THE LEI GROUP

Chemical Biology, Organic Synthesis, Medicinal Chemistry

Characterization and Heterologous Reconstitution of *Taxus* Biosynthetic Enzymes Leading to Baccatin III

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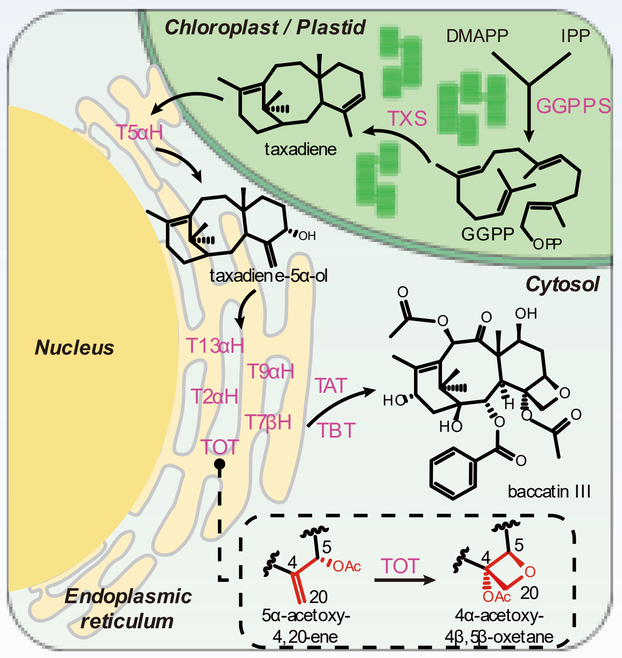
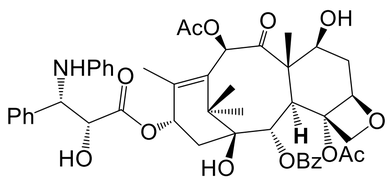
Abstract: Paclitaxel is a well-known anticancer compound. Its biosynthesis involves the formation of a highly functionalized diterpenoid core skeleton (**baccatin III**) and the subsequent assembly of a phenylisoserinoyl side chain. Despite intensive investigation for half a century, the complete biosynthetic pathway of baccatin III remains unknown. Here, we identified a bifunctional cytochrome P450 enzyme (**Taxane oxetanase, TOT**) that catalyzes an oxidative rearrangement in paclitaxel oxetane formation, representing a previously unknown enzyme mechanism for oxetane ring formation. We created a screening strategy based on the taxusin biosynthesis pathway and uncovered the enzyme responsible for the taxane oxidation of the C9-position (**T9αH**). Finally, we artificially reconstituted a biosynthetic pathway for the production of **baccatin III** in tobacco.



Background and Significance

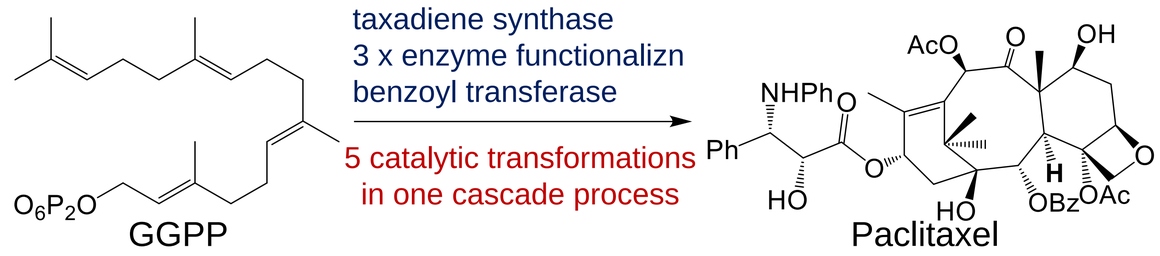
Paclitaxel, derived from the secondary metabolism of *Taxus* genus plants in Taxaceae, has been clinically used to treat various cancers.



