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SYNTHETIC BIOLOGY

ENGINEERING LIFE FOR THE MEDICINE OF THE FUTURE

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SYNTHETIC BIOLOGY: ENGINEERING LIFE FOR THE MEDICINE OF THE FUTURE

If we have to choose a definition of synthetic biology, it could be this: the rational engineering of biological systems to develop applications. This concept encompasses important, radical breakthroughs like modifying the human genome, gene therapies and modern immunotherapy to fight cancer. It also includes modifying bacteria and microorganisms so they take on new properties and can be used in medicine, for recycling or to fight the climate crisis.

This whole world of possibilities means synthetic biology is already considered a basic component, along with artificial intelligence, of the fourth industrial revolution. But this topic also generates lots of debate: both on how to promote and develop it, and on the ethical conflicts that come along with it.

To discuss the latest advances and debates regarding synthetic biology, international experts met for a session of B·Debate, an initiative of Biocat and the "la Caixa" Foundation to promote scientific debate, with the Center for Genomic Regulation (CRG).

CONCLUSIONS

- Synthetic biology offers a world of possibilities that make it a key part of the new industrial revolution.
- The genome is now a treatment goal. This is in large part due to CRISPR, the new gene-editing technique, although it still needs deeper understanding and improvements to expand its applications.
- A significant portion of synthetic biology focuses on modifying bacteria, which can then be applied in fields ranging from vaccines and cancer therapies to recycling plastic and combating the climate crisis.
- The move from basic research to *real-life* applications is still up for debate, as is the wide range of ethical issues that some of these tools bring up.

1. SYNTHETIC BIOLOGY IN MEDICINE: GENETICS AS A TARGET

"**The genome is now a treatment goal**," summed up Prashant Mali, a professor at the University of California, San Diego. This is in large part due to CRISPR, the new gene-editing technique that allows scientists to modify DNA (or RNA), which is much easier and more versatile than previous techniques. This makes it a great tool for lab research, but also for designing therapies.

CRISPR is one of the great hopes for treating genetic diseases caused by only one gene (monogenic disorders) or even for others with many genes involved, but there are still many limitations that must be taken into account. For example, sometimes the tool cuts the DNA in the wrong place (off-target effects) and the cell's own repair mechanisms aren't totally under control yet, so there can be unintended mutations in the place of action (on-target effects). It can even trigger immune reactions, when the organism considers it a foreign body. Mali's group is searching for safer alternatives, for example with enzymes that cut RNA, which conveys information from DNA, that wouldn't cause the body to reject them.

Another complication with CRISPR is **getting the tool to enough of the cells that should be modified**. This line is the focus of the group led by Matthew Porteus, professor of Pediatrics at Stanford. They have developed a method that combines two elements: on one hand, they put in the protein that makes the cut with the RNA to guide it as ribonucleoproteins. On the other, using a specific type of virus, they transport the DNA molds to encourage correct repair. The method seems more efficient and to have fewer problems with rejection. It has already been tested in diseases like sickle-cell anemia and it seems to be advancing through incipient clinical trials.

Porteus is hopeful about the possibilities this tool has to offer, but is also concerned about some of the issues that come along with it. Both ethical, in some cases, and in terms of safety and equality. **If applied to embryos, he advocates for "a functional moratorium" while research advances, and that it be used to achieve "healthier children, not designer children."** Regarding therapies in adults, he believes "it would be a success even if we only cure one patient with sickle-cell anemia, but **how can we have a global impact if many places don't have specialized hospitals to develop it?"**

Another illness researchers hope to begin clinical trials on soon is **hemolytic anemia due to pyruvate kinase deficiency**, a disorder caused by a mutation of just one gene that can be very serious as it causes mass destruction of red blood cells. The group led by José Carlos Segovia, division head at Centro de Investigaciones Energéticas, Medioambientales y Tecnológicas en Madrid (CIEMAT), submitted a trial proposal to the US FDA and the Spanish Agency of Medicines and Medical Products and expects to begin the trial in the coming months. It is based on inserting the right gene using a special type of virus, but they are also working on doing so with the technique developed by Porteus' team, combining ribonucleoproteins and viruses that don't become part of the genome.

