MSU Licensing Opportunity:

Semi-Biosynthesis of Paclitaxels

A faster, more streamlined semi-biosynthetic in vitro process to produce paclitaxel and related anti-cancer drugs.

A shortage of the chemotherapeutic paclitaxel (Taxol®) due to an unreliable pharmaceutical supply chain lead researchers at Michigan State University (MSU) to discover and propose a novel, faster way of producing paclitaxel and related anti-cancer drugs: Using a semi-biosynthetic process, Taxol can now be produced in a more streamlined and faster in vitro synthesis process to quickly ramp up the production during shortages, ensuring the pharmaceutical supply for many breast cancer patients as well as patients with ovarian, lung, bladder, and colon cancers.

Currently, most production for major paclitaxel providers is based on plant cell fermentation technology developed by the German and Canadian biotech company Phyton Biotech, Inc. MSU researchers have developed a non-toxic semi-biosynthetic approach that is simpler, less time-consuming, and easier to control (in vitro) than the currently used production method. This novel MSU technology is a process that uses Tyrocidine Synthetase A (TycA) for the production of phenylisoserinyl CoA thioesters.

The current plant-cell fermentation method uses Taxus cells to produce paclitaxel. Many of the minimally ~18 biosynthetic enzymes accept multiple substrates and produce multiple products creating a complex metabolic network of over 400 taxoids that are difficult to separate. Using enzymes to catalyze a portion of the paclitaxel pathway in vitro has benefits over the current fermentation method. The costs and complexity of engineering the entire linear paclitaxel pathway are avoided, no new enzymes need to be characterized, and unnecessary flux to side products is decreased significantly.

Key Opportunities

- **Faster, more flexible production of paclitaxel & related anti-cancer drugs**
- **More streamlined production process, significantly less side products**
- **Controlled environment, in vitro synthesis**
- **No harsh organic solvents, greener production**
- **Applications for cancer drugs & experimental precursors in research market**

Patent Status
Patent application published, publication # 20150284751

Licensing Rights
Exclusive licensing rights available

Inventors
Kevin D. Walker

Tech ID
TEC2012-0076

Contact
Isi Davis
Tech Marketing Manager
davisnin@msu.edu
517.884.1829

Direct Link
http://msut.technologypublisher.com/technology/23746

Current Method: Complex Paclitaxel Biosynthesis in Plant Cells

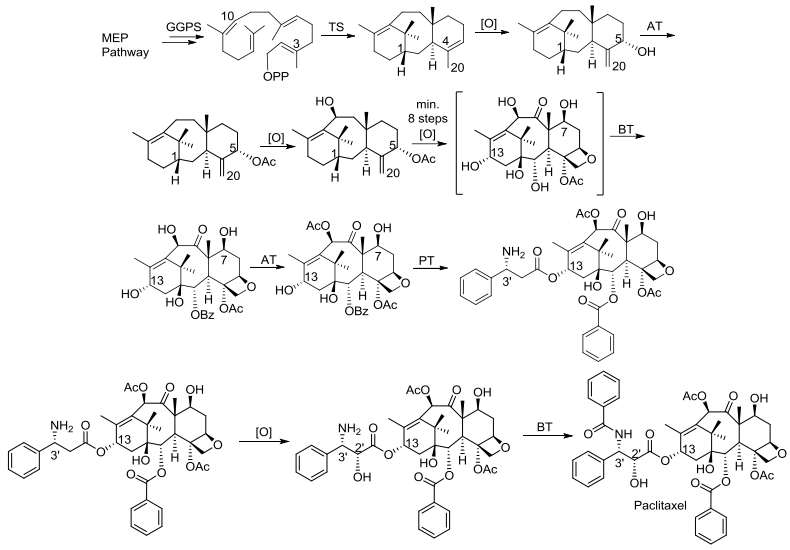

Fig. 1: The current fermentation method uses Taxus cells to produce paclitaxel. Many of the minimally ~18 biosynthetic enzymes accept multiple substrates and produce multiple products. This creates a complex metabolic network of over 400 taxoids, which are difficult to separate.

