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GM ORGANISMS

Prisons without bars

Weighing up the pros and cons of the use of genetically modified (GM) organisms is no easy task — the potential benefits are often great, but the unknown risks posed by the escape and propagation of GM species, or the transfer of transgenes to other organisms, might be even greater.

Although a range of confinement systems have been developed to minimize the survival and spread of GM species and their transgenes, none have managed to combine high levels of functionality and safety. Now, in the July issue of *Nature Biotechnology*, Lothar Steidler and colleagues describe the first system for the therapeutic use of GM bacteria to deliver on both counts.

The authors have designed a technique for the treatment of human

inflammatory bowel disease (IBD), in which GM *Lactococcus lactis* supplies the therapeutic anti-inflammatory cytokine interleukin 10 (IL10) directly to the intestine by *in situ* synthesis. Existing methods of IL10 delivery have undesirable side effects, so the benefits of this system are clear — but what if the GM bacteria escaped into the environment, or the synthetic *IL10* crossed into other microorganisms?

To restrict the transgenic bacteria to the target area, Steidler *et al.* substituted the thymidylate synthase gene *thyA*, which is essential for *L. lactis* growth, with the therapeutic gene encoding IL10, to produce thymidine- or thymine-dependent strains. Thymidine is present in the intestine, but not elsewhere, so the

viability of the strains fell by several orders of magnitude outside of this organ.

But could the GM bacteria regain *thyA* from an endogenous source? Owing to high sequence diversity at the *thyA* locus, acquisition of the gene from other microorganisms is extremely unlikely. Moreover, if the intact gene was gained through homologous recombination, the transgene would be recombined out of the genome, so the GM strains would revert to the unmodified state.

As for transgene escape, the opportunities are highly restricted in these strains. The expression cassette for *IL10* is integrated into the chromosome, so the risk of disseminating the transgene through lateral gene transfer is low. Added to which, phage replication is severely impaired, which prevents phage-mediated transduction.

It seems that Steidler and colleagues have all the exits covered with this strategy. So much so, in fact, that the Dutch authorities have granted permission for one of the strains to be used in the first ever clinical trials of a live GM-bacteria-based experimental therapy in humans. This is a big step forward for GM technology; the wider GM debate, however, is unlikely to be quite so easily contained.

Victoria Kitchener

References and links

ORIGINAL RESEARCH PAPER Steidler, L. *et al.* Biological containment of genetically modified *Lactococcus lactis* for intestinal delivery of human interleukin 10. *Nature Biotechnol.* **21**, 785–789 (2003)