ERA CoBioTech

BioTech Research & Innovation Hack

2021

ERA CoBioTech Funded Projects at A Glance: TRALAMINOL

Enzyme platform for the synthesis of chiral aminoalcohols

PART OF EUROPEAN BIOTECH WEEK

INNOVATION IS IN OUR GENES

TRALAMINOL

Enzyme platform for the synthesis of chiral aminoalcohols

Research teams of TRALAMINOL develop novel enzymes and sustainable processes that allow the one-pot, multi-step biocatalytic synthesis of chiral aminoalcohols by combining enzymatic carboligation and amination reactions

Exploiting nature's catalyst diversity towards the production of complex bioactive molecules

Amino alcohols are a class of diverse compounds that can be used as building blocks for the synthesis of pharmaceuticals and agrochemicals. So far, it is difficult and uneconomical to achieve their synthesis biocatalytically and economically.
TRALAMINOL develops new technology and novel processes that allow the one-pot, multi-step biocatalytic synthesis of industrially useful chiral amino alcohols through the combination of novel and engineered highly selective carboligases and aminotransferases. A multi-disciplinary approach is pursued - involving bioinformatics, metagenomic prospecting, organic synthesis, biochemistry, molecular biology, molecular modeling, and biocatalytic process development. The aim is to discover and/or engineer a powerful and flexible enzyme toolbox for the biocatalytic syntheses of valuable chiral amino alcohols with broad industrial applications and to pilot key processes via the toolbox.
The biocatalytic production of valuable, high in demand compounds will be accelerated and the paradigm will be set for their sustainable and greener industrial production, while at the same time minimizing environmental impact and creating value for the European economy and society.

The TRALAMINOL partners focus on the discovery and development of novel, powerful enzyme catalysts from various protein families, including aldolases, transketolases, amino acid racemases and decarboxylases using different liquid assay technologies in high-throughput mode. Enzymes with high activity, selectivity and robustness under synthetic conditions make up or expand the biocatalytic toolbox for future synthetic applications in sustainable industrial processes.
Secondly, best identified enzyme candidates are assembled in multi-step cascades that avoid the isolation of synthetic intermediates, thereby optimizing the efficiency of the overall process. Procedures are being developed to produce expensive starting materials enzymatically in situ to reduce costs, or by coupling an enzyme-catalyzed equilibrium to an energetically favored step to drive the reaction forward, thereby optimizing overall conversion to product.
Finally, novel reaction cascades are tested in scale-up syntheses of selected target products for demonstration purpose and to benchmark the synthetic efficiency of the methods.

Main results

The TRALAMINOL project has completed most of the tasks originally addressed for its work packages and so far achieved critical advances and remarkable innovation. Thus, hundreds of novel enzymes having interesting activities have been discovered from data mining and metagenomic approaches, characterized for different process-relevant parameters, and arrayed in maximum-diversity panels for substrate promiscuity screening in partner labs.
A novel reductive aminase was identified not only having activity with a broad range of amine and ketone components but also for hydroxyketones, thus delivering various chiral aminoalcohols by a single-step synthesis. Several alternative enzyme combinations involving racemase/transaminase or racemase/aminoacid oxidase were tested successfully to produce 2-oxoacids for immediate consumption by transketolase for asymmetric carboligations. Likewise, several new processes could be developed for the diastereoselective, divergent synthesis of non-canonical amino acids or iminocyclitols by coupling novel aldolases with transaminases or imine reductases. Such compound classes are valuable as such due to their bioactivity, or as chiral building blocks needed for the synthesis of pharmaceutical drugs or agrochemicals.

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Another significant outcome is the successful process development for several industrially relevant products by transaminase catalysis, using complementary approaches of racemate resolution or asymmetric synthesis. As an example, the aldolase/transaminase process for the cascade synthesis of L-homoserine has been studied with an external partner using a mathematic modelling tool for process optimization at high volumetric productivity, which proved applicable even to whole-cell technology.

Future prospect

The economic potential of TRALAMINOL achievements has already been partially exploited, because a variety of enzymes from the novel entries to the biocatalytic toolbox have been made available to large global chemical industries for screening purposes, and thereby several enzymes have been identified as highly promising candidates for process development in the pharmaceutical and agrochemical production area. A number of the output enzymes have already seen significant industrial impact, for example currently producing material for clinical trials. This helps accelerating the biocatalytic production of valuable, high in demand compounds and sets the paradigm for their sustainable and greener industrial production, while at the same time minimizing environmental impact and creating value for the European economy and society, and likely far beyond on a global scale.
The knowledge gained during the research conducted in TRALAMINOL, as well as the remaining challenges and particular limitations identified, will warrant a continued in-depth treatment of the underlying concepts. Therefore, the consortium partners have attempted to expand their successful research platform and recently received a grant for an Innovative Training Network "CC-TOP", funded by the European Union through the Marie-Sklodowska-Curie programme in Horizon 2020.

Several lectures and more than two dozen posters summarizing individual results were presented at different international conferences and were discussed with interested audiences. Furthermore, the scientific research achievements of TRALAMINOL have been published so far in 20 papers published in international journals with high impact and wide distribution in the scientific communities. A further handful of manuscripts is currently close to being finished for submission.
A curiosity is that the corona virus pandemic caused lockdown periods during which the experimental research stalled, but thereby stipulated the writing of review manuscripts on subjects related to the goals of the project that could be published in high impact journals. These titles are "Winning the numbers game in enzyme evolution - fast screening methods for improved biotechnology proteins" (DOI: 10.1016/j.sbi.2020.05.003) or "Biocatalytic routes to anti-viral agents and their synthetic intermediates" (DOI: 10.1039/docs00763c).

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Figure 1: The TRALAMINOL team presenting research achievements at the international BioTrans conference - when physical meetings were still taking place!

Website: https://office.oc.chemie.tu-darmstadt.de/tralaminol/
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