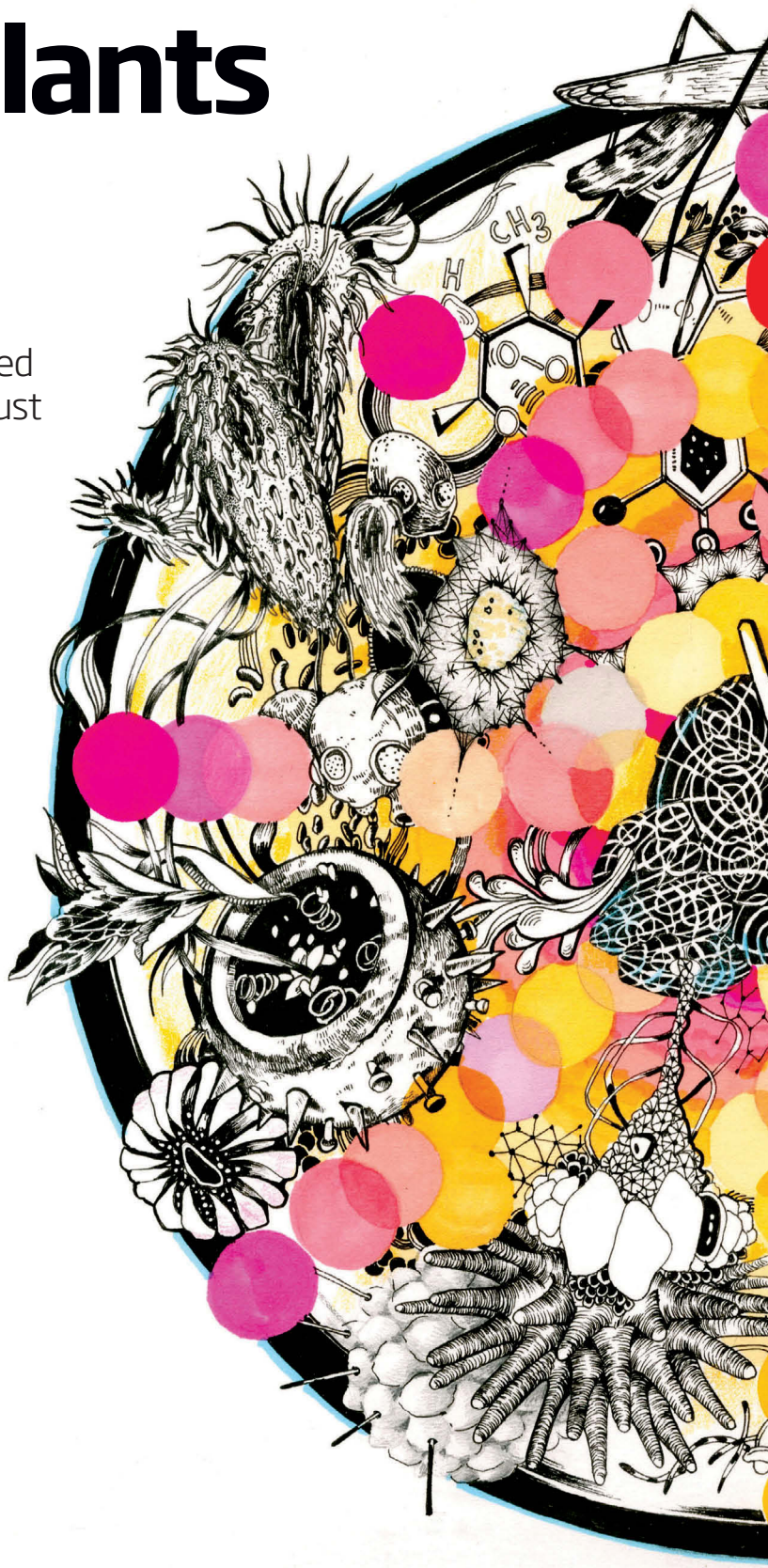
Anything plants can grow...

...we can grow better. We are now brewing our best malaria drug in modified microbes, says **Colin Barras**, and that's just the start of the synbio revolution



A REVOLUTION is brewing in Bulgaria – quite literally. In vats similar to those used to ferment beer, genetically modified yeast is churning out tonnes of a molecule that can easily be turned into the most potent antimalarial drug on the market today, artemisinin.

Before the brewing began, all of the world's artemisinin came from a Chinese plant called sweet wormwood. The supply of farmed artemisinin has been erratic, and shortfalls have sometimes put lives at risk. The yeast in Bulgaria is supposed to guarantee a plentiful, cheap supply, helping the fight against a terrible disease that blights the lives of hundreds of millions.

It is no surprise, then, that yeast-grown artemisinin is being hailed as a triumph for synthetic biology – the engineering of living organisms to do everything from making drugs to mopping up pollution. Here, say those in the field, is proof that this young science is starting to deliver on its promise.

Except the story isn't that simple. The problems with the artemisinin supply have largely been ironed out already. The yeast-grown artemisinin could actually trigger a shortfall in the next year or two rather than prevent one. What's more, it turns out that it would have been quicker and cheaper to make synthetic artemisinin with conventional methods.

So is this really the dawn of a new era? Or are the yeast in Bulgaria a one-off vanity project that will lead nowhere? The answer could soon be arriving on your dinner plate.

The artemisinin story starts in 1967, when Chairman Mao launched a project to find an effective antimalarial to help the

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communist forces in the Vietnam war. A researcher called Tu Youyou began testing traditional Chinese fever remedies and hit the jackpot with sweet wormwood.

When the active ingredient was unveiled to the rest of the world in 1979, the reaction was sceptical: artemisinin looked too unstable to qualify as a wonder drug. "It was the first natural product found that contained this unusual oxygen-oxygen endoperoxide bond," says Silas Cook, a chemist at Indiana University in Bloomington.

Its Chinese origins didn't help either. The drug didn't become widely available until 1999, when Swiss company Novartis launched a pill form containing artemisinin and another antimalarial. Combining drugs like this makes it much harder for the malaria parasite to evolve resistance.

Meanwhile, Jay Keasling at the University of California, Berkeley, had set out to prove that microbes could be turned into chemical factories. His team had decided to start with isoprenoids, a large family of commercially useful molecules found in plants and animals – but which to chose? "Then one day, one of my students showed me a paper on artemisinin," says Keasling. "We thought, gosh – this is something we could make."

Soaring demand

That's because artemisinin can be derived from another chemical called amorphadiene, which just happens to be an isoprenoid. Keasling's team homed in on the genetic machinery needed to produce amorphadiene in yeast, and transferred it to *E. coli* – a much-studied bacterium that is easy to work with.

It was pioneering work. While conventional genetic engineering involves tweaking one or two genes, Keasling had to transfer half a dozen. And he took the approach championed by synthetic biologists: trying to develop a module, or "biobrick", for making amorphadiene that could be plugged into organisms other than *E. coli*.

By 2003 the team had succeeded. Their timing was impeccable. In 2001, the World Health Organization (WHO) had recommended artemisinin combinations as the standard treatment for malaria. Its use was soaring, from 600,000 treatments in 2002 to 5 million in 2004, leading to a shortfall in global supplies. A number of companies came sniffing at Keasling's door.

But Keasling's work was far from finished. Converting amorphadiene into artemisinin is complicated and expensive so the team ›