New Proposal for Paclitaxel Semi-Biosynthesis: One-Pot Biocatalysis of Various Paclitaxels

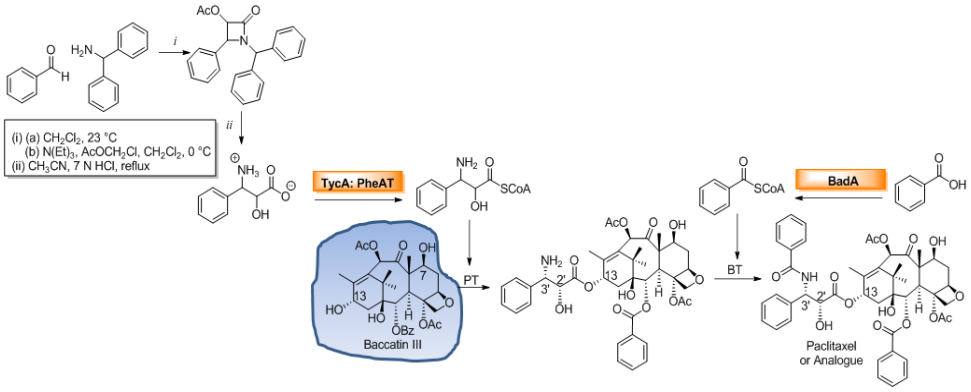

Fig. 2: No side products in controlled system; separating compounds is easier compared to those isolated from a milieu in plant cell cultures.

MSU's novel semi-biosynthetic approach uses enzymes to catalyze a portion of the paclitaxel pathway in vitro, showing clear benefits over the current fermentation method: The costs and complexity of engineering the entire linear paclitaxel pathway are avoided, no new enzymes need to be characterized, and unnecessary flux to side products is decreased significantly.

No harsh solvents are used. Employing green chemistry to address toxicity & safety concerns.

Contact
Isi Davis
Tech Marketing Manager
davisnin@msu.edu
517.884.1829

Current Method for Semisynthesis of Cabazitaxel (Jevtana® Synthesis)

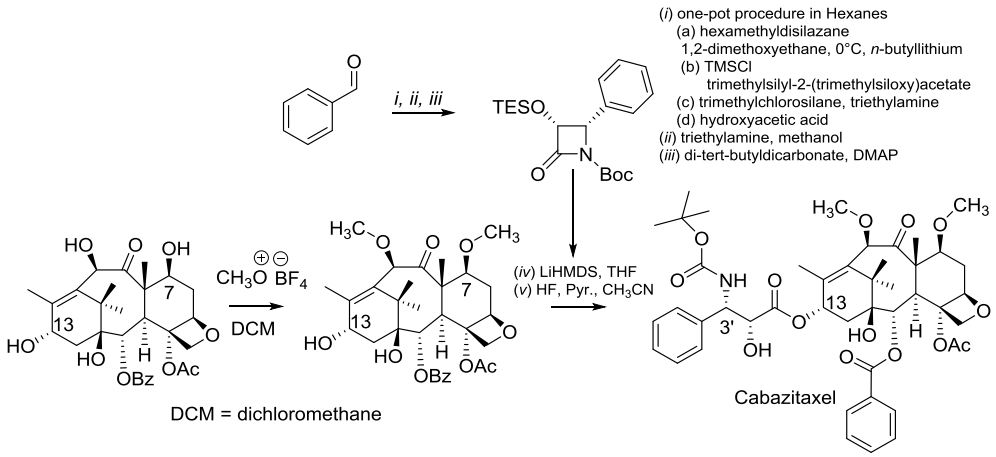

Fig. 3: Petroleum solvents are used throughout the complete semisynthesis process.

Proposed Semi-Biosynthesis of Cabazitaxel Employing Two Enzymes: PheAT and BAPT

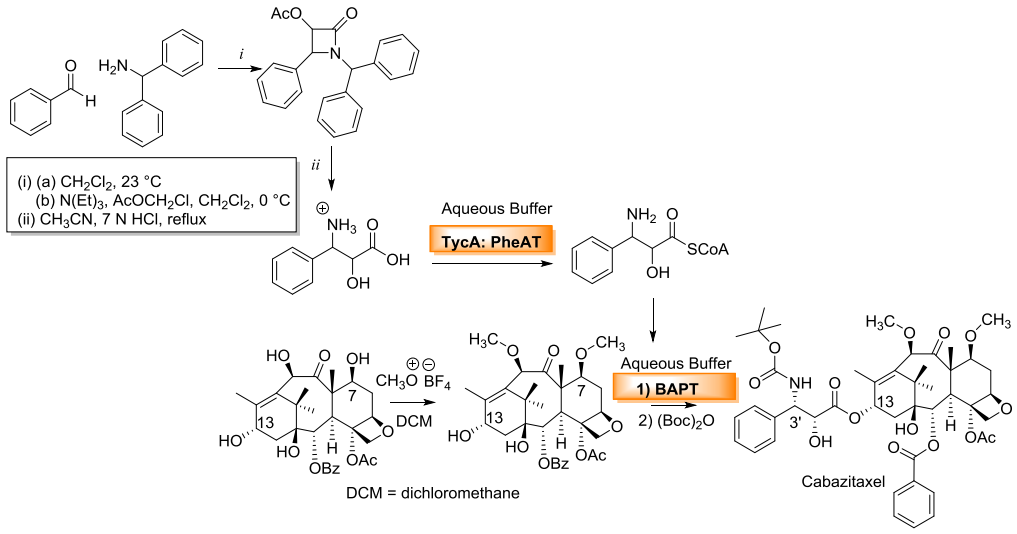

Fig. 4: Chemical protecting group chemistry is reduced by using regiochemistry of enzyme steps. Handling is reduced overall. Water-based buffer steps reduce use of petroleum-based solvents such as hexanes and tetrahydrofuran, addressing safety & toxicity aspects.

