Docket #: S24-220

Enzymes and Platform for High-Efficiency Heterologous Production of Taxanes

Stanford researchers have engineered a heterologous system for the high-efficiency production of numerous taxanes and taxane intermediates. By leveraging newly discovered enzymes in the natural biosynthetic pathway for paclitaxel (Taxol), a key taxane compound, the inventors have achieved dramatic increases in the yield and chemical diversity of manufactured taxanes.

Taxol, a prominent chemotherapy drug used to treat a variety of cancers, and its derivatives are among the best-selling therapeutics across the global market. However, despite its profound clinical relevance, the commercial production of Taxol is hampered by its low natural abundance, the high costs, complexity, and environmental challenges entailed in its extraction and preparation from natural sources, and inefficient synthesis pathways handicapped by poor product yields. By developing a new approach to mine the genome of the yew *Taxus x media*, a natural source of Taxol, the inventors identified previously unknown genes involved in the enzymatic synthesis of the drug. They subsequently harnessed these discoveries to develop a heterologous system in *Nicotiana* plants for the efficient production of multiple taxanes and direct intermediates to Taxol, achieving comparable yields of Taxol intermediates within days that would otherwise require years in yew trees and enabling the manufacture of Taxol analogues that were previously inaccessible via synthesis or extraction from natural sources. Most notably, the inventors have overcome the longstanding bottleneck in heterologous taxane production, an extreme inefficiency of the first oxidation, through inclusion of an NTF-like protein with no precedence in plant metabolism. This protein resolves inefficiencies in taxane oxidation both in plant and yeast heterologous hosts. By informing more efficient, sustainable, and scalable production methods and potentiating the synthesis of next-generation taxanes with enhanced pharmacological properties,

this invention could improve the affordability, efficacy, and accessibility of treatment for cancer patients worldwide.

Stage of Development
Proof of concept

Applications

- Engineered plant or microbial systems for high-efficiency heterologous production of Taxol
- Production of natural or unnatural taxanes with improved pharmacological characteristics

Advantages

- Significantly increased production yields and scalability for Taxol and its intermediates
- Reduced costs, complexity, and environmental challenges relative to traditional Taxol isolation and synthesis methods
- Enhanced synthetic accessibility and tractability of additional taxanes with potentially enhanced therapeutic efficacy

Publications

- Conor James McClune, Jack Chun-Ting Liu, et al. (2025). Discovery of FoTO1 and Taxol genes enables biosynthesis of baccatin III. *Nature*, **643**, 582–592.

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