COMMENT

JEROME SESSINI/MAGNUM

Illegal use of opiates such as heroin and morphine affects more than 16 million people worldwide.

Regulate 'home-brew' opiates

The research community and the public require a fast, flexible response to the synthesis of morphine by engineered yeasts, urge **Kenneth Oye**, **Tania Bubela** and **J. Chappell H. Lawson**.

Every year, thousands of students from across the world compete to build biological systems from pre-existing parts in a competition organized by the International Genetically Engineered Machine (iGEM) Foundation. Last November, to spark discussion on security and health risks raised by synthetic biology, FBI Special Agent Edward You presented an example: the production of opiates from sugar by yeast (*Saccharomyces cerevisiae*) that has been genetically modified.

You's hypothetical scenario is becoming a reality. One week after the iGEM competition, two developers of opiate-producing yeast strains approached us, specialists in biotechnology policy. They had results in advance of publication, and requested advice on how they might maximize the benefits of their research while mitigating the risks. Now, published papers by these researchers — John Dueber at the University of California, Berkeley, and his colleagues[1], and Vincent Martin ▶

of Concordia University in Montreal, Canada, and his colleagues[2] — describe all but one step of an engineered yeast pathway that converts glucose to morphine (see ‘Brewing bad’). Meanwhile, researchers at the University of Calgary have put in place the final piece[3].

Currently, morphine is produced from the opium poppy (*Papaver somniferum*). By providing a simpler — and more manipulable — means of producing opiates, the yeast research could ultimately lead to cheaper, less addictive, safer and more-effective analgesics. And in generating a drug source that is self-replicating and easy to grow, conceal and distribute, the work could also transform the illicit opiate marketplace to decentralized, localized production. In so doing, it could dramatically increase people’s access to opiates.

In recent years, synthetic biologists have produced numerous benign products — antimalarials, scents, flavours, industrial chemicals and fuels — by modifying yeast, bacteria and eukaryotic plants. Opiate synthesis is the first example of synthetic biology facilitating the production of a controlled narcotic; other new production systems for potentially problematic compounds will almost certainly follow.

The synthetic-biology community, in tandem with regulators, needs to be proactive in evaluating the costs and benefits of such dual-use technologies[4]. Here we lay out the priorities for discussions that are crucial to public health and safety, and to the progress of synthetic biology more broadly. These include restricting engineered yeast strains to licensed facilities and authorized researchers and technicians; reducing the attractiveness of engineered yeast strains in the illicit marketplace; and implementing a regulatory approach that is flexible and responsive to changes in understanding and capabilities.

COMPLETE PATHWAY

The technology to make morphine from glucose using yeast has been seven years in the making. Three groups of researchers introduced genetic components from poppy, beetroot and a soil bacterium into the yeast genome, creating strains that can perform chunks of the glucose-to-morphine pathway[1,2,5–7]. A fourth group has developed[3] a strain that can convert one of the intermediate compounds, (*S*)-reticuline, into another, (*R*)-reticuline. With this final step realized, the creation of a single strain of yeast capable of executing the entire pathway is feasible.

> ***“Yeast-based opiate synthesis could also have an significant effect on illicit markets.”***

In principle, anyone with access to the yeast strain and basic skills in fermentation would be able to grow morphine-producing yeast using a home-brew kit for beer-making. If the modified yeast strain produced 10 grams of morphine, users would need to drink only 1–2 millilitres of the liquid to obtain a standard prescribed dose. (Current strains are not this efficient, but titres in this range and even tenfold higher have been achieved for other commercially relevant metabolic products.)

Although this research is intended to enable synthetic production of opiates for legal pain relief, we perceive several challenges. To be competitive, yeast-based production must be more cost-effective than current systems, more secure and more acceptable to regulators, or provide less addictive, safer products. But most opiates are inexpensive to manufacture, administer and transport.

Advances in breeding high-yield poppies reduced the cost of the main wholesale product, known as concentrate of poppy straw, by 20% between 2001 and 2007 to US$300–$500 per kilogram. The design of more commercially valuable opiates will also require collaboration between synthetic biologists, neuroscientists and medicinal chemists among others, and will involve lengthy and expensive clinical trials. What is more, global supply and demand is tightly regulated to limit potential addiction.

