Poppy research creates new cough suppressant supply

A BBSRC-funded research collaboration between the University of York and GlaxoSmithKline has created a new supply of the cough suppressant and potential anti-cancer agent noscapine.

Thanks to discoveries of the genes responsible for producing noscapine in poppies, plants are now being grown commercially which have been bred to contain much larger amounts of noscapine than previously. 80% of the world's noscapine supply now comes from a new poppy variety which arose from this research.

"This has opened up the potential for creating more cough medicines from noscapine than was possible in the past," says Mr Tim Bowser, head of GlaxoSmithKline Australia's Opiates Division at the time of the research.

Noscapine is useful as a cough suppressant because it is effective and has low toxicity. As a result of the York research, noscapine can be produced more easily and cheaply, and consequently more companies are beginning to include it in their cough medicines.

Noscapine is also in phase II clinical trials as an anti-cancer agent. If these trials show it is effective, it could prove a good option for cancer treatment due to its low toxicity in comparison with currently-available anti-cancer drugs.

A University of York/GlaxoSmithKline collaboration led to the discovery of genes involved in producing medicinal compounds in poppies.
Image: Carol Walker

IMPACT SUMMARY

A new variety of poppy containing a larger amount of the cough suppressant and potential anti-cancer agent noscapine has been bred, thanks to a BBSRC-funded research collaboration between the University of York and GlaxoSmithKline.

These poppies provided an estimated 80% of global noscapine supply for cough suppressants in 2017-18. Because of the higher quantity of noscapine in the new poppy variety, extraction is simpler and cheaper, with the result that more companies are beginning to include noscapine in their cough medicines.

Noscapine is beneficial as a cough suppressant because it is effective and has low toxicity. It is also in phase II clinical trials as an anti-cancer agent.

In 2014 Bowser spent 18 months working with Professor Ian Graham[1] and colleagues in the Centre for Novel Agricultural Products at the University of York. This was funded through BBSRC's Flexible Interchange Programme (FLIP)[2], and a broader programme of collaborative research into the production of medicinal compounds in poppies was supported by a BBSRC Industrial Partnership Award[3] with GlaxoSmithKline, and later Sun Pharmaceutical Industries, which acquired GlaxoSmithKline Australia's Opiates Division in 2015.

During these projects, the researchers discovered a gene in the opium poppy that determines which medicinal compounds are produced and which are not[4]. This built on their earlier discovery of a cluster of genes responsible for producing noscapine[5]. These breakthroughs were reported in two landmark papers in the leading journal *Science*.

It was these discoveries which allowed the researchers to breed poppies containing higher quantities of noscapine and, subsequently, a variety of poppies which contains noscapine but not opioid painkillers such as codeine and morphine, making noscapine extraction easier.

More recently, as part of the BBSRC Industrial Partnership Award, the team together with collaborators from China have published the opium poppy genome[6].

"The collaboration with York exceeded our expectations," says Bowser. "I've been involved in a lot of industrial research collaborations in my life, but few have had an impact as quickly as this one."

REFERENCES

1 Professor Ian A Graham FRS, Department of Biology, University of York https://www.york.ac.uk/biology/research/plant-biology/ian-a-graham/

2 BB/L004917/1 FLIP: Developing biorenewables based feedstock and clean chemistry technologies for the pharmaceutical industry https://gtr.ukri.org/projects?ref=BB%2FL004917%2F1

3 BB/K018809/1 Understanding the regulation of alkaloid biosynthesis in opium poppy and breeding new varieties https://gtr.ukri.org/projects?ref=BB%2FK018809%2F1

4 Winzer TH, Kern MF, King AJ, Larson TR, Teodor RI, Donninger S, Li Y, Dowle A, Cartwright J, Bates R, David A, Thomas J, Walker C, Bowser T, Graham IA (2015). Morphinan biosynthesis in opium poppy requires a P450-oxidoreductase fusion protein. Science 349(6245):309-12.

5 Winzer TH, Gazda V, He Z, Kaminski F, Kern MF, Larson TR, Li Y, Meade F, Teodor RI, Vaistij FE, Walker C, Bowser T, Graham, IA (2012). A Papaver somniferum 10-gene cluster for synthesis of the anticancer alkaloid noscapine. Science 336(6089):1704-8.

6 Guo L, Winzer T, Yang X, Li Y, Ning Z, He Z, Teodor R, Lu Y, Bowser TA, Graham IA, Ye K (2018). The opium poppy genome and morphinan production. Science [Epub ahead of print]. doi: 10.1126/science.aat4096.