The proposed semi-biosynthesis eliminates:

- dangerous pyrophoric reagents used, e.g. n-butyllithium,
- silyl-protecting group chemistry; therefore, highly corrosive hydrogen fluoride (HF)
- large volumes of petroleum solvents, e.g. hexanes and tetrahydrofuran

Contact
Isi Davis
Tech Marketing Manager
davisnin@msu.edu
517.884.1829

Current 11-Step Semisynthesis of Docetaxel (Taxotere® Synthesis)

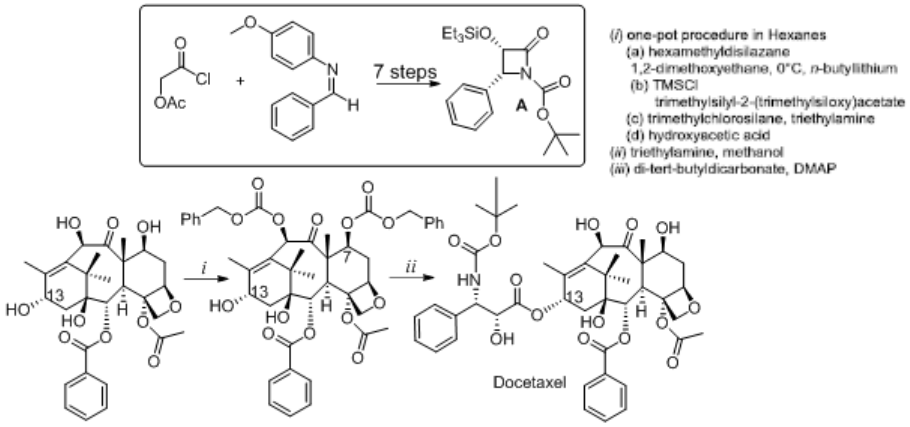

Fig. 5: Petroleum solvents are used throughout the complete semisynthesis process.

Proposed 4-Step Semi-biosynthesis of Docetaxel

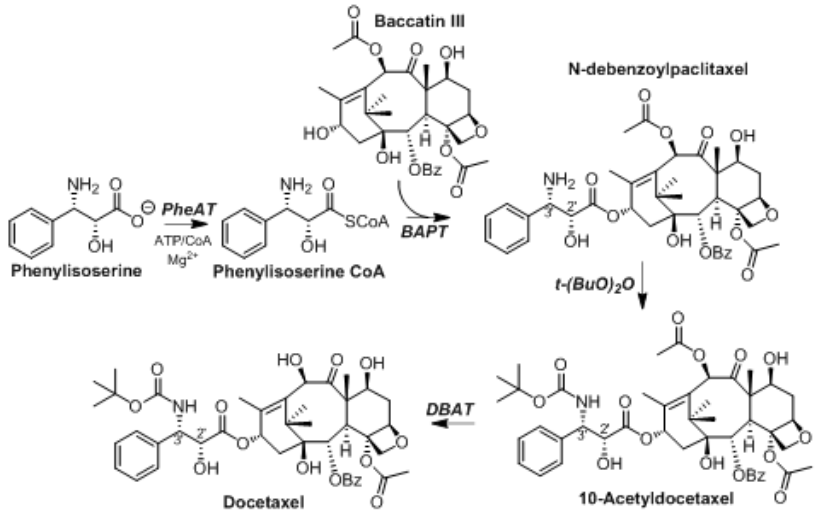

Fig. 6: Coupled-enzyme biosynthesis to make docetaxel (Taxotere). PheAT: CoA Ligase adenylation/thiolation domains, BAPT: maltose binding protein fusion with baccatin III phenylpropanoyltransferase, DBAT: 10-deacetylbaccatin III acetyltransferase.

Key Benefits:

- Reduced handling
- Water-based buffer steps reduce use of petroleum-based solvents such as hexanes and tetrahydrofuran
- Elimination of dangerous pyrophoric reagents used, e.g. n-butyllithium

Semi-biosynthesis of paclitaxel analogues, using water-based enzyme catalysts, is an important step toward a more economic, safer & greener production process.

Contact
Isi Davis
Tech Marketing Manager
davisnin@msu.edu
517.884.1829