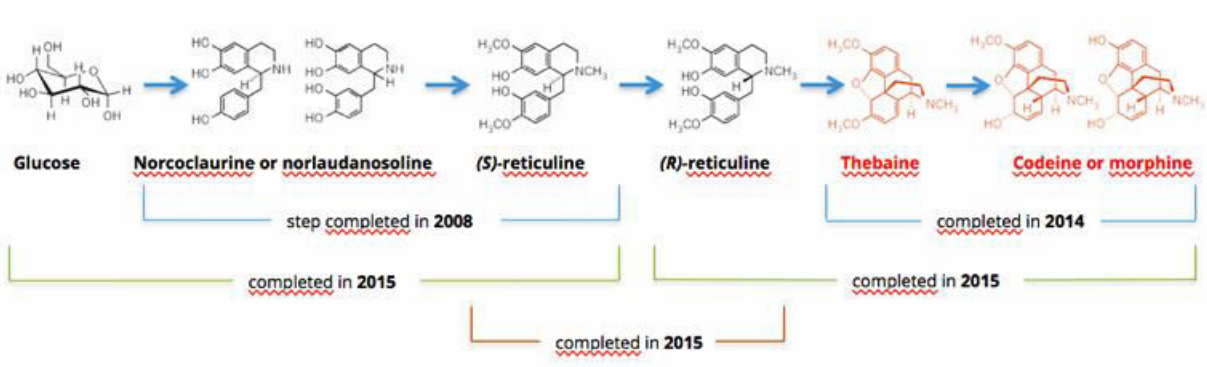
Home-brewed opiates: A call for governance

Recently developed technology to make morphine and other opiates from glucose with synbio-engineered yeast may have an advantage in terms of cost-effectiveness, secureness, safety and decreased addictiveness compared with conventional opiates produced from poppies. But it can also transform the illicit market place. Three scientists from MIT, Boston and the University of Alberta, Canada, call for measures to regulate dual-use.

Producing opiates from yeast

In the 18 May 2015 edition of Nature Chemical Biology a group of US and Canadian scientists describes how they developed a yeast strain that can convert (S)-Reticuline, one of the intermediate compounds in the metabolic pathway of Benzylisoquinoline Alkaloids (BIAs) form glucose[i]. BIAs are a diverse family of plant-specialized metabolites that include codeine and morphine and their derivates. (S)- Reticulin synthesis was already possible in E. coli, but no steps downstream of this intermediate have since been demonstrated in E. coli. Downstream steps have been achieved in bakers yeast *(Saccharomyces cervisiae*[1]): Three other groups recently (and partly simultaneously) published research in which they successfully introduced genes from poppy, beetroot and a soil bacterium responsible for other steps in the metabolic pathway of BIAs in the genome of this well-known production organism [ii]. The possibility to introduce all necessary steps of BIAs' metabolic pathway in the same organism is a great step forward.



Introduction of steps in the metabolic pathway from glucose to opiates and bakers yeast

[1] *Saccharomyces cervisiae* has been instrumental to winemaking, baking and brewing since ancient times.

These achievements would not have been possible without the help of powerful next-generation DNA sequencing (also known as high-throughput sequencing) to elucidate complex metabolic pathways in plants and powerful synthetic biology tools for genetically manipulating cells with new properties faster, cheaper and easier.

Promises

"Microbial synthesis of BIAs holds promises on alternatives to traditional crop-based manufacturing", the research group from the US and Canada writes. Several attempts to increase the yields –and thus decreasing costs- in plant-derived opiates have not been very successful. Although the scientists note that further optimization of yiels in the microbial system is required before production of downstream BIAs is feasible, others point at previous experience with other commercially relevant metabolic products, which shows that it is feasible to do so.
Apart from direct benefits in terms of cheaper drugs to alleviate pain, the US/Canadian research group speculates on more general benefits: "The length and complexity of the BIA pathway also presents a formidable engineering challenge that is likely to spur the development of new tools and techniques for controlling the metabolism of microorganisms."

Dual use

Notwithstanding the potential benefits, there is also a downside to this technology, the US/Canadian team argues: "Because the potential for illicit use of the(se) products, including morphine and its derivates, it is critical that appropriate policies for controlling such strains be established so that we can govern the considerable benefits while minimizing the potential for abuse". In Nature's edition of 21 May 2015 three scientists from MIT, Boston, and the School for Public Health, University of Alberta, further elaborate on the dual-use issue and regulation: "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", they write[iii]. They argue that a drug source like yeast, which is self-replicating and easy to grow, could provide criminal syndicates with an alternative to plant-based opiates, particularly in North America and Europe. Localized production would reduce the costs and increase availability of illegal opiates, thus worsening a worldwide problem of abuse and addiction. Moreover, yeast is also easy to conceal, grow and transport, which would make it more difficult to control the distribution by law enforcement agencies.

