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WHY MICROBES WILL RULE THE WORLD – AND OUR INDUSTRIES

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Microbes have ruled the world for approximately 4 billion years. But the future actually depends on their dominance, some would argue. Why? Because microbes, as well as mammalian cells, can be engineered into producing high-value chemicals and medicine. Therefore, scientists at The Novo Nordisk Foundation Center for Biosustainability are hard at work developing cell factories to benefit us all.

Plastic bags, toys, cancer drugs, fuel, and food ingredients are just some of a huge range of products that are manufactured from chemical materials based on oil or extracted from plants. This way of manufacturing either depletes natural resources or takes up big areas of farmland. Furthermore, use of fossil fuels contributes to increased carbon dioxide emissions. Using cheap biomass, for instance municipal waste or plant stems, would create a sustainable carbon cycle.

But it is still a challenge to synthesize very complex compounds chemically from cheap biomass. Instead of building enormous factories for chemical synthesis, researchers have started looking towards the smallest factories known, namely cells.

When the Novo Nordisk Foundation Center for Biosustainability was established six years ago based on a generous grant from the Novo Nordisk Foundation, the vision was to build cell factories to produce new or existing compounds for the pharmaceutical industry as well as fine chemicals to lessen the environmental impact of our modern living. Today, we have already taken huge steps towards fulfilling this vision.

Hence, a primary aim of the Center is to lead the transformation from a petrochemical industry to a more sustainable bio-based industry in which chemicals and drugs are produced bio-technologically using cell factories.

Figure 1. *Novo Nordisk Foundation Center for Biosustainability. In 2016, the Center moved into a new modern building at the DTU's main campus in Kgs. Lyngby, 12 km north of Copenhagen. The Center is collaborating with biotechnology companies in Denmark and elsewhere and with the chemical industry to promote knowledge exchange and the application of the Center's results. Photo credit: DTU.*

Big effort to put the research into use

The Novo Nordisk Foundation Center for Biosustainability is organizationally a department at the Technical University of Denmark (DTU), and its organization is designed to operate at the interface of basic and translational research. Currently, the Center has nine sections situated in Denmark, USA and Sweden, which conduct prominent academic research. The focus of the sections is on cell factory design using state-of-the-art bio-analytics, molecular biology, genome-scale computational models and high-throughput screening methods. Furthermore, research groups and so-called core units at the Center focus on translating the basic research and maturing it for industrial implementation.

The results are evident

By now, researchers at the Center have already taken big leaps in many areas. For instance, they have managed to

build *E. coli* bacteria that produce large quantities of the amino acid serine, which is otherwise known to be toxic to this bacterium. But using advanced robotics and so-called adapted laboratory evolution, the researchers first trained the bacteria into tolerating high concentrations of serine and then engineered the bacteria into producing large amounts of this particular amino acid [1]. Serine is very interesting commercially, because it is used in makeup, lotions, tube feeding formula, and various nutraceuticals. Also, it can be turned into a variety of chemicals used in plastics and detergents. Other achievements are engineering of *S. cerevisiae* (baker's yeast) into producing cocoa butter lipids [2], anti-malarial medicine [3], and haemoglobin [4] – the oxygen carrier of red blood cells.

In terms of commercializing, the potential of chemicals produced in cell factories is enormous. The turnover of the chemical industry is about 3.8 trillion Euro per year, or about 5% of the world's GDP. This is roughly evenly divided between commodity industrial chemicals and specialty fine chemicals. Many of these chemical compounds can now be made biologically by engineering cellular metabolism and designing microbial cell factories.

Using mammalian cells for producing proteins

Even though yeast and *E.coli* can achieve many of the researchers' goals, these cells often fall short when it comes to producing protein-based drugs. The reason being that therapeutic proteins, i.e. cancer drugs, blood proteins, enzymes for metabolic diseases, vaccines and different human hormones have to resemble human proteins very closely in order not to give an immune response in the patient.

The cellular "machinery" for decorating proteins in yeast and bacteria is very different from that of human cells. Mammalian cells, on the other hand, are a perfect fit for this purpose. The Center's focus is on CHO (Chinese hamster ovary) cell lines, and the goal is to develop robust cell factories that efficiently produce therapeutic proteins with tailored properties.

CHO cells already produce around 70% of all protein-based bio-pharmaceuticals on the market [5]. In 2009, the turnover of the pharmaceutical industry was 460 billion Euro per year, with therapeutic proteins accounting for about 76.5 billion Euro, making this area the fastest growing segment of the industry.

Optimization of cell factories is crucial

Today's CHO cell factories can only produce fairly low amounts of these important pharmaceuticals; about 5-10 grams of active compound per liter, which makes the drugs quite expensive.

Therefore, a big focus area is optimization and upscaling, both when it comes to mammalian and microbial cell factories. Optimizing cell factories will benefit patients, consumers, and the environment. Also, we are working on discovering and producing new drugs and chemicals, that are not on the market today, and ready them for commercialization. This will potentially benefit industries, attract investors and prepare the ground for start-ups and spin-outs and hence contribute to a flourishing biotech industry.

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Figure 2. *Laboratory in the Center for Biosustainability. The interior of the new modern building with its high-tech laboratories and spacious offices, attracts highly skilled researchers from all over the world and fosters an innovative spirit. The Center is also very interested in turning future researchers into leaders and pioneers within sustainable industry. The Center is therefore educating young scientists within the field and currently has about 50 PhD students enrolled. Photo credit: Stamers Kontor.*