Novo Nordisk Foundation Center for Biosustainability
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DTU Technical University of Denmark

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The Novo Nordisk Foundation Center for Biosustainability

Cell factories for a sustainable world

The Novo Nordisk Foundation Center for Biosustainability, Technical University of Denmark, is a first-of-its-kind international center for research on and development of microbial and mammalian-cell–based production platforms.

The Novo Nordisk Foundation Center for Biosustainability (CFB), an international center for the pursuit of knowledge and development of technologies to accelerate the transition from an oil-based to a more sustainable bio-based chemical and pharmaceutical industry, was established in 2011 with a grant from the Novo Nordisk Foundation.

The CFB has brought together high-profile global researchers working in areas such as network reconstruction and *in silico* biology (Bernhard Palsson of the University of California, San Diego), the identification of novel bioactive compounds (Sang Yup Lee of KAIST in Daejeon, South Korea), high-throughput molecular bioscience (Mathias Uhlén of KTH Royal Institute of Technology in Stockholm), bacterial cell factories (Søren Molin of the Technical University of Denmark (DTU) in Lyngby), yeast cell factories (Jens B. Nielsen of Chalmers University of Technology in Gothenburg, Sweden), yeast synthetic biology (Jay Keasling of the Joint BioEnergy Institute in Emeryville, California), Chinese hamster ovary (CHO) cell-line engineering (Gyun Min Lee of KAIST), and glycoengineering of CHO cells (Henrik Clausen of the University of Copenhagen). With this range of expertise, the CFB has the necessary capabilities to design and build cell factories for the sustainable production of compounds ranging from pharmaceuticals, food ingredients and anti-infectives to biodegradable plastics, and fine and bulk chemicals.

The CFB, which will move into its permanent quarters on the DTU campus in the fall of 2016, offers a unique opportunity for potential industrial and academic partners to collaborate on the design, development and implementation of cell-based biosynthesis platforms.

Therapeutic proteins

One of the three main focus areas at the CFB is the design and construction of CHO cell lines that are engineered to produce high yields of therapeutic proteins with homogeneous post-translational modifications. With the full genome sequence of CHO cells now available (after being sequenced by the CFB and collaborators), comprehensive physiological and metabolic models built and CRISPR, a genetic engineering tool, in place, it is possible to construct 'super' CHO cells that are optimized for therapeutic-protein production.

Research at the CFB is focused on the development of CHO cell lines optimized for subsequent expression of particular classes of recombinant proteins, such as monoclonal antibodies, growth factors and blood factors. These optimized cell lines will reduce the development period for CHO cell factories to about six months, representing substantial savings in time and money compared with current approaches, which take between one and two years from design to implementation.

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Antimicrobials

A second area of concentration for the CFB is the identification, characterization and production of natural antimicrobial compounds. This antimicrobial platform combines the center's computational-biology and metabolic-engineering capabilities with a high-throughput co-evolution and screening setup that allows the rapid identification of novel bioactive compounds. The current focus is on compounds produced by *Streptomyces* species.

The CFB is uniquely positioned to rapidly advance innovation in this area through its members' expertise in biosynthetic-pathway identification, engineering and reconstruction, and precursor-pathway optimization for yield improvement. These core capabilities are further complemented by the CFB scientists' capabilities in genome mining to identify secondary metabolite biosynthetic pathways and to perform genome-scale metabolic modeling.

iLoop

The design and optimization of robust microbial cell factories constitutes the third area of focus of the CFB's integrated research and development process. This process is iterative, and the center's goal is to optimize it to a point where the design and implementation of a new microbial cell factory can be achieved in two years at a cost of $20 million or less. With current approaches, best-case scenarios start at a development time of five years and a cost of at least $50 million.

The CFB kicks off the process by selecting target products using both experimental and computational approaches, and by conducting a market-need analysis and initial biological feasibility assessment.

The design phase then starts with the identification of relevant pathways that can be manipulated to control the production of the target compound in cells. This is followed by the CFB's unique optimization process, the so-called iLoop (Iterative Cell Factory Development Loop), which consists of four steps.

First, compound-producing strains are generated using genetic engineering approaches. Then, after an evaluation of their fermentation capabilities and compound yields, promising strains are analyzed using tools such as adaptive laboratory evolution to identify bottlenecks and potential points of intervention for further optimization. With this information in hand, strains are designed *in silico*, and further rounds of implementation and evaluation are conducted until optimal strain performance is achieved.

"The CFB has assembled leading academics in cell-factory design from around the world to form a comprehensive team of Scientific Directors, and has built three technology platforms that are unparalleled in an academic setting," according to Bernhard Palsson, director of the CFB.

Cell-factory partnerships

One of the CFB's missions is to stimulate entrepreneurship, innovation and the development of technologies to drive the establishment of cell factories as a commercially viable alternative to existing fuel and pharmaceutical production platforms. A dedicated CFB business development group supports all of the center's translational activities, providing a one-stop shop for interested collaborators in industry and academia.

The CFB offers many collaboration options; in addition to internally selected and developed projects that provide opportunities for companies to either license or become co-development partners, the center functions as a resource for interested industry partners that need to outsource cell-factory development work or that are seeking a collaborator for specific research and development projects.

"The CFB has a strong interest in partnering with industry given its broad translational focus and is very flexible in terms of potential collaboration structures," said CFB chief business officer Jens Kindtler.

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