What next for human gene therapy?

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Gene transfer often has multiple and unpredictable effects on cells

The high hope of genetic medicine for 30 years has been to develop a way of using recombinant DNA techniques to treat patients through the genes involved in their diseases. As Richard Roblin, scientific director of the Council on Bioethics of the President of the United States, put it in 1979: "There is something aesthetically compelling about cutting to the heart of the problem, by treating the disease at the molecular level, where it originates."[1] Since 1990, this vision has generated a modest industry of bench research and animal studies, culminating in almost 1000 clinical trials in humans around the world, for a wide variety of diseases.[2] In the past few years, however, the field has learned that in genetic medicine, as in war, the "surgical strike" is rarely as clean and effective as theory implies it should be.

After almost a decade without much clinical success,[3] the field has experienced in quick succession its first iatrogenic death,[4] its first apparent "cures,"[5] and then among those cured patients the first instances of serious downstream disease traceable to the main theoretical genetic risk of gene transfer—"insertional mutagenesis".[6] In the first such incident the development of T-cell acute lymphoblastic leukaemia in two of nine research subjects three years after (otherwise successful) gene therapy for their X-linked severe combined immunodeficiency disease was deemed by investigations in France and in the United States to be caused by "insertional mutagenesis at or near the LMO-2 gene with aberrant production of LMO-2 protein."[7] As a result in January 2003 the US Food and Drug Administration placed a "clinical hold" moratorium on all similar studies in the United States. To date this hold has not been lifted although individual protocols continued to be considered on a case by case basis at both the National Institute of Health and the FDA.[8]

Gene transfer research is at a crossroads, and to avoid a quagmire of setbacks that can only undermine international support for its efforts a broader coalition of its neighbours is required in genomics, proteomics, (study of proteomes or the protein complements of genomes), and cell biology, to know which way to turn. Meanwhile it is not too early to plan for the important social policy challenges that will emerge once the field's objective is achieved.

So far the compelling aesthetics of gene therapy have been successful in raising high expectations outside the field, and that is part of its dilemma. Advocates for patients with rare diseases continue to press for the right of families to take the risks of gene transfer research on behalf of their loved ones.[9] The World Anti-Doping Association, which monitors performance enhancing drug use in international sports, has begun seriously to entertain the prospect that undetectable gene transfer interventions could help elite athletes cheat.[10] And science policy organisations, such as the American Association for the Advancement of Science, have begun to highlight the risk that human germ line genetic modifications could occur first in the relatively unregulated clinical sphere of international infertility medicine.[11] In these contexts, desperation, national pride, and professional foolhardiness may thrust gene therapy unwillingly into political and ethical minefields that its current regulatory structures cannot help navigate.

One of the early lessons of the international effort to map and sequence the human genome has been the discovery that the human species makes do with far fewer genes than had been predicted: roughly 35 000 rather than 150 000.[12] This discovery might seem to simplify the gene therapists' mission, but it actually has the opposite implications. To produce the vast host of proteins used by human cells, our genes must be capable of "multitasking," by having their component coding regions rearranged and recombined with subunits of other genes for transcription. This versatility means that mutations in a gene—therapeutically induced or otherwise—will ramify through the cellular proteome in multiple directions, depending on how the modified coding region is used by the cell. Moreover, the orchestration of this complex dance is primarily in the hands of the cellular environment, not the nuclear genome. This clouds the surgical metaphor for genetic modification considerably. Gene transfer is more like introducing rabbits to Australia than it is like a heart transplant: it makes change in a cellular ecosystem that will almost always be pleiotropic in its effects, and often in unpredictable ways.

To date, gene transfer researchers have invested heavily in building "rabbit proof fences," designed to contain the molecular effects of misdirected genetic insertions. It may be prudent now to focus on learning more about the cellular dynamics of correctly targeted gene transfers, taking advantage of the tools and knowledge that the next few years of research in genomics and proteomics will bring. In the meantime, now is the time for the gene transfer research community to become more involved in shaping the social policy context for their work.[13] Desperate parents, unscrupulous coaches, and adventuresome infertility specialists will all need the aid of skilled scientists to take the steps that could compromise further medical progress in genetic medicine. If gene transfer researchers are alert to these issues, accurate in their advertising, and articulate about the moral convictions that guide them, the field can go far to secure its pride of place in the new world of genetic medicine now beginning to emerge.

