

MICE TIMES

Life created in the lab

With the diversity of possible applications with Synthetic Biology, opportunities and risks are close bedfellows.

“Synthetic Biology” – what is it? “Synthetic” has the sound of “artificial”; on the other hand, biology as the science of life describes and researches everything that is “natural”. How do they fit together? The aim of Synthetic Biology is not only to research and describe life processes, but also to shape and restructure them or even completely imitate them in artificial systems. Knowledge and methods feed into Synthetic Biology not only from molecular biology and organic chemistry, but also from nanotechnology, information technology and, of course, the engineering sciences.¹

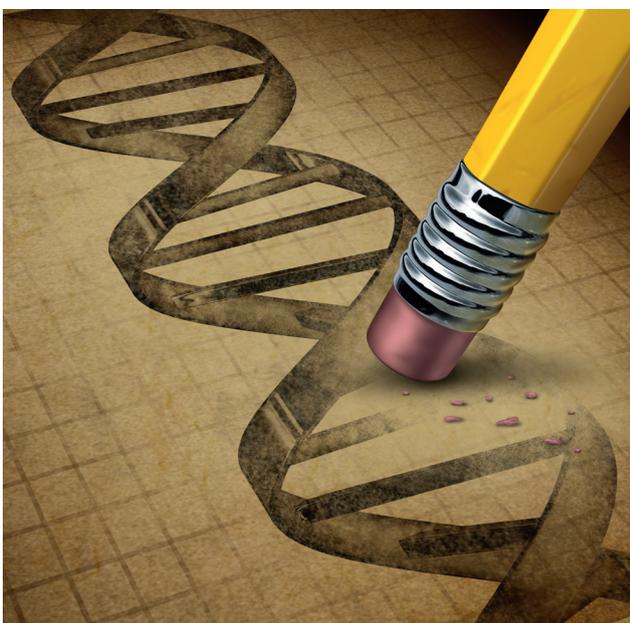
Synthetic Biology is still quite young. It promises solutions for shortages and threats with which humanity currently has to struggle: whether with food or medical supplies, the availability of fuel or pollution of the environment. Yet the diverse applications and also the name given to the technology (which has been in existence for more than 10 years) elicit a highly ambivalent response.

A prime example of how bioengineers work can be found in the projects of Christina Smolke and her team from Stanford University in the US. “We are headed for a new era in which we will no longer had

to confine ourselves to what nature can do” says the chemical engineer and cell biologist. Processes that occur in nature, for example for the manufacture of medicines, could be “borrowed” and, with the aid of genetic engineering, built into miniature living factories that ultimately produce what we want.²

The miniature factories that Smolke is talking of here are yeast cells. In the researcher’s laboratory, they manufacture medicines – a property that are not endowed with by nature. Smolke’s yeasts synthesize opioids such as thebaine and hydrocodone, medicinal substances that are traditionally obtained from the opium poppy. For the production of these substances, poppies are cultivated on an area of 250,000 hectares worldwide each year. The idea behind the research is that billions of yeast cells should likewise be able to produce the opioids needed in future, but within a substantially smaller area.

For this purpose, Smolke’s team has equipped the yeast with molecular machinery that can also do this. In the nano-factories, more than 20 enzymes are involved in the synthesis process. Not all of them come from the poppy; some come from bacteria, and others even come from rats. The Stanford researchers incorporated the genetic blueprints for these enzymes into the yeasts, which ultimately produced the desired medicinal substances from sugar.³



Synthetic Biology changes genomes

It's like a few dozen soldiers from different units who had never collaborated before not coming together for a Mars expedition, says Smolke. You prepare the soldiers – by which Smolke means the various enzymes – to work together on what is completely unknown terrain as yet (namely the yeast cell). In its latest coup, the group used this method to produce noscapine, likewise a medically effective natural substance obtained from the poppy that is used as an antitussive agent. In experiments in animals, this alkaloid also inhibited the formation of metastases in breast and prostate cancer.⁴

Synthetic Biology not only uses yeast cells as nano-factories – bacteria or algae are also used in an effort to produce medicines, vaccines, chemicals and also fuels. In this way, for example, researchers in California managed some years ago to get the chemical 1,4-butanediol, which is needed in large quantities in industry, produced by fermentation – using bacteria. 1,4-Butanediol is not formed in nature by any known organism to date.⁵

In a further application, genetically modified microalgae produce an algae oil designed to be used as a palm oil substitute in the production of detergents. The flavour and aroma molecule vanillin, which is no longer produced using biotechnology or chemical synthesis, as before, but with the aid of genetically modified yeast cells, has already been on the market in the US since 2014. The molecular machinery with which plants synthesize vanillin naturally was incorporated in the yeasts for this purpose.⁶

Synthetic Biology promises the creation of crops with optimized characteristics (e.g. a higher concentration of nutrients or vitamins and resistant to pests or drought). Some groups are working on tailored microorganisms that can detect environmental pollution and immediately render it harmless. Some researchers even see the technology as a possible way of “bringing back” extinct animal species, such as the mammoth, to our planet.