Governance: 4 measures

The scientist propose 4 types of measures that should limit the possibilities of dual-use: technical measures, screening, security measures and regulation.

Examples of technical measures are the design of yeast strains that are less appealing to criminals, e.g. by focusing on opiates with less street value such as thebaine, biocontainment measures that make it difficult to grow the yeast outside a professional

lab or applying a DNA watermark by which organisms can be traced.

Screening of orders for synthesized DNA sequences that could be used in constructing opiate-producing yeast and customers of DNA synthesis services was already proposed several years ago[2].

In addition to measures designed to keep the yeast strain in controlled environments that are licensed by regulators for biosafety reasons, security measures should be designed to avoid 'intended escape' of the yeast strain for illicit use, such as screening of lab personnel.

The Single Convention on Narcotic Drugs (SCND) of 1961 is an international treaty to prohibit production and supply of specific (nominally narcotic) drugs and of drugs with similar effects except under licence for specific purposes, such as medical treatment and research. The SCND entered into force in August 1975 and as of February 2015 it is signed by 185 state parties, which includes all members of the United Nations with the exception of 3 African and 6 small states in the South Pacific. Article 23 of the SCND, which sets the rules for National Opium Agencies, typically focuses on cultivation of opium poppy. Like the SCND existing laws do not yet take into account the possibility of bioengineered yeast strains and should therefore be extended to opiate-producing yeast strains.

Discussion

Before further discussing proposed measures to avoid illicit use of any technology or application we should reflect more on the question whether (widespread) illicit use is a real risk and what type of measures are effective. Will it really be easy for anyone with some basic knowledge and skills to construct and/or grow a yeast strain with a complex metabolic pathway for opiate production in sufficient quantities? If there is a real risk, then what can we learn from existing practices of illicit use, for instance in the production of chemical drugs such as methamphetamine, XTC or GHB? What measures would be most effective in terms of avoiding criminal practices and abuse?

Finally, we should also think of potential undesired side effects of new production methods for opiates and dual-use measures. Poppy growers risking to lose their source of income without being offered an alternative may have consequences for the economic and political stability of the whole region.

[2] See for instance:
Schmidt M, Giersch G. (2011) DNA Synthesis and Security. In: DNA Microarrays, Synthesis and Synthetic DNA. Editor: Marissa J. Campbell. Nova Publishers

Garfinkel M S, Endy D, Epstein GL, Friedmann RM (2007) Synthetic genomics: options for governance.

Strategies aiming for destruction of poppy fields were intensely debated during western military presence in Afghanistan. "Destroying poppy fields in isolation (i.e. without applying parallel measures) is counterproductive", the former Dutch minister of Defense wrote in response to questions from the national parliament concerning the poppy cultivation in the Uruzgan province of Afghanistan[3].

Poppy field in Afghanistan: Local economy at risk? (Photo by Davric, Wikimedia)

Provided that it is a real issue in the case of opiate producing yeast strains, the dual-use issue requires careful consideration of alternative options in the context of a complex reality. Thus type of debate should include more actors than scientists and security agencies. Active participation of stakeholders –those who can affect or will be affected by the introduction of a new technology- will help to broaden the debate and to include other perspectives and useful tacit knowledge[4].

References

[i] DeLoache, W.C. *et.al.* An enzyme-coupled biosensor enables (*S*)-reticuline production in yeast from glucose, *Nature Chem. Biol.* (2015), http://www.nature.com/nchembio/journal/vaop/ncurrent/full/nchembio.1816.html

[ii] Fossati, E. *et.al.* Synthesis of Morphinan Alkaloids in Saccharomyces cerevisiae. *PLoS ONE* **10**, e0124459 (2015), http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0124459 .

Beaudoin, G.A.W. Characterization of Oxidative Enzymes involved in the Biosynthesis of Benzylisoquinoline Alkaloids in Opium poppy (Papaver Sonferum). PhD thesis, Univ. of Calgary (2015), available at http://hdl.handle.net/11023/2115 .

Thodey, K, Galanie, S. & Smolke, C.D. A microbial biomanufacturing platform for natural and semisynthetic opioids. *Nature Chem. Biol.* **10**, 837-844 (2014), http://www.nature.com/nchembio/journal/v10/n10/abs/nchembio.1613.html .

[iii] Oye, Kenneth, Bubela, Tania & Chappell H. Lawson, J. Regulate 'home-brew' opiates. *Nature* **521**, 281-283 (2015), http://www.nature.com/news/drugs-regulate-home-brew-opiates-1.17563

[3] A Dutch 'Deployment Task Force' was active in the province of Uruzgan, Afghanistan, between March 2006 and August 2010

[4] The approach developed by the STEPS Centre in the UK is an example of more inclusive methods that have been developed in recent years. http://steps-centre.org/wp-content/uploads/final_steps_overview.pdf