LEGAL CONSIDERATIONS

Various international conventions and national laws are designed to prevent diversion to illegal markets. Countries that manufacture opiates commonly use large, secure industrial facilities. Australia further enhances security by growing a thebaine-rich poppy variety; thebaine is toxic to ingest and is not easily converted into morphine. It is difficult to predict how the main international body, the International Narcotics Control Board (INCB), would react to a new production system for opiates. The INCB is unlikely to slash current opium-production quotas and disrupt current legal opiate-trade patterns to accommodate yeast-based production. This would limit the ability of new producers to enter the market.

Meanwhile, yeast-based opiate synthesis could have a significant effect on illicit markets. Currently, opiates are sold illegally through two main channels. First, prescription pain medications such as oxycodone and hydrocodone are pilfered, prescribed improperly or prescribed legitimately but then sold on illegally by patients. Second, illegally cultivated opium poppies in countries such as Afghanistan, Myanmar, Laos and Mexico are processed into heroin and distributed by criminal networks that sell them at street prices several dozen times the production costs[8].

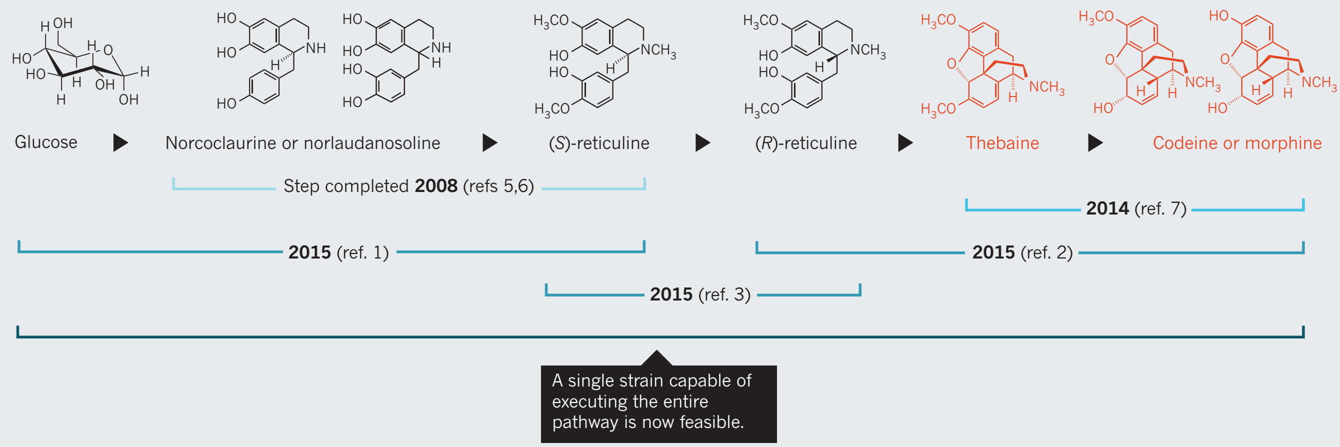
Yeast-based production of opiates could provide an alternative system for current criminal networks, particularly in North America and Europe, where the drugs are in high demand. Because yeast is easy to conceal, grow and transport, criminal syndicates and law-enforcement agencies would

HOW HWEE YOUNG/EPA/CORBIS

In principle, a home-brew kit for beer-making could be used to make morphine.

BREWING BAD

Researchers have completed all the steps of an engineered pathway in yeast that make the controlled substances thebaine and morphine from glucose.



have difficulty controlling the distribution of an opiate-producing yeast strain. All told, decentralized and localized production would almost certainly reduce the cost and increase the availability of illegal opiates — substantially worsening a worldwide problem. Globally, more than 16 million people use opiates illegally.

FOUR RECOMMENDATIONS

There are two major challenges to developing and implementing a flexible and proportionate regulatory approach for this research. Current regulations for engineered organisms focus on pathogenic organisms such as the anthrax bacterium and smallpox, not on yeasts. And the array of national and international drug regulators and law-enforcement agencies that would need to be involved have different practices and norms.

