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Gene therapy and the germline

Germline gene therapy and somatic gene therapy are two quite different proposals, and the legitimate concerns and risks of the former should not be used to stall progress on the latter. The biomedical research community should act quickly and decisively to divorce the two before pushing ahead with well-conceived postnatal and fetal somatic gene therapy protocols.

That gene therapy continues to attract some of the best minds and major funding despite having few successes to its name is testament to the great potential of this technique. When challenging but technical issues surrounding efficient and selective delivery, and continued and appropriate expression of the therapeutic gene are overcome, gene therapy could revolutionize a large sector of the medical community.

Following French Anderson's well-publicized and welcome move to have the US Recombinant DNA Advisory Committee (RAC) review two human fetal gene therapy protocols, fetal (or *in utero*) gene therapy has become the 'talk of the biomedical town'. And as Holm Schneider and Charles Coutelle explain in their Commentary (see page 256 of this issue), there are good reasons to extend gene therapy trials to the fetus: The high level of cell division in the fetus suggests that *in utero* gene therapy may result in better cellular uptake of vectors and their therapeutic genes; the still-developing immune system is more likely than a more mature postnatal immune system to accept this foreign invader; and finally, the early correction of genetic defects will often avoid irreparable damage to the developing fetus. Paul Billings presents the counterargument (see page 255), stressing the difficulty involved in monitoring the safety of such protocols (and particularly subtle or long term adverse effects); the fact that there are alternatives to *in utero* gene therapy; and of course the considerable shortcomings of current gene therapy protocols.

But the mere mention of fetal gene therapy more often than not leads to a quite different discussion—that of germline alterations. Indeed, the possibility that somatic gene therapeutics may find their way to the recipient's germline and from there become part of the heritable genetic make up of the subject (also discussed in the above Commentaries) is often at the center of objections to the procedure. So far, only a few studies of this potential have been published, and none have shown any risk to the germline. Certainly the issue should be addressed and *in utero* animal trials should incorporate an assessment of the risk to the germline. But this issue should not stand in the way of future research and, when the time comes, human trials.

Even more troubling is the recent spread of the germline risk argument to include postnatal gene therapy trials. Philip Noguchi, Director of the Division of Cellular Therapies at the Food and Drug Administration (FDA), confirms that concern with germline spread is so great that after successful animal studies, some researchers have found their postnatal human gene therapy clinical trial protocols stalled over the germline issue. This is relatively new development at the FDA—traditionally, human trials have been approved without the need to examine the germline risk.

The RAC advises the FDA on such issues, and at a January 1999 meeting to discuss *in utero* gene therapy, the question of germline risk was tackled. James Wilson, director of the Institute for Human Gene Therapy at the University of Pennsylvania Medical Center, explained that because gene therapy vectors spread beyond the site of distribution, they find their way into the circulation and therefore inevitably into the gonads. Thus, there is a finite chance that vectors could integrate into the germline genetic material. Examination of gonadal tissue taken from animals used in post natal somatic gene therapy protocols confirms that gene therapy vectors injected intramuscularly do occasionally make their way to the gonads. But is an untoward effect on the germline likely?

Wilson has considered the efficiency of transduction within the gonads, the likelihood that such a transduction event involves a germ cell (as opposed to the preponderance of non-germ cells found in the gonads), and the chance that a vector insertion event might lead to a genetic defect. His conservative estimation of the overall risk of a negative outcome due to inadvertent germline gene transfer is in the order of a one in a billion chance or less! Of course these calculations are at best an approximation based on only a broad examination of the issues. But in conjunction with experimental data, they suggest that the risk that somatic gene therapy trials, postnatal or *in utero*, have a heritable component is not only unlikely, but so unlikely as to be an unnecessary distraction from the pursuit of effective *in utero* and postnatal gene therapy.

Data on gonadal and germ cell vector transfer is relatively easy to gather, and as it accumulates, these risks will be refined. While demanding that such analyses be incorporated into all future animal and human gene therapy trials, the FDA and other regulatory bodies around the world should resist inevitable pressure from luddites, and perhaps the politicians that listen to them, to delay these important trials because of a vanishingly small germ cell risk. Meanwhile, the community should start serious and open-minded discussions on the pros and cons associated with germline gene therapy itself—a completely separate issue.