biopharmadealmakers profile

The Novo Nordisk Foundation Center for Biosustainability
www.biosustain.dtu.dk

DTU Technical University of Denmark
DTU Biosustain
The Novo Nordisk Foundation Center for Biosustainability

Sustainable production of novel antimicrobials

The Novo Nordisk Foundation Center for Biosustainability at the Technical University of Denmark, a first-of-its-kind international center for research on and development of microbial and mammalian-cell-based biochemical production platforms, has pioneered an integrated process to optimize and scale up the development and sustainable production of novel antimicrobials.

The Novo Nordisk Foundation Center for Biosustainability (CFB) at the Technical University of Denmark (DTU), an international hub for the development of new knowledge and technologies to accelerate the transition from current oil-based practices to a more sustainable bio-based chemical and pharmaceutical industry, was established in 2011 with a grant from the Novo Nordisk Foundation.

Bringing together top researchers working on network reconstruction, novel bioactive-compound discovery, high-throughput molecular bioscience, bacterial cell factories, yeast cell factories, yeast synthetic biology, Chinese hamster ovary cell-line engineering, and glycoengineering, CFB covers the complete development cycle—from design to implementation—of so-called cell factories for the sustainable production of compounds ranging from pharmaceuticals to fine and bulk chemicals.

CFB represents a unique opportunity for potential industrial and academic partners to collaborate on the development of novel cell-based biosynthesis platforms. Here we highlight one of CFB's key programs: the New Bioactive Compound Project for the discovery and production of novel antimicrobials.

Antimicrobials

A key development area at CFB is the identification and production of novel natural antimicrobials. The emergence of multidrug-resistant pathogens over recent decades and a lack of novel antimicrobial compounds in the pipeline have made the discovery of new bioactive compounds critical.

CFB is uniquely positioned to advance innovation in this area through its expertise in genome mining to identify secondary-metabolite biosynthetic pathways, in reconstruction and engineering of biosynthetic pathways, and in optimization of precursor pathways for improvement of overall yield.

Microorganisms remain one of the best sources of natural products (NPs) with new antimicrobial characteristics. Although traditional compound screening has delivered good results, recent advances in genomic and metabolic analysis have created new and exciting possibilities for the discovery of novel antimicrobials. Microbial genome analysis, for example, has revealed the presence of biosynthetic gene clusters (BGCs) associated with the biosynthesis of NPs with antibacterial properties.

CFB's antimicrobial-compound platform combines the center's high-throughput coevolution and screening technology for the discovery of novel bioactive compounds with computational biology and metabolic engineering capabilities for the identification of relevant pathways and the design of optimized antimicrobial-producing strains, respectively.

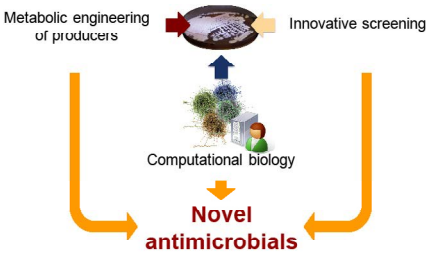

Figure 1: The CFB New Bioactive Compounds Discovery platform. The platform integrates innovative screening, computational biology and metabolic engineering.

Taking an integrated approach

To maximize the identification of novel antimicrobials, CFB has developed an integrated workflow that spans the entire cycle, from initial strain screening to the production of therapeutic lead compounds for large-scale testing.

The first step in the process is screening of CFB's proprietary collection of actinomycetes for novel antimicrobial activities. Using an automated and reproducible adaptive laboratory evolution approach, CFB researchers induce strains to produce bioactive NPs.

Once a bioactive strain has been identified and the active NP has been characterized via mass spectrometry, the team turns its attention to the critical task of identifying the BGCs that are potentially involved in the biosynthesis of those NPs. To achieve this, CFB harnesses its strength in metabolic modeling of secondary metabolism to pinpoint potential genes involved in the biosynthesis of a particular NP, and it combines that information with comprehensive genome-mining approaches that use the antibiotics and Secondary Metabolite Analysis SHell (antiSMASH), a software platform for the automatic identification and analysis of BGCs in bacterial and fungal strains. This represents the most advanced solution available for identifying and characterizing the genetic components of novel antimicrobial-compound production.

Next comes the generation of native and non-native producer strains of newly identified antimicrobial compounds. CFB is developing platform actinomycete strains for the heterologous expression of secondary metabolic pathways, and a set of unique, state-of-the-art high-throughput cluster-cloning and expression tools to manipulate these platform strains and the antimicrobial producers.

Some of the most advanced tools being developed and deployed at CFB are CRISPR-based genome-engineering protocols for actinomycetes. These include optimized approaches for the editing of single BGC genes and the deletion or insertion of entire BGCs, as well as the use of CRISPR interference (CRISPRi) to silence entire BGCs.

The streamlined integration of all these approaches allows CFB to develop high-yield producer strains that generate the amounts of antimicrobial compounds necessary to support the preclinical activities required to advance novel antimicrobials to human therapeutic applications.

"Our unique integration of world-class metabolic engineering know-how into the antimicrobials discovery-and-development process brings us into an excellent position for finding candidates for novel antimicrobials," said Tilmann Weber, co-principal investigator of the New Bioactive Compounds Section at CFB.

Antimicrobial partnerships

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

CFB offers a number of opportunities for collaboration. In addition to internally selected and developed projects that provide opportunities for companies to become codevelopment partners or licensees on particular compounds, the center also functions as a resource for interested industry partners that need to outsource some of their antimicrobial-development work or that want to collaborate on their own 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's CBO Jens Kindtler.

contact
Jens Kindtler, CBO
The Novo Nordisk Foundation Center for Biosustainability
Kgs. Lyngby, Denmark
Tel: +45 4525 8000
Email: jwki@biosustain.dtu.dk