Paclitaxel (Taxol)
anticancer

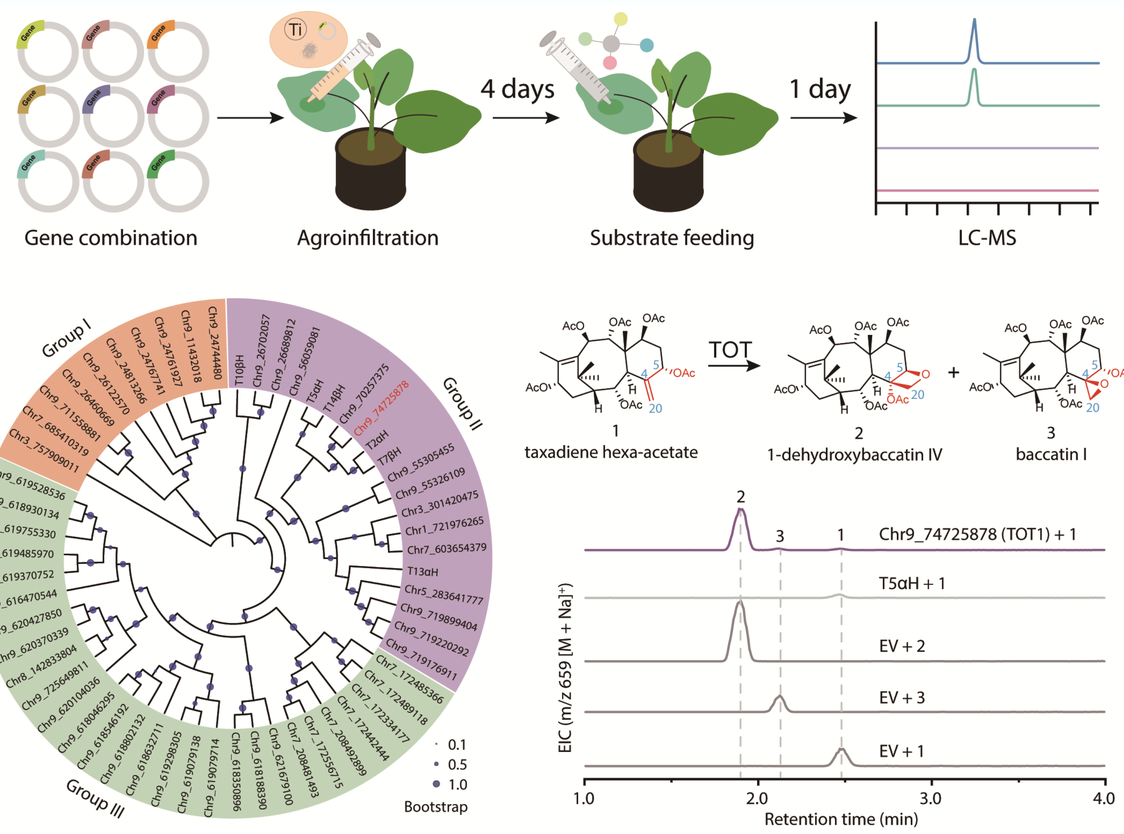
- Important ovarian, breast cancer treatment worldwide.
- Global demands exceed a metric tonne annually.
- Structural core available from European Yew *Taxus Baccata* allows semisynthesis, production

Biosynthesis of Paclitaxel:

