SYNTHETIC BIOLOGY

Modified yeast produce opiates from sugar

Engineered microbes raise hopes for better medicines and concerns about illicit drugs

By **Robert F. Service**

Move over, poppies. In one of the most elaborate feats of synthetic biology to date, a research team has engineered yeast with a medley of plant, bacterial, and rodent genes to turn sugar into thebaine, the key opiate precursor to morphine and other powerful painkilling drugs that have been harvested for thousands of years from poppy plants. The team also showed that with further tweaks, the yeast could make hydrocodone, a widely used painkiller that is now made chemically from thebaine.

"This is a major milestone," says Jens Nielsen, a synthetic biologist at Chalmers University of Technology in Göteborg, Sweden. The work, he adds, demonstrates synthetic biology's increasing sophistication at transferring complex metabolic pathways into microbes.

By tweaking the yeast pathways, medicinal chemists may be able to produce more effective, less addictive versions of opiate painkillers. But some biopolicy experts worry that morphinemaking yeast strains could also allow illicit drugmakers to brew heroin as easily as beer enthusiasts home brew today—the drug is a simple chemical conversion from morphine. That concern is one reason the research team, led by Christina Smolke, a synthetic biologist at Stanford University in Palo Alto, California, stopped short of making a yeast strain with the complete morphine pathway; medicinal drug makers also primarily use thebaine to make new compounds.

Synthetic biologists had previously engineered yeast to produce artemisinin, an antimalarial compound, but that required inserting just a handful of plant genes. To get yeast to make thebaine, Smolke's team coaxed the cells to express 21 genes in total, including many added from a diverse set of species (see graphic); making hydrocodone took 23 genes.

Their success, reported online this week in *Science*, caps a race to install the complex opioid pathway in yeast. Last year, Smolke's team reported engineering yeast to carry out the tail end of the process, going from thebaine to morphine. In April, Vincent Martin, a microbiologist at Concordia University in Montreal, Canada, and his colleagues said they had created yeast that could go from an earlier intermediate compound called R-reticuline to morphine. A few weeks later, John Dueber, a synthetic biologist at the University of California, Berkeley, and colleagues announced yeast that carries out most of the first half of the pathway, going from glucose to another intermediate compound, S-reticuline. Finally, two groups reported in late June that they had identified the long-sought enzyme needed to carry out the chemical transformation in the middle, S-reticuline to R-reticuline.

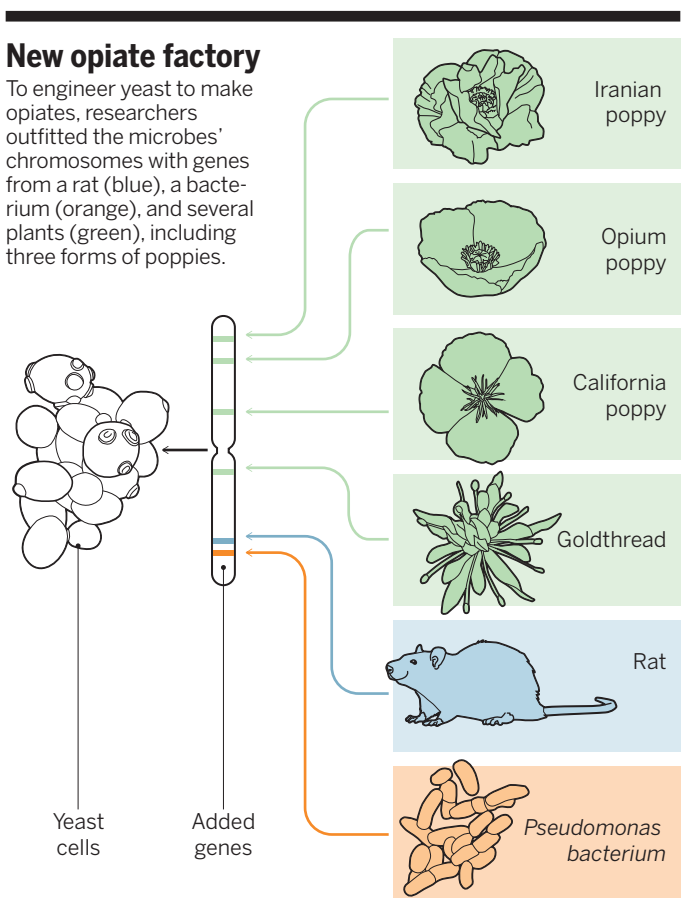
Even so, many predicted it would take years to put all the pieces together. As it turns out, back in May, Smolke and her colleagues had already largely finished the task. "It shows this field is really moving fast," says Kenneth Oye, a biotechnology policy expert at the Massachusetts Institute of Technology in Cambridge.

The most important challenge, Smolke says, was increasing the efficiency of each step so losses wouldn't build up. In one step, for example, a plant enzyme called SalSyn was doing a poor job of converting R-reticuline to another compound called salutaridine. Eventually, Smolke's team discovered that the yeast made the enzyme incorrectly, attaching the wrong sugars to it. The researchers fixed the problem by reengineering the inserted plant gene.

Smolke plans to go on tinkering. The microbes need to increase output of thebaine by a factor of 100,000 for drug companies to be interested in using them to make medicines. That won't be easy. But Martin notes that researchers boosted the output of the artemisininmaking yeast by a similar amount. "It will happen," he says. "The only question is how fast." Smolke recently formed a company called Antheia, based in Palo Alto, that aims to push that pace.

To keep up with the yeast engineers, Oye says policy experts need to develop rules to limit the risk of unintended uses of engineered microbes. In the case of opiatemaking yeast, such rules might forbid developing strains to produce illicit drugs, such as heroin, and require scientists to build in genes that prevent the microbes from living outside of a controlled laboratory environment.

Not everyone is worried about home-brewed opiates. Andrew Ellington, a synthetic biologist at the University of Texas, Austin, calls such fears "overblown." The idea that producing vanishingly small quantities of opiates through fermentation is somehow going dwarf the problem of illegal drugs made from poppies is "laughable," he says. But Martin disagrees. "Poppy fields are not readily available to someone in Chicago, whereas yeast can be made available to anyone." ■



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