Beyond gene therapy as such, which corrects DNA permanently, there are new forms of cancer immunotherapy, called **CAR-T**. They consist in extracting defense cells from the patient, modifying them in the lab and putting them back into the patient's blood to attack the tumor. The modification tends to be a work of 'engineering' to add an 'artificial' receptor that is particularly powerful and specific, generally targeting a specific type of cells in the immune system. This is why it is being used already for certain types of leukemia and lymphoma, and **there are more than 200 clinical trials currently underway**. **One of them is being done at Hospital Clinic Barcelona** and "involves over 150 professionals," explains Manel Juan, head of the Immunology section at the Hospital and one of the trial leaders.

Another way to fight cancer is being studied in the group led by Luis Ángel Fernández, principal investigator at the Spanish National Center for Biotechnology in Madrid (CNB-CSIC). It consists in **modifying bacteria so they specifically target tumors** and can fight them. They are doing this with a harmless variety of *Escherichia coli* with information added so they produce *adhesins*, specific proteins that take them to the tumor. Information has even been added so they will produce injectosomes, filaments that act like molecular syringes and are normally found in dangerous varieties. In this case, the aim is to inject therapeutic molecules into tumor cells.

Bacteria are really one of the most attractive fields of synthetic biology, and with the most potential, with applications in medicine and beyond.

2. BACTERIA AS A KEY ELEMENT IN SYNTHETIC BIOLOGY

"**Bacteria are the perfect organisms for synthetic biology, mainly due to their simplicity**," explained Jordi García Ojalvo, a professor at Pompeu Fabra University in Barcelona. It is important to remember that we already co-exist with them, and they make up a diverse ecosystem inside our bodies, which is why it is "important to understand how they live together, communicate and interact." For example, "we know a lot about how antibiotics work," Ojalvo said, "but, generally, on isolated species, not a community, and **a bacteria's response can be different depending on what other types it lives with**." Ojalvo's group is working on being able to predict this type of communications in 'synthetic' bacteria.

'Engineered' bacteria can also be used to fight other bacteria. This is the work of the group led by María Lluch-Senar at CRG in Barcelona, who have used *Mycoplasma pneumoniae* bacteria to create a harmless 'chassis' to build therapeutic elements onto, which attack dangerous, resistant bacteria like those that cause ventilator-associated pneumonia. Or they can also be used to develop **vaccines**, designing 'à la carte' bacteria that optimize immune response without the risk of infection, like the group led by Carole Lartigue, at the French National Institute for Agricultural Research.

But the applications go beyond medicine, strictly speaking.

"**Our planet is sick, mainly as a result of human actions**," reminded Víctor de Lorenzo, research professor at the Spanish National Research Council in Madrid (CSIC). This is happening in part because biological metabolism isn't the same as industrial metabolism: the former is more or less circular, while the latter generates a huge amount of non-recyclable waste. "Some of the measures to combat this are reactive (decreasing production) but can we be proactive?", he asked. Some paths lie in synthetic biology. **His group is working to reprogram *Pseudomonas putida* bacteria, which can be very interesting for transforming industrial plastics into biodegradable products.**

"**The most pessimistic climate-change models have been confirmed**," lamented Ricard Solé, ICREA professor at Pompeu Fabra University in Barcelona. To fight this, his group has introduced **the concept of 'terraformation'**, referring not to recreating the

environment of Earth on other planets, but on the Earth itself, which is now under threat. Their study and action proposal consist in using synthetic biology to revert situations caused, for example, in particularly arid zones. This approach isn't without problems and risks, but "every congress has to have a controversial speaker," added Solé. "Right now, the industry isn't very interested. In general, they are more concerned with making money than saving the planet. But we think it could work," he concluded.

PANEL DISCUSSION 1: TRANSLATIONAL DIRECTIONS OF SYNTHETIC BIOLOGY

"**There is a point when technology goes from being *interesting* to *investment-worthy*, and I think synthetic biology is at that point**," said Lluis Pareras, founder of Invivo Capital in Barcelona. Moving from research to investment and real-life application of advances was the topic of the first of two panel discussions at this B·Debate session. Pareras recognized that something is hovering around in the world of synthetic biology, because "it's hard to understand the exact definition of synthetic biology: is it really engineering or is it an evolution of traditional techniques? In any case, it's here and it's in clinical practice, which as an investor makes me almost paranoid."

