Researchers genetically engineer micro-organisms into tiny factories

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Microorganisms may soon be efficiently and inexpensively producing novel pharmaceutical compounds, such as flavonoids, that fight aging, cancer or obesity, as well as high-value chemicals, as the result of research being conducted by University at Buffalo researchers.

In work that could transform radically the ways in which many of these compounds are produced commercially, the UB researchers are genetically engineering microorganisms, such as E. coli, into tiny, cellular factories. Several patents related to this work have been filed by UB. The team also is in discussions with companies in the U.S. and abroad.

First Wave Technologies, Inc., a technology development company based in UB's New York State Center of Excellence in Bioinformatics and Life Sciences, which is collaborating with the UB group, recently received a highly competitive Phase I Small Business Innovation Research (SBIR) grant from the National Science Foundation to focus on the biosynthesis of a popular group of flavonoids called isoflavonoids.

"Ultimately, we want to be able to take a designed E. coli off of the shelf and drop into it the enzymes that constitute a particular biosynthetic pathway in order to make exactly the product we want," said Mattheos A. G. Koffas, Ph.D., assistant professor of chemical and biological engineering in the School of Engineering and Applied Sciences and leader of the UB team.

The UB approach to synthetic chemistry addresses some of the major challenges in conventional industrial production of specialty chemicals.

Through the use of specially adapted bacteria, specialized enzymes and natural feedstocks, microbial biosynthesis reduces or eliminates the need for petrochemical sources, elevated temperatures, toxic heavy metal catalysts, extremes of acidity and dangerous solvents, Koffas said.

In addition, the natural enzymes the UB researchers are using can facilitate chemical reactions that are difficult to accomplish through conventional chemistry, such as chiral synthesis, glycosylations and targeted hydroxylations, common but challenging steps in many syntheses.

“We are finding out how we can actually ‘train’ microbial systems to produce high yields of chemicals to be used as pharmaceuticals and to make production processes more efficient, less expensive and more environmentally friendly,” Koffas said.

As with any commercial endeavor, process efficiency is a critical concern, he noted.

In work published in Applied and Environmental Microbiology in June, Koffas and his colleagues produced about 400 milligrams of flavonoids per liter of cell culture, far above the next highest yield of about 20 milligrams per liter produced by other microbial synthesis efforts.

“We have done this by increasing the amount of precursor available and re-engineering the native microbial metabolism,” he explained, adding that they have taken different approaches to identifying the pathways that lead to the biosynthesis of precursors for desired compounds.

“Further improvement of production yields are possible and various

approaches are being pursued by our team at this time," he said.

Another major challenge for microbial biosynthesis is that the enzymes required for certain chemical steps have special requirements that the host cell cannot meet efficiently, Koffas said. In some cases, the enzyme needs to be re-engineered, while in others the host cell needs modification.

Koffas' lab recently achieved the functional expression in E. coli of P450 monooxygenases, enzymes that are used widely in nature, but are not readily expressed in most industrially important microorganisms.

"P450 is very important in the synthesis of natural products," said Koffas. "For example, both Taxol, the breast cancer drug that is currently produced from plant cultures, and artemisinin, the anti-malaria drug, have P450 enzymes in their biosynthetic pathways."

The Koffas lab has introduced ways to modify both the P450 monooxygenase enzymes and the host cell, thereby improving their yield of flavonoids.

Microbial biosynthesis methods also are making it easier to create analogs of existing drugs, as well as new molecules for a broad range of therapeutics.

The UB researchers are particularly interested in developing novel molecules that can be used to treat chronic diseases, such as type II diabetes and obesity.

They also are using the methods to produce specialty compounds, such as natural pigments, that could replace chemical dyes in food.

Koffas' goal is to employ these microbial synthesis methods for a wide

variety of applications.

Flavonoids, which are of interest to pharmaceutical companies because of their antioxidant and anti-carcinogenic properties, are difficult to produce using currently available methods.

Microbial synthesis strategies also are being adapted by the UB researchers for the biosynthesis of other commercially significant classes of compounds, including vitamins, anti-cancer drugs, anti-parasitic drugs, dyes and food supplements.

The UB group is working on boosting yields further and hopes to achieve pilot scale production of flavonoids by the end of this year.

Source: University at Buffalo

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