Yeast process gives rise to research progress

Science Re-engineering a familiar ingredient and the discovery of new compounds mark big steps in fighting the disease, writes *Clive Cookson*

Looking to the future: the discovery of a promising new class of antimalarial compounds has fuelled optimism in the fight against the disease Getty Images

When it comes to science, malaria can no longer be regarded as a neglected disease. Spending on malaria research and development rose rapidly during the first decade of this century – propelled by increased commitments from charitable foundations such as Gates and Wellcome, as well as the pharmaceutical industry and government agencies such as the US National Institutes of Health – and is running at around $700m a year.

Given the long time lag in medical research between discovery and commercial application, as safety and efficacy of drugs and vaccines are tested in clinical trials, it is too soon to see spectacular results from the extra R&D funding. But several scientific papers and announcements over the past few months have given encouraging indications of new weapons in the battle against malaria.

The recent development with most immediate commercial application was the publication this month in the journal Nature of a new production process for artemisinin, the key ingredient of the combination therapies recommended by the World Health Organisation. At the same time Sanofi, the French pharmaceutical group, announced plans for large-scale production of artemisinin, using the new process, in collaboration with two non-profit organisations, PATH and OneWorld Health.

Besides its importance for the fight against malaria, the announcement is also significant because it heralds the first industrial-scale application of "synthetic biology", the discipline that takes genetic manipulation to a stage beyond the simple addition of one or two genes.

The nine-year programme to develop a cheaper and more reliable source of artemisinin – a natural product derived until now from the sweet wormwood plant – has involved extensive re-engineering of baker's yeast to make the yeast cells convert glucose into artemisinic acid in a fermenter. This precursor molecule is then transformed into artemisinin itself through a more conventional chemical process catalysed by light.

Engineering the yeast to produce commercially viable quantities of artemisinic acid required the insertion into yeast of enzyme genes from the sweet wormwood plant and, equally importantly, various DNA control regions to make sure that the enzyme production switches on and off in the correct sequence.

Several partners took part in the artemisinin programme, which started in the lab of synthetic biology pioneer Jay Keasling at the University of California, Berkeley, and continued through research by Amyris, a biotech start-up company, and Sanofi.

> '[ELQ-300] is one of the first drugs to kill the malaria parasite in all three stages of its life cycle'

The yield is now 25 grammes of artemisinic acid per litre of yeast fermentation culture – enough for Sanofi to make 35 tonnes of artemisinin this year and 50 to 60 tonnes in 2014, which corresponds to about 100m doses of malaria treatment.

Artemisinic acid will be produced in a fermentation facility in Bulgaria and converted into artemisinin at Sanofi's Garessio drug factory in Italy.

Operating on a no-profit, no-loss production model, Sanofi expects to sell artemisinin at the lower end of the price range of the plant-derived product. Its factory could supply one third to a half of world demand, but the company says it wants to avoid driving plant-based producers out of business. The idea is to smooth out the unevenness of supply and price fluctuations that have characterised the artemisinin market so far.

The other big news recently on the drug development front was the discovery of a very promising class of antimalarial compounds, published last month in the journal, Science Translational Medicine.

This project, involving an international research team funded by the non-profit Medicines for Malaria Venture and the National Institutes of Health, is far further from commercial application than the artemisinin process but could eventually be more important.

The new compounds, which go by the tongue-twisting name of 4(1H)-quinolone-3-diarylethers, show strong activity in lab tests against *Plasmodium faciparum* and P vivax, the parasite species that causes most malaria cases.

The "lead compound" in this group, known as ELQ-300, acts against the parasite at several stages of its life cycle. ELQ-300 is extremely potent when tested in mice with malaria, although this does not necessarily mean that it will work so well in humans when clinical trials start a year or two from now.

"This is one of the first drugs ever to kill the malaria parasite in all three stages of its life cycle," said Dennis Kyle, professor of global health at the University of South Florida.

"So it may become part of a new generation therapy that not only treats sick people and prevents them from getting ill but also blocks the transmission of malaria from mosquitoes to humans . . . If the drug can break the parasite life cycle, we may ultimately eradicate the disease."

Wiping such a complex disease as malaria off the fact of the earth may seem like a fantasy but epidemiologists insist that, armed with the right drugs, vaccines, diagnostics and mosquito control measures, we can do it. As a recent paper in the journal Science put it, "malaria elimination can proceed like a ratchet, country by country and region by region, culminating in global eradication".