ERA CoBioTech

# BioTech Research & Innovation Hack

# 2021

# ERA CoBioTech Funded Projects at A Glance: MISSION

## Streamlined Streptomyces cell factories for industrial production of valuable natural products

PART OF EUROPEAN BIOTECH WEEK

INNOVATION IS IN OUR GENES

# MISSION

## An industry-driven value chain to optimise the production of bioactive compounds for drug development

***Researchers with EU-funded MISSION project are using specially optimised actinobacteria chassis strains to produce bioactive natural products for various industrial applications.***

### The great potential of bioactive natural products

Natural products cover a unique chemical space particularly well-suited for the development of pharmaceuticals and many other potential agricultural and medical applications. However, the number of new chemical entities, particularly anti-infective drugs, which reached clinical development has substantially decreased over the past decades, despite the rapidly emerging resistance in human pathogenic bacteria against established antibiotics. Indeed, there exists an almost untapped potential resource of novel metabolites from genome mining as identified from actinomycetes genome sequencing. However, the majority of the corresponding biosynthetic gene clusters are either silent under standard laboratory conditions or encoded compounds are only detected at nanogram quantities in the crude extracts. To successfully explore the potential of novel bioactive molecules, we need a robust production platform enabling the supply of natural products, their derivatives, analogs and mimetics in large quantities (multi gram scale) which is still one of the major obstacles in drug discovery and development processes. MISSION aims to contribute by reversing this situation and to bring back natural products to the forefront of drug discovery and development. Enhanced scalable supply is a key to enable reasonable and cost-effective development timelines. Industrial chassis will significantly accelerate the drug development life cycle, namely the later phases of pre-clinical and entire clinical studies. MISSION will increase the throughput in discovering and screening for new promising drug leads via efficient expression of native and rewired silent/cryptic gene clusters from various unexplored and currently uncultivated bacteria. A conservative estimation is a 50% time decrease in preclinical stages – which offers a significant potential reduction in the lifecycle for the development of new antibiotics (or other drugs based on secondary metabolites).

### Multidisciplinary approach

***Synthetic biology approach***

MISSION uses design and construction principles of synthetic biology to fabricate antibiotic gene clusters and to control their expression in programmable chassis through standardized synthetic genetic elements.

***Systems biology approach***

Building on the innovative expertise of its key partners and their undisputed leadership in systems biology, MISSION addresses the iterative integration of "multi omics" analysis from joint experiments with modelling and design to improve production in bacterial chassis.

***Biotechnological approach***

*S. rimosus* has been used at the industrial scale for more than 50 years as the producer of oxytetracycline. Therefore, by applying this advanced industrial host, it will be possible to bring the production process of a target heterologous product with promising biological activity rapidly to the industrial scale, thus ensuring sufficient quantity and quality of the target compounds.

***Sustainable production and conversion of different types of feedstocks and bioresources into added-value products***

We will develop a new value chain to the mature high-value pharmaceutical product clavulanic acid, an important product of Lek d.d. (NOVARTIS/Lek, Slovenia). The newly developed process will display synergies to other microbial products upon pathway diversification in the created chassis strains *S. rimosus.*

***New products, value-added products and supply services***

In the scope of the MISSION, novel compounds with extremely valuable activity, which were difficult to produce with native Actinomycetes and myxobacterial strains will be produced at substantially higher yield.

***Sustainable industrial processes***

The existing technologies for the industrial production of oxytetracycline are based on the most economical and widely available raw material, thus ensuring one of the most sustainable bioproceses in the fermentation industry to date.

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**Consortium:**

Saarland University, (Germany)

Helmholtz- Zentrum für Infektionsforschung, HZI/HIPS, , Saarland University, (Germany)

University of Ljubljana, (Slovenia)

Novartis (Lek pharmaceuticals d.d.), (Slovenia)

ENTRECHEM, (Spain)

**Project duration:**

1 January 2018 - 31 December 2021

**Total budget:** 1.8 €M



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**Main results**

MISSION has combined systems and synthetic biology together with advanced bioengineering tools and generated a multi-layer based technology, which will bring about the following innovations:

- Panel of hyper-producing chassis based on the industrial oxytetracycline producer: This chassis with reduced and fine-tuned genomes is expected to increase the stability of the cells in long-term fermentations and to channel more metabolic potential to the biosynthesis of the heterologous biomolecules.
- Highly efficient synthetic metabolic pathways: Genomic interventions in a fine-tuned, advanced cell are expected to disrupt existing regulatory networks controlling various metabolic processes. We have generate synthetic operons providing sufficient target product precursors.
- High-value bioactive small molecules: MISSION provided access to several bioactive molecules and their derivatives (griselimycin, mithralogs,indolocarbazoles, myxopyronin, cyclooctatine) via expression of corresponding biosynthetic gene clusters in the developed chassis. They will be channelled into the development pipelines of the industrial partners.
- Systems biology optimization: MISSION has provided a technology pipeline that recruits multi-omics data, modelling and data translation technologies for knowledge-based development to access complex natural products. The achievements envisioned will generate excellent opportunities for high tech SMEs to enter into this so far high-risk field with validated innovative approaches at different points of the value chain.

**Future prospect**

Boosting technological innovation in European industries to maintain leadership in biotechnology, particularly in the pharmaceutical industry.

MISSION creates a roadmap for biotechnology innovation. First, it uses the principle of iterative design-build-test cycles; these cycles collect and integrate data, information and knowledge from various disciplines. Moving beyond traditional biotechnology research, typically separated fields, e.g., strain and process development, are tightly connected in our concept, promising synergistic benefits, novel development speed and enhanced production performance. Using this approach, we expect to overcome major research and development hurdles in industrial biotechnology, such as (i) poor process performance in terms of yield and productivity and (ii) the difficulty to extrapolate lab scale results to the large scale. Second, the strong integration of multi-omics analysis throughout the development chain continuously provides a rich set of data on the compound of interest, facilitating later approval for production and market entry. Third, the implementation of novel background-free production strains is expected to reduce the production of many impurities, which otherwise would require cost-intensive downstream purification. In addition, the innovative MISSION concept of natural product development will fill the pipelines of European biotechnology and pharma companies with promising bioactive natural products that will result in strong innovation in downstream drug development processes.

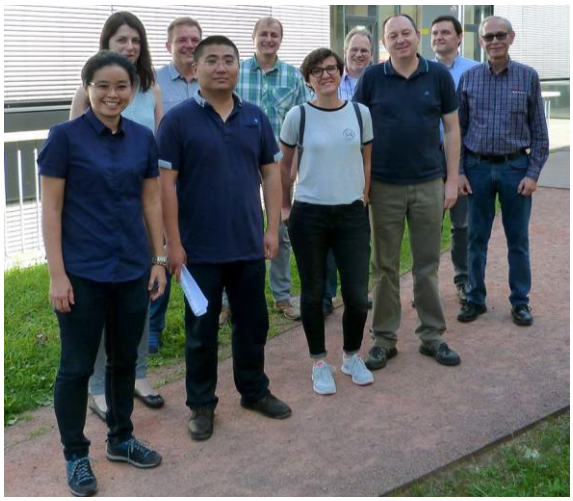

*Figure 1: MISSION Consortium*

**Website:** https://www.mission-bio.eu/
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