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EMBO reports

Opinion

"Poppy" yeast

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I am old enough to have taken part in the international project to sequence the first eukaryotic genome—that of *Saccharomyces cerevisiae*—which was released in 1996. Twenty years later, scientists from academic and commercial institutions are now involved in the first wholesale construction of a eukaryotic genome: the Yeast 2.0 Project [1]. The construction of whole genomes from scratch is defined as a *bottom-up approach* in synthetic biology. One of the aims of such work is to reduce genome size and construct a minimal cell factory for industrial applications. These synthetic yeast chromosomes will have unique features to allow scientists to easily reshuffle, eliminate or add new genes [2] in order to engineer cells for efficient production of a desired compound. Synthetic biologists also use a *top-down* approach to insert functional biological components into natural genomes. This has been used in yeast to produce natural molecules of pharmaceutical value, such as artemisinin acid [3]. Currently, many compounds are not chemically synthesized because it is cheaper and more efficient to extract them from plants. The products of synthetic biology could easily replace plants as the source, especially as yeast fermentation is a matter of days, while plants need months or years to grow.

Saccharomyces cerevisiae is a generally safe organism that has been used for thousands of years to produce wine, beer, bread and chocolate. But the recent publication of an elegant piece of synthetic biology could transform this mostly harmless organism into an "illicit" one: Smoke and co-workers have expressed in yeast the entire biosynthetic pathway of thebaine, a precursor of morphine, and the semi-synthetic opioid hydrocodone, by combining genes from plants, mammals and bacteria [4]. They used yeast as a production platform because it allowed them to perform spatial engineering—that is, expressing heterologous genes in different organelles such as mitochondria and the endoplasmic reticulum. This amazing achievement opens up the possibility to produce codeine or morphine by fermentation [5, 6]. These drugs, which are of great pharmaceutical value, are used for pain relief and are usually extracted from the plant *Papaver somniferum* because their chemical synthesis is not commercially competitive. At present, the yields from yeast are not high, but it seems inevitable that *bottom-up* and *top-down* technology will eventually combine to introduce the entire biosynthetic opiates pathway into a yeast synthetic genome to generate cells that overproduce morphine—which is classified by most countries as a dangerous narcotic, aside from its medical use, and can be processed into heroine.

Is the scientific community ready to manage the consequences of the fruits of synthetic biology? I see two concerns on which we should reflect. First, morphine-producing yeast are a clear case of dual-use technology: they could either be used to produce cheaper, less addictive, safer and more effective analgesics, or they could be used to produce illicit drugs from ubiquitous substrates by fermentation. There are historic examples from periods of prohibition in the USA and elsewhere that show that it is nigh impossible to stop bootleggers from abusing cheap and easy-to-use technology to produce illegal narcotics. Unfortunately, technology does not come much cheaper or easier than yeast cells, which can be easily cultured and transported—sealed in a sterile pot of anti-wrinkle cream on an airplane, for example, as I have done with my favourite yeast mutants. The authors of the current study were well aware of the dual-use nature of their work, so they contacted technology policy experts [7] and have taken a number of precautions to avoid illicit use of such strains.

Second, I believe that there should be a broad and ongoing dialogue between researchers, health experts, scientists and law enforcement agencies in order to monitor the progress of synthetic biology projects with dual-use applications; for instance, a yeast cell factory able to produce botulinum toxin for therapeutic use could also be used as a biological weapon. International regimes on dual-use control, such as the Australia Group, are already monitoring new and evolving technologies, including synthetic biology, given their potential for abuse. I hope that, in the future, engineered yeast strains to produce dual-use molecules or illicit drugs, which are so far not included in any controlled biological agent lists, would be at least restricted to facilities or laboratories with an appropriate licence.

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