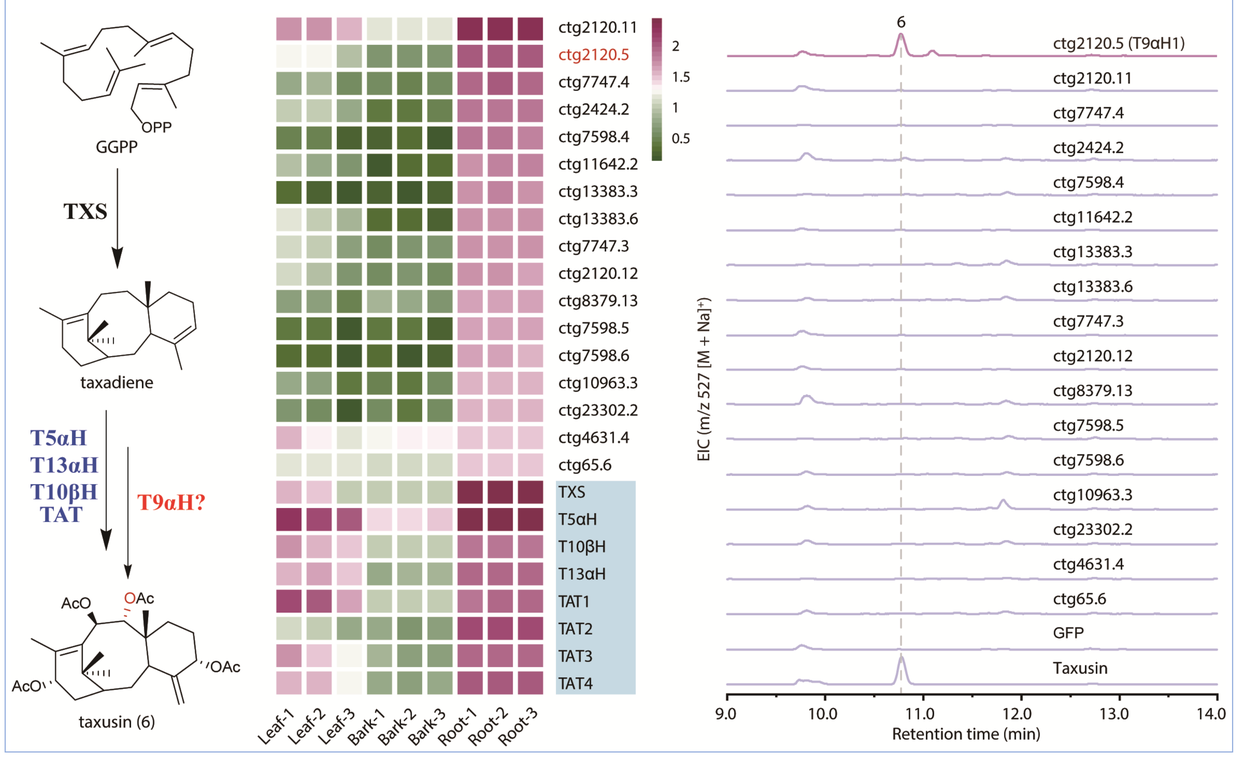


One strategy currently used to produce paclitaxel is chemical semisynthesis, using paclitaxel precursor **baccatin III**. However, several essential steps in forming **baccatin III** remain unknown.

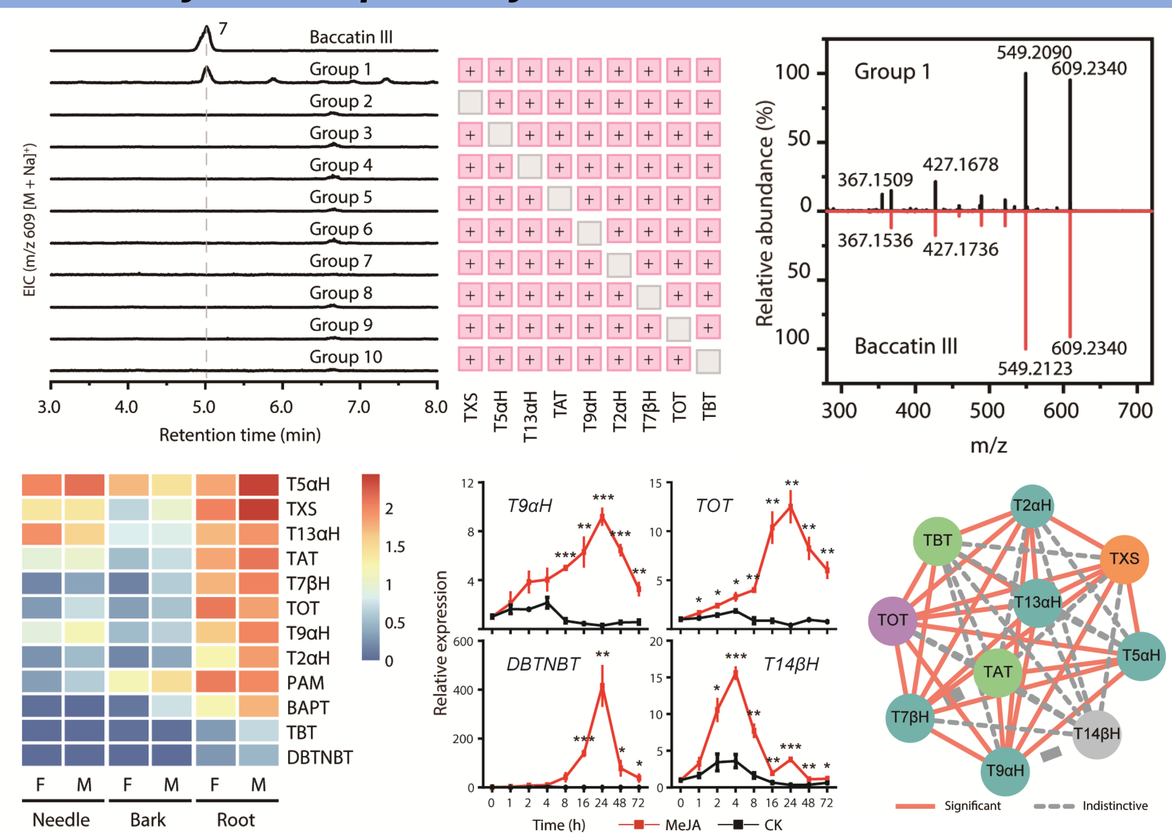
TOT1 is responsible for oxetane formation



Identification of T9αH1 for C9 hydroxylation



Biosynthetic pathway constitution of baccatin III



Xiaoguang Lei's Group

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Research on bioactive plant natural products:

(1) Biosynthesis of plant natural products.

(2) Identification of new functional plant natural products.

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