Affibody scaffolds improve sesquiterpene production in Saccharomyces cerevisiae

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Enzyme fusions have been widely used as a tool in metabolic engineering to increase pathway efficiency by reducing substrate loss and accumulation of toxic intermediates. Alternatively, enzymes can be co-localized through attachment to a synthetic scaffold via non-covalent interactions. Here we describe the use of affibodies for enzyme tagging and scaffolding. The scaffolding is based on the recognition of affibodies to their anti-idiotypic partners in vivo, and was first employed for co-localization of farnesyl diphosphate synthase and farnesene synthase in *S. cerevisiae*. Different parameters were modulated to improve the system, and the enzyme:scaffold ratio was most critical for its functionality. Ultimately, the yield of farnesene on glucose $Y_{SFar}$ could be improved by 135% in fed-batch cultivations using a 2-site affibody scaffold. The scaffolding strategy was then extended to a three-enzyme polyhydroxybutyrate (PHB) pathway, heterologously expressed in *E. coli*. Within a narrow range of enzyme and scaffold induction, the affibody tagging and scaffolding increased PHB production 7-fold. This work demonstrates how the versatile affibody can be used for metabolic engineering purposes.

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