ERA CoBioTech

BioTech Research & Innovation Hack

2021

ERA CoBioTech Funded Projects at A Glance: SynBioMet

Synthetic Biology for Sustainable Production of the Methionine Analogon HMTB

PART OF EUROPEAN BIOTECH WEEK

INNOVATION IS IN OUR GENES

SynBioMet

Synthetic Biology for Sustainable Production of the Methionine Analogon HMTB

Our project aims at developing a microbial fermentation process to produce 2,4-dihydroxybutyric acid (DHB), by applying concepts of Synthetic Biology. DHB is a precursor of the methionine analogon HMTB which is used as a supplement in poultry diets.

Project coordinator:

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Consortium

TU Dresden, (Germany)

INSA-Toulouse (France)

ESPCI, (France)

Adisseo, (France)

Project duration:

01/06/2021 - 31/05/2024

Total budget: 1.0 M€

Application of Synthetic Biology to produce the non-natural metabolite DHB

(L)-2,4-dihydrohybutyric acid (DHB) is a precursor for the facile chemical synthesis of the methionine analogon HMTB, which is mainly used as a feed supplement in poultry diets and currently is exclusively produced from petrol. Sugar-based synthesis of DHB could, therefore, render the production of HMTB more sustainable. However, the microbial production of DHB is an extremely challenging problem since DHB is not a natural metabolite in life cells thus rendering classic metabolic engineering approaches unfeasible. To get access to DHB, we have recently developed three synthetic metabolic pathways, which enable microbial synthesis of this compound starting from glucose. In the present project, we shall optimize rate-limiting activities in these pathways by advanced enzyme engineering approaches. Eventually, the optimized pathways will be incorporated into producer strains where they are operated in parallel to enable industrially relevant DHB yields and productivities.

Advanced enzyme engineering as the cornerstone of metabolic pathway development

The implementation of high-performing metabolic pathways for the biosynthesis of DHB requires improved enzymes. We shall use innovative approaches to engineer these activities. Specifically, we will use both a microfluidic and a growth-based screening system to identify improved enzyme variants. The microfluidic system relies on cell-free expression, characterization, and sorting of enzyme variants at unprecedented throughputs. This novel technology enables the exploration of a very large sequence space, thus, drastically increasing the probability of identifying better-performing enzymes. In parallel, we have conceived an in vivo screening system, which couples the biosynthesis of DHB to growth. Accordingly, the DHB-dependent tester strains will be transformed with a library of mutated genes, and improved enzyme variants will be isolated from faster growing cells. Eventually, improved enzymes will be assembled into pathways, which will be expressed in producer strains, which are optimized regarding carbon flux repartitioning and cofactor supply to maximize the DHB yield.

Expected results

The major objective of our project is to develop producer strains and fermentation processes, which enable the production of DHB at industrially relevant yields and productivities. While the use of DHB for the production of the methionine analogon HMTB is the main interest of the project partners, it is of note that DHB is an extremely versatile platform molecule. Among others, it can be converted to propanediol, 1,2,4-butanetriol or gamma-butyrolactone by (bio)chemical means, or polymerized into biodegradable plastics with new exiting material properties. Apart from the production of an industrially relevant platform molecule, another outcome of our project will be the development of novel enzyme engineering methods, which can be applied in other Synthetic Biology endeavours. In particular, the generic cell-free microfluidic expression and screening system gives rise to unprecedented throughputs and will open interesting perspectives for enzyme engineering.

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