

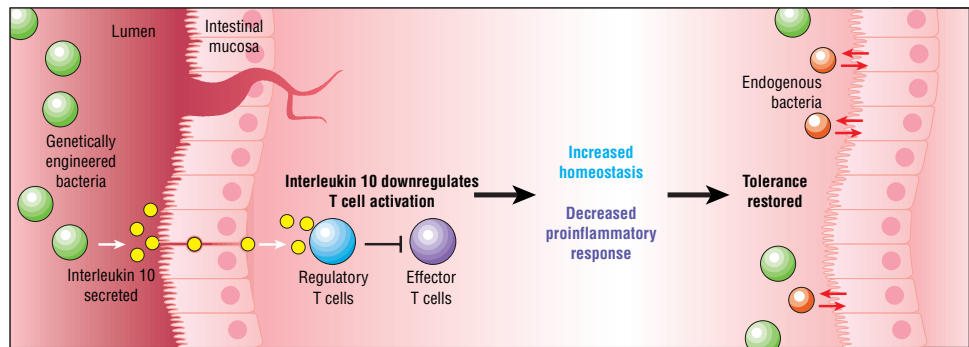
New cytokine treatment for inflammatory bowel disease

Abi Berger *BMJ*

Bacteria that produce cytokines could be used to treat inflammatory bowel disease (IBD), if the results of research in mice are reproduced in humans.

Belgian scientists have engineered a non-pathogenic bacterium that produces interleukin 10, an anti-inflammatory cytokine that reduces inflammatory colitis. Because the genetically engineered bacterium survives stomach acid the cytokine can be delivered direct to the inflammatory target in the colon. This could reduce the dose needed and any systemic effects (*Science* 2000;289:1352-4).

The team, led by Dr Lothar Steidler, a molecular biologist at Ghent University and Flanders Interuniversity Institute for Biotechnology, has been using the bacterium *Lactococcus lactis* to produce cytokines since 1995. The researchers' interest in this particular species developed when they discovered that, unlike other bacterial expression systems, *L. lactis* is not killed as soon as it releases cytokines. They thought that *L. lactis* might therefore be a good system for delivering cytokines directly to



The cytokine interleukin 10 (yellow) is secreted in the intestinal lumen of mice by genetically engineered bacteria (green). Interleukin 10 traverses the gut epithelium, probably by a paracellular route as epithelial permeability is increased during inflammation. It suppresses the inflammatory immune response in the gut mucosa by promoting the activity of regulatory T cells (blue)

the host, so they looked for an existing disease known to require cytokine treatment.

Inflammatory bowel disease in humans responds to high dose intravenous interleukin 10, but this cannot be administered orally because stomach acid destroys it. Dr Steidler hypothesised that an oral delivery system that effectively bypassed the stomach might provide a treatment which would cut the dose of interleukin 10 required and also reduce the risk of systemic side effects.

Dr Steidler and his colleagues genetically engineered *L. lactis* to produce interleukin 10. They then created two different mice models of inflammatory bowel disease. In the first model a chronic colitis was induced by feeding dextran sulphate sodium to the mice over several weeks.

When the recombinant bacteria were introduced into the mice stomachs, they survived the acid environment and released interleukin 10 in the colon. The severity of the colitis was halved.

The second mouse model had its interleukin 10 gene knocked out. The resultant mice were shown to develop inflammatory bowel disease spontaneously within 8 weeks of life. When the team administered the genetically engineered *L. lactis* to these mice at 3 weeks of age, the colitis did not occur in the first place.

Serum concentrations of interleukin 10 were not found to be high, despite good uptake by the inflamed cells of the gut mucosa. "These non-colonising bacteria have been used for hundreds of years in the dairy industry and are safe to humans," says Dr Steidler.

Two technical hitches must be ironed out, however, before human trials can be considered. Human interleukin 10 is slightly different from murine interleukin 10, so the *L. lactis* will have to be re-engineered. The second obstacle is that human bile is stronger than mouse bile and is likely to kill the bacteria as they pass through the stomach and duodenum. "We're going to have to create an encapsulated version of the *L. lactis*," explained Dr Steidler.

According to Dr Fergus Shanahan at Cork University Hospital in the Republic of Ireland, these results are important. "It raises issues about genetically modified food being used for therapeutic use," he said. "In principle, it's just another step to delivering vaccines in a similar way." □

Dutch waiting lists increase despite £36m campaign

Tony Sheldon *Utrecht*

Waiting lists for hospital treatment in the Netherlands increased by 2% last year, despite a 130 million guilder (£36m; \$54m) initiative to reduce them. A report commissioned by the government, presented to parliament last week, concludes that an increase in demand has left waiting times "unacceptably long."

Waiting times for individual specialties, however, have improved. In orthopaedics they have dropped from 16 to 12 weeks and in ophthalmology from 16 to 15 weeks. Capacity too has increased, with 20 000

more operations carried out, but the number waiting for treatment has reached about 150 000.

The Dutch health minister, Els Borst, has called for all hospitals to publish waiting times on the internet to enable patients to choose the fastest treatment. Since April the Dutch Hospitals Association's internet site (www.nvz-ziekenhuizen.nl) has published details of some hospital waiting times, updated each month and broken down into specialties and regional averages.

The number of hospitals par-

ticipating is increasing, but the scheme is voluntary, and a minority still provide no, or incomplete, information—largely, said the Dutch Hospitals Association, because of technical difficulties in gathering the figures.

Patients' organisations suspect, however, that some hospitals are reluctant to advertise poor performance. Ms Borst argues that patients have a right to this information. "I feel that by the end of the summer, information on waiting times should be completely available," she said.

Waiting times have long been a contentious issue in Dutch medicine. In 1998 a joint platform to tackle the problem was launched by all the main health-care organisations, including the Royal Dutch Medical Association (*BMJ* 1998;316:959). It has drawn

up a list of maximum waiting times for routine treatment that should be achieved by 2003. These require 80% of clinical treatment to be carried out within five weeks.

Ms Borst agreed that some waiting times remain unacceptable but emphasised that it is the length of the wait, not of the lists, which is important. □

Correction

Study questions ethics of covert medication

We wrongly attributed the photograph which accompanied this article (12 August, p 402) to Panos Pictures; it should have been credited to Format Photographers. We apologise for this error.