news

'Combination of niacin–lovastatin is already available in the USA and some statin–niacin combinations may become available in Europe in the future', said Anthony Wierzbicki from St Thomas' Hospital in London. 'Given compliance issues with multiple drugs… and the need for multiple medications in patients with CHD, combinations are the only way forward', he added. 'Polypills are on the horizon- but, my personal opinion is that the individual formulations must be tested, and the multiple dose combinations needed for flexibility make a polypill a complicated solution', concluded Taylor.

References

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Silence of the poppies: a new source of drug precursors

Jane Bradbury, janeb@sciscribe.u-net.com

Australian researchers have used RNA interference (RNAi) technology to metabolically engineer the opium poppy for the first time. Unexpectedly, by silencing one of the last enzymes in the biosynthetic pathway leading to codeine and morphine, the researchers produced a poppy that accumulates reticuline, a nonnarcotic alkaloid intermediate, well upstream of codeine [1]. 'Our research opens up the possibility of forcing the accumulation of potentially useful intermediates that do not normally accumulate to any extent in the poppy,' says Philip Larkin of CSIRO Plant Industry (Canberra, Australia; http://www.pi.csiro.au).

Designer poppies

Opium poppy is one of the oldest cultivated medicinal plants – the Sumerians grew *Papaver somniferum* in 6000 BC for its analgesic properties. Codeine and morphine, alkaloids that accumulate in the latex of the poppy, are two of the most important analgesics in use today. Other intermediates in the morphine biosynthetic pathway are also of medical importance, particularly as feedstuffs for drug synthesis. The intermediate thebaine, for example, is used to synthesize the analgesics buprenorphine and oxycodone.

'To achieve our long-term objectives of improving the yields of useful intermediates, we need to understand which genes in the pathway leading to codeine and morphine are limiting; we need to understand the control of secondary metabolism in the poppy,' explains Larkin, who collaborates with Tasmanian Alkaloids (http://www.tasalk.com.au), a major producer of the world's legally traded opiates.

Larkin and co-workers recently used RNAi to silence codeine reductase (COR), a multigene family of enzymes that convert codeinone and morphinone to codeine and morphine, respectively [1]. 'We designed a hairpin RNA construct to regions found in all the COR genes and, somewhat surprisingly, obtained poppies that accumulate reticuline, a compound that is formed seven enzyme steps before codeinone.' Reticuline, notes Larkin, is the starting point for the synthesis of bisbenzylisoquinoline alkaloids, some of which have shown promise as antimalarial and anticancer compounds. 'The existence of this transgenic poppy might encourage drug discoverers to follow up on interesting bioactivities that can be made from reticuline,' he suggests.

> 'The poppy is a fantastic platform for pharmaceutical production'

Understanding alkaloid biosynthesis

'We have seen similar results in California poppy,' comments plant biotechnologist Peter Facchini (Department of Biological Science, University of Calgary, Canada; http://www.bio.ucalgary.ca), 'in that by removing just one enzyme in the alkaloid synthesis pathway, we disrupted the whole pathway [2]. Larkin's well-done research provides important insights into a complex process about which we know relatively little but which we need to understand before we can engineer poppies to produce useful intermediates.'

Both Larkin and Facchini believe that poppies have a great future for drug discovery and development. 'The opium poppy is going to become the number one system for learning how plants make alkaloids,' says Facchini. 'What we learn in poppies might help us to understand how the periwinkle makes vinblastine, for example,' and ultimately lead to better sources for this and other plant-derived medicinal compounds. 'The poppy is a fantastic platform for pharmaceutical production,' agrees Larkin, 'but drug discovery teams and plant geneticists need to work together to exploit it fully. With good collaborations, we may be able to get the poppy to do some of the fancy chemistry necessary for the discovery and production of new drugs.'

References

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2 Park, S.U. *et al.* (2003) Modulation of the berberine bridge enzyme in transgenic root cultures of California poppy alters the accumulation of benzophenanthridine alkaloids. *Plant Mol. Biol.* 51, 153–164

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