immune responses. Indeed, Weinberg thinks the greatest therapeutic potential for OX40 regulation could lie in cancer therapies.

'Our group and others have now shown that giving an agonist OX40 antibody to mice with tumours has profound proinflammatory effects leading to the eradication of tumours in several models,' he said. The treatment also increases the number of memory T cells, thereby enhancing antigen specific cellular immunity.

OX40 conservation

Fortunately, the OX40 molecule is highly conserved between mice and humans and both Hussell and Weinberg hope that OX40 technologies will reach the clinic soon. Plans are afoot to test it on healthy individuals and asthmatics – a group who could benefit greatly as viral infections exacerbate asthma.

However, Weinberg sounds a note of caution. 'Unfortunately, these recombinant fusion proteins are expensive to produce and therefore expensive for treatment,' he said. But, he added, 'If small molecules could be found to inhibit OX40 specifically, then you could possibly treat flu symptoms with a nasal spray and everyone could take advantage of this technology at a reasonable price.'

Reference

1 Humphreys, I.R. *et al.* (2003) A critical role for OX40 in T cell-mediated immunopathology during lung viral infection. *J. Exp. Med.* 198, 1237–1242

Making sense of gene therapy

Helen Dell, BMN News

Plans to repair, rather than replace, defective genes have taken a tentative step closer to the clinic, report US researchers who have used RNA enzymes to successfully repair the product of a disease gene in mammalian cells.

Repair versus replace

Repairing genetic instructions has 'significant advantages' over traditional gene therapy, which aims to replace faulty genes, says Bruce Sullenger, Professor of Surgery at Duke University School of Medicine in North Carolina, USA (http://www.duke.edu).

The problem with the traditional approach to gene therapy is that when a healthy gene is inserted to replace a defective version, it is inserted at random. This can cause problems because the gene loses much of its surrounding DNA, which contains regulatory information, and the replacement gene can also interfere with its new neighbours.

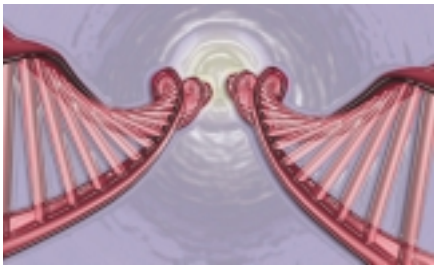
Sullenger likens gene therapy to correcting a spelling mistake in a document. If the correct version of a faulty word is re-inserted in the text at random, as with the traditional approach to gene therapy, the word is not going to make sense, and could interrupt the flow of another sentence.

RNA repair addresses this issue of context because the gene remains where it is, upregulated and downregulated as usual. 'The mutant instructions are made at the right time in development and differentiation, and in the right amounts,' said Sullenger. 'So we think we will recapitulate the right expression better by repairing them.'

Ribozymes

Sullenger uses an RNA enzyme (ribozyme), called a Group I intron, to repair RNA. These introns cleave RNA at two sites, discarding the intervening RNA, before joining the ends back together.

Crucially, if the ribozyme has a sequence attached to its tail end, it sticks this into the RNA gap before gluing the whole thing back together; replacing one piece of RNA with another. In addition, the ribozyme recognizes its cleavage sites by base-pairing, so by changing the ribozyme sequence, it can be engineered to cut at different targets.



Sullenger is looking at sickle-cell anaemia, which is caused by a defect in the gene encoding beta-globin. 'The intricacies of globin gene expression have made the development of treatments... based on gene therapy difficult,' says Sullenger, making it an ideal candidate to test out the RNA repair approach.

His team has already repaired the beta-globin RNA in red blood precursor cells from people with sickle-cell anaemia, but the process was only transient and very inefficient.

Now, the researchers have engineered the ribozyme into a viral vector to enable longer-term expression in cultured cells. They also added several structural components to the ribozyme to optimize its repair capabilities and specficity. These ribozymes are capable

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of repairing between 10% and 50% of defective beta-globins in cell culture.

From mouse to man

If this were transferred to human patients, the proportion of repaired RNA would be a clinically relevant, according to Sullenger. '50% would take you from being a sickle-cell person with two copies to basically being a carrier, which is normal,' he said. ' However, there is also good evidence that suggests that if you did it even at 10%, you would reduce the severity of the disease.'

Sullenger now plans to test the technology in a mouse model of sickle cell anaemia. 'Can we repair that level of RNA in those animals and observe a phenotypic effect on sickle cell disease?' he asked. 'Hopefully if that pans out, well then we'll consider clinical trials.'

The work is interesting, says Alfred Lewin, Professor of Molecular Genetics and Microbiology at the University of Florida (http://www.ufl.edu). But he is cautious about how easily the technique will transfer to an animal model, or to humans. 'This was done by transfection of non-relevant cells,' he said. 'So they have high level of expression of target and high level of expression of ribozyme, much higher than they could hope to achieve *in vivo*. [It] would be enough to encourage me to go ahead into the mouse or human cells. But just because this worked doesn't mean that that will work.'

The work was presented at the 53rd annual meeting of the *American Society of Human Genetics* 4–8 November 2003 (http://www.ashg.org).

Please see our new Monitor section, which now includes News in Brief and People, p. 43

Ethics board review of biomedical research: improving the process

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Although researchers often find the process of research ethics board (REB) review of research frustrating, time-consuming and of limited value, REB review provides essential safeguards for research subjects and helps to ensure that research on human subjects conforms to stringent ethical and legal standards. Improvements in the process of REB review would benefit numerous stakeholders, including both research subjects and researchers.

Having participated in ethics review of biomedical research protocols at four institutions, I have some sense of the strengths and weaknesses of REBs (known in the United States as Institutional Review Boards, or IRBs) and the processes they use to assess the ethical adequacy of research protocols. Unfortunately, REBs are understudied social institutions. Although REBs play an important organizational and societal role in evaluating research projects, they are only sporadically subject to empirical study and analysis [1–3]. Raymond DeVries, a sociologist at the University of Minnesota, is one of a small cadre of researchers investigating the 'black box' of REB review of biomedical research [4]. Further qualitative and quantitative research will probably shed considerable light on the overall adequacy of REB activities. Do a handful of vocal interlocutors skew the deliberations of REB members toward particular outcomes? Are there reasonably consistent review processes across REBs? Are REBs sufficiently equipped and staffed to ensure that researchers properly address their recommendations and criticisms? Are REB members adequately trained in assessing research protocols? Do they have a clear sense of the standards that ought to be applied to the ethical assessment of research protocols? Careful study of the performance of REBs would help ascertain whether or not regulatory standards and institutions serve their function or are in need of revision in various settings.

Given the dearth of studies that assess the functioning of REBs, I propose to draw upon my practical experience as a member of four of these boards and offer several suggestions concerning how the process of ethics review of biomedical research might be improved. My experience is limited to hospital and university-based REBs in Canada and I have never served as a member of commercial, for-profit REBs. Consequently, I have no personal insight into how effectively 'commercial' boards function. Research by University of Toronto law professor Trudo Lemmens

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