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INFECTIOUS DISEASES

New routes to antimalarials?

The natural plant product artemisinin is highly effective against multidrug-resistant strains of malaria. However, obtaining artemisinin, both from the natural source and chemically, is laborious and costly. Writing in *Nature*, Ro and colleagues describe the genetic engineering of *Saccharomyces cerevisiae* to potentially provide a more facile, cheaper route to artemisinin from the precursor artemisinic acid, which has implications for the development of more affordable treatments for malaria.

The small quantities of artemisinin — a sesquiterpene lactone — obtained both by extraction from the leaves of the wormwood tree (*Artemisia annua*) and its total laboratory synthesis render artemisinin-based therapies unaffordable for most malaria sufferers. As exemplified by Ro and colleagues, manipulating microorganisms to produce a molecule gives an extra level of control over the production process. Artemisinic acid production is guaranteed and the risk of contamination with other terpenes is reduced, and both factors contribute to improving the cost-effectiveness of the production of the desired molecule, artemisinin.

Artemisinic acid is the final product of a five-step transformation that starts with farnesyl pyrophosphate (FPP). In the FPP biosynthetic pathway, the majority of FPP is converted to sterols. By genetically engineering *S. cerevisiae*, the authors were able to maximize the concentration of FPP available for artemisinic acid biosynthesis by both increasing FPP production and blocking its use in sterol synthesis. The transformation of FPP into artemisinic acid requires only two other enzymes. Amorphadiene synthase first catalyses the conversion of FPP to amorpha-4,11-diene, which is usually the first committed step in artemisinin biosynthesis. Next, a sequence of three oxidation reactions produces artemisinic acid. A cytochrome P450 (CYP450) has been shown to catalyse the first transformation — the hydroxylation of amorphadiene. Genetic screening of the *A. annua* sequence and BLAST analyses identified a novel CYP450 gene, *CYP71AV1*. Gas chromatography-mass spectrometric analysis of cell cultures and *in vitro* enzyme assays with artemisinic alcohol and artemisinic aldehyde — the two intermediates in this pathway — revealed that CYP71AV1 catalyses all three reactions.

The authors reported yields of 100 mg artemisinic acid per litre of culture, with >95% of artemisinic acid being recovered. These high yields led the authors to speculate that the artemisinic acid is transported out of the cells but remains bound to the cell surface. Taking advantage of this characteristic, the authors were able to purify the crude product in a single, inexpensive step using gel chromatography, with, on average, 76 mg of pure artemisinic acid recovered. The chemistry for the conversion of artemisinic acid to artemisinin is well established and efficient, and so, if the microbial production of artemisinic acid could be optimized, the yields recovered could be high enough to significantly reduce the cost of artemisinin combination therapies.

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ORIGINAL RESEARCH PAPER Ro, D.-K. *et al.* Production of the anti-malarial drug precursor artemisinic acid in engineered yeast. *Nature* **440**, 940–943 (2006)
FURTHER READING Khosla, C. & Keasling, J. D. Metabolic engineering for drug discovery and development. *Nature Rev. Drug Discov.* **2**, 1019–1025 (2003)