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Microbial platform for production of aromatic compounds

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Introduction

Polyketides form the basic building blocks of numerous natural products, which are in use in pharmaceuticals, food additives and other fine chemicals. Many of these polyketides possess very specific cyclic and aromatic conformations. The programmable platform we aim to create will be able to efficiently and directly produce a vast array of polyketide derived compounds. The platform will be integrated in a well known heterologous host to

improve the predictability and engineering options of the platform.

The basic platform will allow production of polyketides of different lengths and folding patterns. The biosynthesis of the polyketides is divided into different steps and by swapping either domains between enzymes or whole enzymes between pathways the length of the polyketides or the individual folding pattern can be directed towards a desired product. Further development of the platform will be combinations of more enzymes to enlarge the possible chemical diversity of the platform.



The synthesis of the polyketide backbone is carried out by polyketide synthases. These can have many different origins, but we have focused on synthases from type I and III PKS systems. The goal is to make nonreduced polyketide backbones, which can then subsequently be modified by other enzyme types included in the platform. After the backbone has been formed the next step in the platform is the folding of the backbone into a cyclic and aromatic system. Each polyketide backbone can be folded in many different polyketide scaffolds depending on the chosen foldase. Thus one backbone can lead to many different scaffolds. The formed polyketide scaffolds can be
further modified to yield greater chemodiversity. This can be done e.g. via specific
methylation or amination, or via reduction
or oxidation of the initial scaffold. The final
number of products, which this platform will
be able to produce, is only limited to the
number of enzymes, which are included.

Cell factories

The host organism for this platform will be heterologous to ensure a platform with a high degree of predictability and great engineering options. We are currently working with both *Escherichia coli* and



Saccharomyces cerevisiae as both of these organisms are well characterized, easy to cultivate, offer many

genetic tools and little background chemistry to interfere with our platform.

Many systems for genetic engineering exists for both organisms. In *E. coli* expression with the Duet vectors from Novagen[®] allows for combination of up to eight genes in a single strain [1], leading to fast strain construction and combination of many different enzymes. In yeast, defined integration sites currently allow for chromosomal integration of up to 14 genes [2], with possibility of elevated expression via the CASCADE system [3].

References

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Acknowledgements & Contact

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