Engineers build mini drug-producing biofactories in yeast

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Researchers at the California Institute of Technology have developed a novel way to churn out large quantities of drugs, including antiplaque toothpaste additives, antibiotics, nicotine, and even morphine, using mini biofactories--in yeast.

A paper describing the research, now available online, will be featured as the cover article of the September issue of *Nature Chemical Biology*.

Christina D. Smolke, an assistant professor of chemical engineering at Caltech, along with graduate student Kristy Hawkins, genetically modified common baker's yeast (Saccharomyces cerevisiae) so that it contained the genes for several plant enzymes. The enzymes allow the yeast to produce a chemical called reticuline, which is a precursor for many different classes of benzylisoquinoline alkaloid (BIA) molecules. The BIA molecules are a large group of chemically intricate compounds, such as morphine, nicotine, and codeine, which are naturally produced by plants.

BIA molecules exhibit a wide variety of pharmacological activities, including antispasmodic effects, pain relief, and hair growth acceleration. Other BIAs have shown anticancer, antioxidant, antimalarial, and anti-HIV potential.

"There are estimated to be thousands of members in the BIA family, and having a source for obtaining large quantities of specific BIA molecules is critical to gaining access to the diverse functional activities provided

by these molecules," says Smolke, whose lab focuses on using biology as a technology for the synthesis of new chemicals, materials, and products. However, the natural plant sources of BIAs accumulate only a small number of the molecules, usually "end products" like morphine and codeine that, while valuable, can't be turned into other compounds, thus limiting the availability of useful new products.

To their reticuline-producing yeast, Smolke and Hawkins added the genes for other enzymes, from both plants and humans, which allowed the yeast to efficiently generate large quantities of the precursors for sanguinarine, a toothpaste additive with antiplaque properties; berberine, an antibiotic; and morphine.

The researchers are now in the process of engineering their yeast so that they will turn these precursor molecules into the final, pharmacologically useful molecules. "But even the intermediate molecules that we are producing can exhibit important and valuable activities, and a related area of research will be to examine more closely the pharmacological activities of these metabolites and derivatives now that pure sources can be obtained," says Smolke, who estimates that her system could be used for the large-scale manufacture of BIA compounds in one to three years.

Smolke and Hawkins also plan to extend their research to the production of BIAs that don't normally exist in nature.

"If one thinks of these molecules as encoding functions that are of interest to us, the ability to produce nonnatural alkaloids will provide access to more diverse functions and activities. By expanding to nonnatural alkaloids, we can search for molecules that provide enhanced activities, new activities, and not be limited by the activities that have been selected for in nature," says Smolke.

"Our work has the potential to result in new therapeutic drugs for a

broad range of diseases. This work also provides an exciting example of the increased complexity with which we are engineering biological systems to address global societal challenges," she says.

Source: California Institute of Technology