line between synthetic biology and traditional genetic engineering is somewhat blurred, modifying the genome of microorganisms already has several different applications. For example, in 1978 scientists created a bacteria that produces insulin and the hormone taken by diabetics today comes from this genetically modified bacteria. More recently, in 2013, the use of synthetic artemisinin, a malaria drug produced very effectively by modified yeasts, gained approval. In the future, scientists expect to see bacterial systems that, once introduced into our bodies, **can take care of smart delivery of drugs like antibiotics and insulin** right when we need them. "But they are highly complex systems that must have maximum security. We're still far from that," says García-Ojalvo. Other applications seem to be closer, like **immunotherapy for cancer, designing new antibiotics or recycling plastics. Even the possibility of creating safer modified organisms** that use synthetic amino acids not found in nature.

## IMMUNOTHERAPY, GREAT PROMISE TO FIGHT CANCER

Immunotherapy is one of the great promises to fight cancer. In fact, in 2013 the journal *Science* named it the scientific event of the year.

One part of immunotherapy is based on CAR therapy and consists in modifying the patient's own lymphocytes to fiercely attack tumor cells, especially those of blood tumors. In the laboratory, they are given a receptor that recognizes, for example, a specific type of lymphocyte (some of which are dividing out of control), adding a system so that they are attacked and destroyed. Although some results are being seen, it isn't exempt from problems: so far it only works on certain tumors and can have side effects when it also attacks healthy cells, or in some cases provoke an excessive response that is difficult to stop.

Wendell Lim's laboratory is working to improve these weaknesses. For example, adding another receptor that would act as a switch: if a drug is administered that binds to it, the response is activated; when the drug is no longer administered, it turns off. Another example: adding new, more specific layers of receptors for each tumor that don't attack healthy cells.

## SEARCHING FOR NEW ANTIBIOTICS

The growing, improper, use of antibiotics is leading to an increase in the microorganisms that are resistant to them, and this is a growing threat. In the laboratory of Sven Panke, professor in the Department of Biosystems Science and Engineering at ETH Zurich, they use two promising antibiotics generated naturally by bacteria as a start. His team is testing modifications like the incorporation of artificial amino acids to give rise to new functions.

## RECYCLING PLASTICS

"Many industrial designs are made to last, so they won't degrade," explains Víctor de Lorenzo, professor in the Systems Biology Program at the Spanish National Center for Biotechnology in Madrid. "Bacteria haven't yet had time to figure out how to do it."

In his laboratory, they work with a specific type of bacteria, called *Pseudomonas putida,* that can break down certain types of plastic like that used in water bottles. But they aren't very efficient and need to be improved. To do so, they try to organize them so they will join forces and work in teams: "It's what we call bacterial origami," he says. To do so, they get rid of part of their genome and add the information needed to produce new adhesins, molecular "stickers" at the disposal of researchers. They are even working to make the bacteria not only break down the plastic but also turn it into a new biodegradable compound that can be used.

## UNKNOWN FUNCTIONS IN MICROORGANISMS

For Farren Isaacs, professor at Yale University, "**we are moving from the era of reading genomes to that of writing them.**" Even that of adding a new language. This scientist uses a technique known as MAGE, which allows him to introduce numerous changes into a genome at once, and then amplify them greatly, creating a huge list of new combinations. It is an "evolution machine" that speeds up natural processes so that in just a few days, for example, they made a bacteria produce huge amounts of lycopene, the red pigment found in tomatoes.

But it also allows them to introduce the necessary changes to make certain DNA sequences change their meaning. There are hundreds of possible amino acids, but nature only uses roughly 20 for life. Isaacs' team has used that change in meaning to incorporate new amino acids never before used in a living being. They have literally expanded the genetic code. This could be used to create new functions, like microorganisms that produce new biopolymers, but also to improve safety: new organisms that die outside the laboratory, as nature doesn't provide them with the amino acids they require.