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Milking goats for malaria vaccine

Henry Nicholls, BMN News

A herd of transgenic goats in Massachusetts, USA, could save millions of lives, claim the biotechnologists who developed them. Their milk contains the key ingredient of a malaria vaccine, say the researchers, and can yield up to 5 kg of this protein a year.

Vaccine candidates: MSPs

The malarial merozoite surface proteins (MSPs) are amongst the most promising candidate molecules for a vaccine against the disease, say researchers. The idea is that injection of these foreign proteins will sensitize the immune system to detect and destroy any infected red blood cells, which bear the MSPs on their surface.

MSP-based vaccinations have already been tested on humans in Papua New Guinea and are effective at reducing parasite load and raising an immune response. If ongoing studies can show that these antigens also protect against infection, there could be great demand for producing them on a commercial scale.

And transgenic goats that secrete MSP1 in their milk could meet that demand, says Harry Meade, Vice President of Research and Development at GTC Biotherapeutics, MA, USA (http://www.gtc-bio.com). 'I don't think anybody has any other system that they could contemplate making these kinds of levels as cheap as what you can in milk,' he said.

The amount of MSP that can be reaped from more conventional transgenic organisms, such as *Escherichia coli*, is far lower, agrees Manuel Alfonso Patarroyo, a Biochemist at the Fundación Instituto de Inmunología de Colombia.

Synthesis and purification

MSPs have a high AT content, he says. In prokaryotes like *E. coli*, there is a

shortage of tRNAs that hybridize to the AT motif, which limits synthesis of the transgenic protein in these bacteria. What is more, MSPs tend to be insoluble, says Patarroyo. This makes them difficult to purify. 'You usually have to extract them from inclusion bodies and after that refold them,' he said. But you can't be sure that the refolded protein has the same structure as the native protein in the malaria pathogen, he says.

None of this is a problem in the milk from the Massachusetts goats, argues Meade. 'We don't understand why,' he said. It could be that because the mammary gland's primary function is secretion, it is not spending energy growing, as do cells in culture, he says. 'We can produce a number of different fusion proteins and normally non-secreted proteins at nice levels and they're properly folded by our standards.'

Each goat can produce 1 g of MSP1 in a litre of milk. In a year, a goat can produce between 500 and 800 litres, so a herd of 50 goats could yield 25 kg of crude protein a year. Following purification, there would be at least 5 kg of protein to use for a vaccine, Meade estimates. 'That's a lot of doses,' he said. 'With a herd of goats, you could cover the world.'

Trials of *Combination B*

In Papua New Guinea, an MSP-based vaccination - *Combination B* - has already been trialed on 120 children. It contains three *Plasmodium falciparum* blood-stage proteins – MSP1, MSP2 and ring-infected erythrocyte surface antigen (RESA). It caused few adverse events and raised an immune response in the children, report Blaise Genton of the Swiss Tropical Institute in Basel (http://www.sti.ch) and colleagues [1].

Although the study was not designed to test whether *Combination B* conferred protection on the children, it was able to reduce the parasite load of those infected with *P. falciparum*. MSP2 definitely had a role in this reduction, says Genton, so future work will focus on variants of MSP2 rather than on MSP1 and RESA. 'Phase IIb trials should start in 2005 and results available in 2007,' she said.

Meade, however, continues to work on an MSP1-based vaccine based on advice from his NIH-backers. 'I'm not at all a malaria expert,' he said. 'I just milk goats.'

Reference

1 Genton, B. *et al.* (2003) Safety and immunogenicity of a three-component blood-stage malaria vaccine (MSP1, MSP2, RESA) against *Plasmodium falciparum* in Papua New Guinean children. *Vaccine* 22, 30–41

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