Discovery opens door for synthetic opioids with less addictive qualities

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Making opioids from sugar instead of from field grown opium poppies has the potential to solve many of the problems associated with manufacturing strong pain killers.

Epimeron Inc. ("Epimeron"), a Calgary-based biotechnology company, has taken a major step toward that goal with its announcement of the isolation of a novel gene from the opium poppy (Papaver somniferum). The gene encodes the enzyme thebaine synthase, which had previously been hypothesized, but never found, until now. Thebaine is the essential starting point in the synthesis of widely-prescribed pharmaceuticals, including the analgesics oxycodone and hydrocodone and the addiction treatments buprenorphine and naltrexone.

The breakthrough announced today enables the completion of commercial, non-plant-based biosynthetic manufacturing systems for active opioid agents and intermediates. It also opens the door to the creation of new opioid molecules, some with new characteristics such as reduced addictiveness. The discovery was published May 28, 2018 in a *Nature Chemical Biology* article titled "A pathogenesis-related 10 protein catalyzes the final step in thebaine biosynthesis."

Microbial production of active pharmaceutical ingredients from sugar as source material promises to replace current opioid manufacturing methods that rely on opium poppies for raw ingredients. Current regulatory requirements and commercial practices require the importation of crushed poppy straw from producer countries such as India and Turkey. The imported ingredients are then processed locally to the final pharmaceutical products. Legal opium poppy farming in producer countries is plagued by diversion of legitimately made controlled substances into the illicit drug trade.

Local biosynthetic manufacturing directly from sugar will eliminate the need for opium poppy raw materials and thus decrease, or eliminate, diversion as a source of illicit ingredients. Moving away from outmoded plant ingredient purification techniques also enables improved quality and consistency, simplified logistics compared to moving narcotic raw materials around the world and avoids using fertile land that could better be employed for food production.

In addition, the microbial manufacturing strains will provide a basis from which to develop novel less addictive opioids not currently accessible from the plant or traditional chemistries. Until now it was not commercially viable to attempt to make certain modifications to the opioid molecule, but microbial biosynthesis now makes them possible. From these, numerous candidate pharmaceuticals will arise for testing, and some of these may well be superior to currently marketed products.

"While that next crucial breakthrough still lies ahead of us, the beneficial impact that such new medicines would have on society takes your breath away," said Joseph Tucker, Ph.D., CEO of Epimeron.

Peter Facchini, Ph.D., chief scientific officer of Epimeron said, "Our demonstrated expertise in research and entrepreneurship will continue to drive this important endeavour. We've made great progress so far, and this announcement is an indication of the potential that lies ahead in developing new drugs to manage pain."

"We are delighted with this announcement which is an excellent example of how a nearly decade-old investment in large-scale genomic science can yield concrete benefits to Canada in terms of new technologies and economic growth for Canadian firms such as Epimeron," said Dr. Gijs van Rooijen, chief scientific officer with Genome Alberta.

"The discovery of the thebaine synthase gene is significant. This work has unlocked the path to transforming the commercial production of opiates and indicates the very real potential of developing non-addictive opioids. It is satisfying to witness how Dr. Faccini's comprehensive research has transitioned into creating a considerable impact," states Dr. John Wilson, director, Physical and Life Sciences, Innovate Calgary.

More information: Xue Chen et al, A pathogenesis-related 10 protein catalyzes the final step in thebaine biosynthesis, *Nature Chemical Biology* (2018). DOI: 10.1038/s41589-018-0059-7

Provided by Epimeron