Bacteria used as factories to produce cancer drugs

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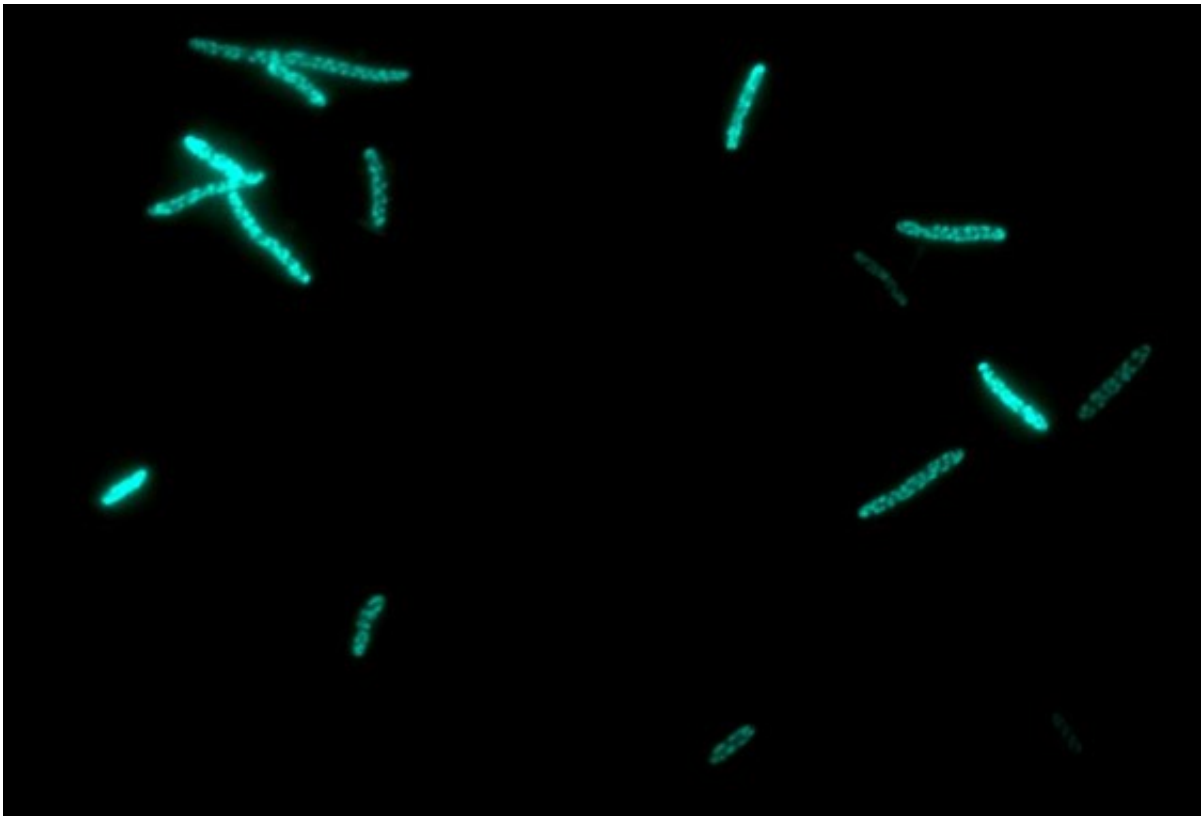

Factories of E. coli bacteria, producing P450, bound to green fluorescent protein. Credit: DTU

Researchers at the Novo Nordisk Foundation Center for Biosustainability in Denmark have developed a method of producing P450 enzymes used by plants to defend against predators and microbes in bacterial cell factories. The process could facilitate the production of

large quantities of the enzymes, which are also involved in the biosynthesis of active ingredients of cancer drugs.

P450 is the name of a type of cytochrome, a specialised enzyme. These are used by plants to synthesise chemical compounds with many different functions, but their main use is in defending against herbivores, insects and microbes.

"These powerful compounds can be used as active ingredients in drugs for treating diseases such as cancer and psoriasis," SINC was told by the Spanish researcher Darío Vázquez-Albacete, the lead author of a paper describing a new method of producing the enzymes in bacterial cell factories.

The findings of the study, developed at the Novo Nordisk Foundation Center for Biosustainability, a research facility managed by the Technical University of Denmark, were published in the journal *Biotechnology and Bioengineering*.

According to Vázquez-Albacete, "the new technique is a significant step forward, as plants produce P450 enzymes in very small amounts, extraction is very complex and sometimes we have to use polluting chemical synthesis processes which involve the use of oil derivatives. Additionally, some plant species such as the yew (Taxus baccata), from which the cancer drug Taxol is obtained, are endangered species."

Large-scale production

"We have developed tools which will allow the proteins from plants that produce these compounds to be recognized by the bacterial molecular machinery. The aim is to use bacteria because they arecapable of growing rapidly in controlled fermenters, allowing us to produce large quantities of the enzymes," says the researcher.

To achieve these results, the researchers modified and transferred P450 genes from plants to E. Coli bacteria and to check whether the microbes could produce larger quantities of these enzymes than existing methods.

Vázquez-Albacete says that "in order for the bacteria to properly express the enzymes, the corresponding DNA sequence must frequently be modified to facilitate 'decoding' by the bacteria's system."

In the study, the team developed a toolbox of 'auxiliary' DNA sequences, allowing them to express around 50 P450 enzymes from different plants in E. coli.

Some of these enzymes are involved in synthesising the natural compound ingenol, which is used to treat psoriasis and is currently manufactured using traditional chemical techniques. Other P450s are used to produce the cancer drug Taxol.

The researcher stresses that plants generate a variety of interesting compounds to protect them from the sun and from predators, dehydration, etc. "Many of these are synthesised by P450s, whose function is still very little understood, so there is enormous potential to discover new compounds."

More information: Dario Vazquez-Albacete et al. An expression tag toolbox for microbial production of membrane bound plant cytochromes P450, *Biotechnology and Bioengineering* (2017). DOI: 10.1002/bit.26203

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