

## Metabolic engineering of *Saccharomyces cerevisiae* for production of germacrene A, a precursor of beta-elemene - DTU Orbit (09/11/2017)

### Metabolic engineering of *Saccharomyces cerevisiae* for production of germacrene A, a precursor of beta-elemene

Beta-elemene, a sesquiterpene and the major component of the medicinal herb *Curcuma wenyujin*, has antitumor activity against various types of cancer and could potentially serve as a potent antineoplastic drug. However, its current mode of production through extraction from plants has been inefficient and suffers from limited natural resources. Here, we engineered a yeast cell factory for the sustainable production of germacrene A, which can be transformed to beta-elemene by a one-step chemical reaction in vitro. Two heterologous germacrene A synthases (GASs) converting farnesyl pyrophosphate (FPP) to germacrene A were evaluated in yeast for their ability to produce germacrene A. Thereafter, several metabolic engineering strategies were used to improve the production level. Overexpression of truncated 3-hydroxyl-3-methylglutaryl-CoA reductase and fusion of FPP synthase with GAS, led to a sixfold increase in germacrene A production in shake-flask culture. Finally, 190.7 mg/l of germacrene A was achieved. The results reported in this study represent the highest titer of germacrene A reported to date. These results provide a basis for creating an efficient route for further industrial application re-placing the traditional extraction of beta-elemene from plant sources.

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