Increased communication and coordination will be required among public-health experts, scientists, regulators and law-enforcement agencies. Potential international focal points for dialogue are the INCB and the international expert groups on biosafety and biosecurity regulation.

The following four issues warrant immediate consideration.

Engineering. Yeast strains should be designed to make them less appealing to criminals. For example, strains could be engineered to make only opiates with limited street value, such as thebaine. Alternatively, weaker strains could be engineered to make it harder for people to cultivate and harvest opiates outside established laboratory settings. Strains could be engineered with unusual nutrient dependencies, for instance. Such methods of 'biocontainment' have been developed in *Escherichia coli*. Opiate-producing yeast strains could also contain a marker, such as a DNA watermark, that makes them more readily identifiable to law-enforcement agencies.

Screening. Because there is some — albeit low — risk of criminal syndicates synthesizing opiate-producing yeast strains using published DNA sequences, commercial organizations that make stretches of DNA to order should be alerted. The sequences for opiate-producing yeast strains should be added to the screening criteria used by these providers. Overseen by two voluntary consortia, the International Association of Synthetic Biology and the International Gene Synthesis Consortium, these criteria currently cover only pathogens.

Security. Efforts should be made to keep opiate-producing yeast strains in controlled environments that are licensed by regulators. Physical biosecurity measures — including locks, alarms and systems for monitoring the use of laboratories and materials — could help to prevent the theft of yeast samples. Laboratory personnel should be subject to security screening. Similarly, assigning liability and penalties may dissuade researchers from sharing strains with anyone who is not legally authorized to work with them.

Regulation. The current laws covering opiates, such as the US Controlled Substance Act and its worldwide equivalents, should be extended to cover opiate-producing yeast strains, to make their release and distribution illegal.

The right choices in the regulation of this dual-use technology will set a precedent for other fast-emerging biotechnologies. In fact, biologists working on yeast-based opiates have already led the way on the most important aspect — namely, their willingness to take responsibility for the tools they are developing. But for them, this article would not have been written.

Other genomic engineers are following this path. Developers of the gene-editing tool CRISPR/Cas9 have called for proactive engagement with risks before altering populations of animals and plants in the wild or manipulating human reproductive cells[9,10]. With all the signs that synthetic biology is coming of age, this type of responsible conduct is imperative. ■ SEE NEWS P.267

Kenneth A. Oye *and* **J. Chappell H. Lawson** *are associate professors in the Department of Political Science, Massachusetts Institute of Technology, Cambridge, Massachusetts, USA.* **Tania Bubela** *is professor and associate dean for research at the School of Public Health, University of Alberta, Edmonton, Canada.*
e-mail: oye@mit.edu

1. DeLoache, W. C. *et al. Nature Chem. Biol.* http://dx.doi.org/10.1038/nchembio.1816 (2015).
2. Fossati, E., Narcross, L., Ekins, A., Falgueyret, J. P. & Martin, V. J. J. *PLoS ONE* **10,** e0124459 (2015).
3. Beaudoin, G. A. W. *Characterization of Oxidative Enzymes Involved in the Biosynthesis of Benzylisoquinoline Alkaloids in Opium Poppy* (Papaver somniferum). PhD thesis, Univ. Calgary (2015); available at http://hdl.handle.net/11023/2115
4. Bubela, T., Hagen, G. & Einsiedel, E. *Trends Biotechnol.* **30,** 132–137 (2012).
5. Hawkins, K. M. & Smolke, C. D. *Nature Chem. Biol.* **4,** 564–573 (2008).
6. Fossati, E. *et al. Nature Commun.* **5,** 3283 (2014).
7. Thodey, K., Galanie, S. & Smolke, C. D. *Nature Chem. Biol.* **10,** 837–844 (2014).
8. International Narcotics Control Board. *Report of the International Narcotics Control Board on the Availability of Internationally Controlled Drugs: Ensuring Adequate Access for Medical and Scientific Purposes* (INCB, 2011).
9. Oye, K. A. *et al. Science* **345,** 626–628 (2014).
10. Baltimore, D. *et al. Science* **348,** 36–38 (2015).