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editorial

Rise of the planet

Human gene therapy has a short but chequered history. The recognition, in the 1980s, that many human diseases were caused by recessive single gene mutations, led inevitably to the idea that such defects could be corrected by the same technology that facilitates the creation of transgenic animals.

At an early stage, scientists and clinicians explicitly eschewed the idea of making genetic modifications to the germline, even in the case of fatal diseases. This was partly to assuage public concern that such technology could be misused for eugenic purposes widely considered unethical and tainted by association with the Nazi genocide. More prosaically, the techniques for engineering changes in the genome were so novel that their safety could not be assured. Even if such hurdles could be overcome, the unpredictable effects upon subsequent generations were considered a sufficient reason to observe a self-imposed moratorium on any such 'playing with evolution'. Germline manipulation of the human genome remains largely a taboo subject, of greater interest to Hollywood than Bethesda [1]. Indeed, editing even plant and animal genomes remains highly controversial and tightly restricted, if not completely prohibited, in many jurisdictions.

Three decades later, it is time to reassess the issue in the light of our greatly expanded knowledge of genetics, and the rather limited success of non-germline approaches to genetic therapy to date.

With the route blocked to germline transgenesis, the era of somatic gene therapy was born. In outline, the method seeks to replace a defective gene in those cells whose function is compromised, thus overcoming the deficiency. Numerous variations on this theme seek to target the gene or its expression to specified cell types, control its integration into the genome, incorporate molecular 'safety triggers' or limit the immune response to the modified cells. The experimental nature of somatic gene therapy dictated that initial trials were conducted only in cases of severely debilitating and inevitably fatal diseases. The inherent difficulties of targeting tissues within the body also restricted it, at first, to cell types where an *ex vivo* approach could be employed, such as blood. But even this approach to treat diseases such as severe combined immunodeficiency met with only limited success. Therapeutic benefits were seen, but were typically temporary, and some patients succumbed to serious or even fatal side-effects, for example, through the oncogenic effects of random insertions in the genome.

These tragic outcomes cast a long shadow over subsequent trials. For a long time, almost the only diseases for which such an approach was contemplated were end-stage cancers, where the risk of novel neoplasms can be considered a side issue, as for radiotherapy or treatment with genotoxic drugs. Unfortunately, gene therapy for cancer, even when cleverly targeted, suffers the same methodological flaw as these older, cruder therapies, namely the practical impossibility of zapping every single tumour cell, including quiescent progenitor-type cells that may be the primary reservoir of disease. Some remissions have, however, been reported.

A few brave attempts to develop the field are now under way, but fundamental safety and efficacy problems remain. Even when a non-immunogenic delivery system can be employed, a replacement gene typically elicits an immune reaction against what is, to the patient's immune system, a foreign gene product. To be permanently effective, any such therapy requires at least a partial disabling of the recipient's immune system, thus replacing one disease with another. The oncogenic risk associated with random insertions, as well as the common problem of transgene silencing can, in theory, be overcome by the use of targeted insertion systems based on site-specific recombinases. This has proven to be a powerful tool for creating transgenic animals in research. However, to be effective, it requires a specific landing pad in the recipient genome, and thus implies the prior use of germline genetic manipulation. In the future, it should be possible to use customized recombinases with enhanced specificity to target only one or a few 'benign' insertion sites in the human genome, permissive for transgene expression. But this has not yet been achieved. In weighing the ethical objections against germline gene therapy, we need to take account of the persisting problems with its somatic cousin.

In the case of recessive disorders, preimplantation diagnosis offers a simple and safe alternative approach, although many people have ethical or religious objections to this procedure as well. But what if it were to be ascertained that making a specific alteration to the human genome could protect against Alzheimer disease or malaria? What if adding just a few additional copies of a tumour suppressor gene such as p53 could provide lifetime resistance to most common cancers? Preimplantation diagnosis is clearly useless for diseases acquired through somatic mutation or via epigenetic errors during development. Would it be ethical to withhold prophylactic germline 'therapy' if it could ensure the alleviation of suffering on a massive scale? Germline manipulation is already marching towards approval in the UK for mitochondrial DNA disorders [2]. To some this is the thin end of the wedge: to others it is a chink of light in a dark landscape.

At some point in the future, humanity will have to face such questions. I believe that the continuing rapid progress in elucidating the underlying basis of disease must lead to feasible preventative strategies based on genetic technologies that essentially exist already. We need to be ready with answers.

REFERENCES
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Howy Jacobs

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