The idea of being able to create new organisms or functional units with sheer inexhaustible characteristics in the laboratory arouses the excitement of investors. Compared with 2011, the total amount invested in Synthetic Biology research projects tripled

to an estimated 1.2 billion dollars by 2016.⁷ Some investors see in DNA as the new programmable material of the future (to succeed silicon).

For all the excitement and opportunities that the new technology offers, the risks are at least as great. “Synthetic Biology differs from the steam engine in the one essential respect that you are working not with a machine, but with living organisms that can develop their own life,” says microbiologist Margret Engelhard from the European Academy of Technology and Innovation Assessment.⁸ So, while you can plan how these machines should function, the way in which their independent existence develops is beyond the scope of any such planning. “Products of Synthetic Biology may have unforeseen properties. Moreover, complex creatures that multiply independently and interact with their environment are hardly capable of being “brought back”, writes the German Life Sciences Association (V BIO).⁹

The idea of restoring extinct animal species to life with the aid of Synthetic Biology sounds appealing. It would be less so if researchers created disease pathogens that had already been eradicated or were on the brink of being eliminated. In 2002, for example, researchers succeeded in recreating the polio virus in the laboratory. This is exactly the virus that the WHO has been trying to banish from the planet in a difficult and costly 30-year campaign known as the Global Polio Eradication Initiative (GPEI).¹⁰ The same applies to the smallpox virus, which was eradicated back in 1980 and was produced artificially in the laboratory by Canadian scientists in 2017 – dubious successes with mena-



Synthetic Biology creates optimized crops

cing potential. It defies the imagination to consider what the consequences might be if a pathogen against which the world's population no longer had any immune defence were to re-emerge as the result of an accident or a bioterrorist attack.

The example of disease pathogens illustrates how closely the opportunities and risks of Synthetic Biology are intertwined. Dutch researchers, for example, are creating artificial microorganisms to develop them further as novel vaccines. A minimalist approach is taken to equip tiny globules surrounded by a layer of fat with molecular tools, enabling the desired antigen against which an immune defence is to be created to be formed directly in the globules. In addition, signalling substances are formed that stimulate the immune system. As a kind of basic vaccine module, these artificial microbes could be equipped with different genetic blueprints for the pathogens against which an immune defence is to be created. In tests in mice, this kind of vaccination elicited a stronger antibody response than a control vaccination that was likewise tested.¹¹

With the tools at their disposal, bioengineers can create DNA and genomes, artificial cells and cells with a minimal genome, modify biomolecules and

“re-programme” cells. The latter is a speciality of Ron Weiss, from the Massachusetts Institute of Technology in Cambridge, Mass., USA, one of the pioneers of Synthetic Biology. Weiss's team creates biological circuits, analogous to electric circuits, with which it endows cells with new properties. These “cell upgrades” comprise between three and 15 genes, and to estimate how safe and effective they are, they test its biological programs for example on laboratory mice.¹²

Unlike classical gene therapy, no longer is a single gene incorporated in cells to correct a disease-causing defect, but a tiny program that provides for better control of the intensity and timing of the therapeutic intervention. Weiss's team uses modified herpes simplex viruses, for example, which only infect and destroy cells in the body if they are cancer cells.¹³ In the experiment in mice with a breast, skin or brain tumour, this has already proved successful – but there is still a long way to go before it can be used in humans.



Yeast cells in Petri dishes

Sources:

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- ² <https://med.stanford.edu/news/all-news/2018/04/researchers-engineer-yeast-to-manufacture-complex-medicine.html>
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- ¹² <https://www.tagesspiegel.de/wissen/neue-genmedizin-mit-apps-gegen-krankhe-zellen/20942568.html>
- ¹³ <http://science.sciencemag.org/content/359/6376/eaad1067>

It would be ideal if we could understand the complex mechanisms in living organisms without animal experiments. Unfortunately this is not possible yet. The dilemma will remain for quite some time: basic research without animal experiments would mean abandoning medical progress. "Mice times" reports on success stories in medical research that were only possible due to animal experiments.

IMPRESSUM

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