A clear evolution of these techniques is CRISPR, the genetic cut-and-paste technology the intellectual property rights to which have not yet been resolved, with open legal disputes still pending resolution. "**The problem with patents is painful for all parties and, as an investor, makes me nervous**," recognized Sylvain Sachot, director of investment at Asabys Partners.

Pareras offered **a few tips for developing a product of this nature**: be clear on the intellectual property rights, take into account that science tends to advance faster than regulatory issues, send a clear message to society, surround yourself with a good team, focus on areas with a real clinical need and base your company on products with solid data from research on animals and in pre-clinical models.

In the debate, the issue came up of **how to improve the relationship between academia (more *classical* research) and companies**, which are more focused on product development and the market. For John L. Collins, Operations and Commercial director

at SynbiCITE in London, specific communication regarding resources and solutions should be encouraged, instead of just being satisfied with the *desire* to collaborate. According to Pareras, academia is a great place to think, but not so much to *do.* And "if you're genuine and have good ideas, companies will listen to you," assured Laia Crespo, head of Europe at Sanofi Ventures.

How, then, to bring these *useful applications* from academia to the market? "It's probably a good idea to create a start-up," said Pareras, "although each experience can have and require a different path." Crespo agreed, saying the path "depends on the technology. The first thing is to speak with the technology transfer office at your institution." According to Collins, you shouldn't go to the United States: "80% of start-ups fail there, while almost the reverse is true in Europe. **First look at Europe. We're doing things smarter here**," he said, provocatively. And within Europe, "**Barcelona has the potential to be a great place to give a project that push**."

PANEL DISCUSSION 2: ETHICS, PHILOSOPHY AND SCIENTIFIC RESPONSIBILITY

In the 1997 film **Gattaca**, parents can choose their unborn child's genetic characteristics, giving rise to potentially 'superior' individuals, with all the ethical debates that come with that. Are we there yet?

"It's no longer just a film, **these things are already happening in some parts of the world**," said Lluís Montoliu, a researcher at the Spanish National Center for Biotechnology in Madrid, and one of the foremost CRISPR experts in Spain. Montoliu spoke of two genome-edited girls born in China and the announcement around the same time that something similar could happen in Russia (which led to widespread criticism from various associations). He then made it clear that he was just being provocative, because "**we aren't really there yet. Just for eye color we would have to take multiple genes into account**." We aren't ready for that sort of 'designs' yet, but what seems clear is that "it's hard to be both emotional and pragmatic here," said Marc Güell, a researcher at Pompeu Fabra University and one of the leaders of this B·Debate session.

"**The main question we will have to answer is what do we want?**" said Sonja Erikainen, researcher at the Centre for Health, Technologies and Social Practice at the University

of Leeds. Because "**many times it's hard to distinguish between a treatment and an improvement. Preventing a disease, for example: is that an improvement or a treatment**?" Montoliu believes this issue is so complicated that we will probably have to study it on a case-by-case basis, but he is sure that "when we talk about improvements, it's generally a euphemism for eugenics." This doesn't mean that times aren't changing: the lines are blurring in some cases and one day we will surely have to consider some of these possibilities.

Montoliu warned of several **dangers that haven't yet been resolved**. For example, no one is monitoring who buys the CRISPR tools. Also in terms of safety: what are known as **off-target** effects (cuts in unintended locations of the DNA) can be contained more or less, but less is made of **on-target** effects, which are undesired mutations in the right cut spot caused because we don't fully control the repair mechanisms yet. "This is less important in the lab. If we experiment with 20 mice, we can choose the one that comes out right. But we can't do that with embryos in real life."

Pere Estupinyá, the moderator for the panel, put forth a question: **Then, when will the time come?** That question is very broad, ranging from modifying embryos to different types of therapies in adults. Some of them are already in the clinical trials phase, but generally in very specific areas like the eyes or modifying cells in the lab, not in vivo. Montoliu is clear: "**when it's safe**." But there is also room for debate here. Erikainen believes **we have to consider the patient's right to treatment when there is no other option**, which could also affect the feasibility of clinical trials, which require a group of patients who aren't administered the drug in order to establish its efficacy. "**I don't have the answers, but I do think that we have to ask ourselves these ethical questions**," he noted.

And this one, too: **the question of price**, which in most cases are astronomical today, with therapies costing around €500,000 per patient. "Now we're in the fireworks stage, but I'm sure they will drop dramatically," said Montoliu. "It's a question of negotiation, and governments should be part of it."