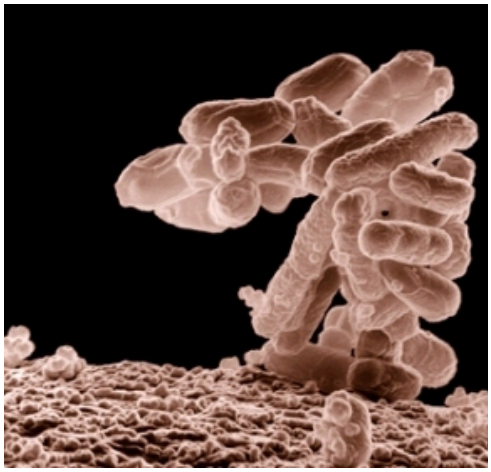
Getting bacteria to do a plant's job

Researchers engineer microbes for low-cost production of pr of anticancer drug Taxol and other pharmaceuticals.

Anne Trafton, MIT News Office

October 1, 2010



A close-up view of E. coli.

Throughout human history, plants have been a source of potent medicines, including many cancer drugs discovered over the past few decades. However, it is quite difficult to discover such drugs and obtain them in large quantities from the plants or through chemical synthesis.

MIT researchers and collaborators from Tufts University have now engineere bacteria to produce large quantities of a critical compound that is a precurso cancer drug Taxol, originally isolated from the bark of the Pacific yew tree. Tl can produce 1,000 times more of the precursor, known as taxadiene, than ar engineered microbial strain.

The technique, described in the Oct. 1 issue of *Science*, could bring down th manufacturing costs of Taxol and also help scientists discover potential new cancer and other diseases such as hypertension and Alzheimer's, said Greg Stephanopoulos, who led the team of MIT and Tufts researchers and is one authors of the paper.

"If you can make Taxol a lot cheaper, that's good, but what really gets people the prospect of using our platform to discover other therapeutic compounds declining new pharmaceutical products and rapidly escalating costs for drug development," said Stephanopoulos, the W.H. Dow Professor of Chemical Er MIT.

Taxol, also known as paclitaxel, is a powerful cell-division inhibitor commonly treat ovarian, lung and breast cancers. It is also very expensive — about $1(dose, although the cost of manufacturing that dose is only a few hundred dol (Patients usually receive one dose.)

Two to four Pacific yew trees are required to obtain enough Taxol to treat on in the 1990s, bioengineers came up with a way to produce it in the lab from c plant cells, or by extracting key intermediates from plant material like the nee decorative yew. These methods generate enough material for patients, but d produce sufficient quantities for synthesizing variants that may be far more p treating cancer and other diseases. Organic chemists have succeeded in syr Taxol in the lab, but these methods involve 35 to 50 steps and have a very lc they are not economical. Also, they follow a different pathway than the plants makes it impossible to produce the pathway intermediates and change them new, potentially more powerful variations.

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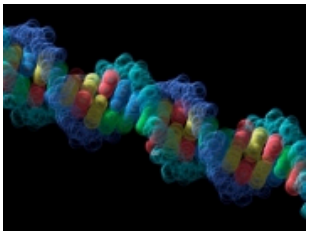

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“By mimicking nature, we can now begin to produce these intermediates that makes, so people can look at them and see if they have any therapeutic pro Stephanopoulos. Moreover, they can synthesize variants of these intermedia have therapeutic properties for other diseases.

Improving efficiency

The complex metabolic sequence that produces Taxol involves at least 17 in steps and is not fully understood. The team's goal was to optimize productio two Taxol intermediates, taxadiene and taxadien-5-alpha-ol. E. coli does not produce taxadiene, but it does synthesize a compound called IPP, which is tw away from taxadiene. Those two steps normally occur only in plants. MIT pos associate Ajikumar Parayil recognized that the key to more efficient productic integrated pathway that does not allow potentially toxic intermediates to accu accomplish this, researchers took a two-pronged approach in engineering E. produce taxadiene.

First, the team examined the IPP pathway, which has eight steps, and focuse those reactions that had been determined to be bottlenecks in the synthesis there is not enough enzyme at those steps, so the entire process is slowed d then engineered the bacteria to express multiple copies of those four genes, the bottlenecks and speeding up IPP production.

To get E. coli to convert IPP to taxadiene, the researchers added two plant g modified to function in bacteria, which code for the enzymes needed to perfo reactions. They also varied the number of copies of the genes to find the mo combination. These methods allowed the researchers to boost taxadiene pro 1,000 times over levels achieved by other researchers using engineered E. c 15,000 times over a control strain of E. coli to which they just added the two plant genes but did not optimize gene expression of either pathway.

Following taxadiene synthesis, researchers advanced the pathway by adding critical step toward Taxol synthesis, the conversion of taxadiene to taxadien-5 This is the first time that taxadien-5-alpha-ol has been produced in microbes still several more steps to go before achieving synthesis of the intermediate b from which Taxol can be chemically synthesized. “Though this is only a first s very promising development and certainly supports this approach and its pot Blaine Pfeifer, assistant professor of chemical and biological engineering at author of the *Science* paper.

Now that the researchers have achieved taxadiene synthesis, there are still a to 20 steps to go before they can generate Taxol. In this study, they showed can perform the first of those steps.

Joseph Chappell, professor of plant sciences at the University of Kentucky, s team’s yield of taxadiene is impressive, but the addition of several hydroxyl m which is required to produce baccatin III, will likely prove more difficult. “They’ one (hydroxylation), but it remains to be seen if they’ll be able to couple this other hydroxylation events needed to build the baccatin III molecule,” he said

Stephanopoulos and Pfeifer expect that if this technique can eventually be u manufacture Taxol, it would reduce significantly the cost to produce one gram drug. Researchers could also experiment with using these bacteria to create