Researchers develop a yeast-based platform to boost production of rare natural molecules

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Many modern medicines, including analgesics and opioids, are derived from rare molecules found in plants and bacteria. While they are effective against a host of ailments, a number of these molecules have proven to be difficult to produce in large quantities. Some are so labor intensive that it is uneconomical for pharmaceutical companies to produce them in sufficient amounts to bring them to market.

In a new study published in *Nature Communications*, Vincent Martin outlines a method to synthesize complex bioactive molecules much more quickly and efficiently.

One of the principal ingredients in this new technique developed by the biology professor and Concordia University Research Chair in Microbial Engineering and Synthetic Biology is simple baker's yeast.

The single-cell organism has cellular processes that are similar to those of humans, giving biologists an effective substitute in drug development research. Using cutting-edge synthetic biology approaches, Martin and his colleagues in Berkeley, California were able to produce a large amount of benzylisoquinoline alkaloid (BIA) to synthesize an array of natural and new-to-nature chemical structures in a yeast-based platform.

This, he says, can provide a blueprint for the large-scale production of thousands of products, including the opioid analgesics morphine and codeine. The same is true for opioid antagonists naloxone and naltrexone, used to treat overdose and dependence.

A long journey from gene to market

Martin has been working toward this outcome for most of the past two decades. He began with researching the genetic code plants use to produce the molecules used as drugs by the pharmaceutical industry. Then came transplanting their genes and enzymes into yeast to see if production was possible outside a natural setting. The next step is industrial production.

"We showed in previous papers that we can get milligrams of these molecules fairly easily, but you're only going to be able to commercialize the process if you get grams of it," Martin explains. "In principle, we now have a technology platform where we can produce them on that scale."

This, he says, can have huge implications for a country like Canada, which has to import most of the rare molecules used in drugs from overseas. That's especially relevant now, in the midst of a global pandemic, when fragile supply chains are at risk of being disrupted.

"To me, this really highlights the importance of finding alternative biotech-type processes that can be developed into a homemade, Canadian pharmaceutical industry," he adds. "Many of the ingredients we use today are not very difficult to make. But if we don't have a reliable supply process in Canada, we have a problem."

Healthy savings

Martin admits he is curious to see where the technology leads us. He believes researchers can and will use the new platform for the commercialization and discovery of new drugs.

"We demonstrate that by using this platform, we can start building what is called new-to-nature molecules," he says. "By experimenting with enzymes and genes and the way we grow things, we can begin making these into tools that can be used in the drug discovery process. We can access a whole new structural space."

More information: Michael E. Pyne et al, A yeast platform for high-level synthesis of tetrahydroisoquinoline alkaloids, *Nature Communications* (2020). DOI: 10.1038/s41467-020-17172-x

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