Docket #: S22-165

Method for Biosynthesis of Tetrahydropapaverine and Semi-Synthesis of Papaverine in Yeast

Stanford researchers have engineered yeast strains for de novo biosynthesis of tetrahydropapaverine (THP) and a semi-synthetic production of papaverine with high efficiency. THP and papaverine are both medicinally important plant natural products (PNP), and they have experienced supply shortage especially in recent years due to COVID-19 pandemic. Traditional supply of PNP rely on slow plant growth stage and extraction of active pharmaceutical ingredient from the plants, and a more efficient and flexible supply chain is needed to meet the spikes in medical demands.

The Stanford group resolved the current difficulties by engineering a yeast strain with heterologous expression of two enzyme variants that exhibit altered substrate specificity. Through protein engineering and activity optimization, the scientists tuned the target specificity and improved the overall yield rate of biosynthesized THP by 600-fold. They also designed an aqueous oxidation condition of biosynthesized THP to produce papaverine, increasing the yield of the equivalent reaction to 15%. The new fermentation-based production of clinically relevant PNP significantly increase the yield of THP and papaverine and alleviate the supply chain shortages.

Applications

- Manufacture of THP for downstream synthesis of atracurium or cisatracurium
- Synthesis of papaverine for clinics and pharmaceuticals
- General microbial fermentation methods for development of additional enzymes capable of biosynthesizing relevant natural products

Advantages

- Fast and flexible supply chain: biosynthetic method significantly accelerates the production of THP with fermentation-based production
- Minimum resources needed: materials required for biosynthesis are readily available
- Optimized yeast strains: the engineered yeasts are highly selective and efficient

Patents

- Published Application: WO2024015152

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