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Persistent atrial fibrillation: rate control or rhythm control

Rate control is not inferior to rhythm control

Atrial fibrillation is the commonest sustained tachyarrhythmia encountered in clinical practice.[1] With an ageing population and improved survival of patients with cardiac disease its prevalence continues to rise.[2] It is associated with a doubling of overall morbidity and mortality from cardiovascular disease[3] and is the most common cause of embolic stroke.[4] Restoring sinus rhythm holds the theoretical advantage of reducing the risk of thromboembolism and need for anticoagulation and improved haemodynamics and quality of life. However, most current anti-arrhythmic drugs have limited efficacy and several side effects. With the use of anti-arrhythmics and serial electrical cardioversion for early relapse up to 53% of patients are in sinus rhythm at one year,[5] but only 25% remain so at five years.[6] Considerable controversy therefore exists as to whether rhythm or rate control is the more appropriate management for most patients with persistent atrial fibrillation. Five recent trials have looked specifically at this issue.

The PIAF study was the first randomised published study to compare rate versus rhythm control in 252 patients with persistent atrial fibrillation (of <1 year's duration).[7] The investigators reported no difference in the one year primary end point of improvement in symptoms between the two groups, but higher admission rates and more frequent adverse drug effects occurred in the rhythm control group. This study included only symptomatic, younger patients (mean age 60 years) and had a short follow up period (one year).

Similar findings were reported in the equally small (205 patients) HOT CAFÉ study (mean age 61 years).[8] Again more patients were admitted to hospital in the rhythm control group ($P<0.0001$), despite a measurable improvement in exercise tolerance at one year follow up.

A longer follow up (mean 19.6 months) was employed in the STAF pilot study (in press), although numbers were again small (200 patients with ≤ 2 years' duration, mean age 66 years).[9] This study showed that selecting patients with an increased risk of recurrence of atrial fibrillation was, not surprisingly, associated with a low rate of sinus rhythm in the rhythm control group (23% after three years), in spite of up to four cardioversions and up to four anti-arrhythmic drugs for each patient. There was no difference between the two treatment groups in terms of the combined incidence of death, stroke or transient ischaemic attacks, cardiopulmonary resuscitation, and systemic embolism. Again, except for increased admissions in the rhythm control group, there was no difference in secondary end points.

Two larger studies recruited older (and truer to "real life") patients with longer follow up. The RACE study randomised 522 patients (mean age 68 (SD 9) years) with recurrent persistent atrial fibrillation to either rate control or rhythm control.[10] After a mean follow up of 2.3 (0.6) years, no difference was seen ($P=0.4$) in the primary composite clinical end point of death from cardiovascular causes, heart failure, thromboembolic complications, bleeding, pacemaker implantation, and severe adverse drug effects between the rate (17.2%) and the rhythm control group (22.6%).

The landmark AFFIRM study, the largest to date, also had the longest follow up.[11] It randomised 4060 patients (mean age 69.7 years) with a history of atrial fibrillation and increased risk of stroke. It is the only study large enough to have looked at mortality as a separate end point. The primary end point of overall mortality (at five years) was no different between those assigned to rhythm control (356 deaths) and those assigned to rate control (310 deaths; $P=0.08$), although some separation in the survival curves was evident from two years in favour of the rate control group. Furthermore, there was no difference in the composite secondary end point of death, disabling stroke, disabling anoxic encephalopathy major bleeding, and cardiac arrest. As in other studies, a rhythm control approach was associated with a higher rate of admission and more adverse drug effects, with a greater rate of treatment crossover (27.3% at three years and 37.5% at five years).

In conclusion, although these five randomised trials have compared heterogeneous groups of patients, several consistent messages have emerged for patients for whom cardiologists felt that randomisation to rate or rhythm control was an acceptable strategy. Firstly, with current anti-arrhythmics a rhythm control approach does not lead to an improvement in symptom control or quality of life or a reduction in clinical events in the short to medium term. In fact, in the longer term, mortality may increase. Secondly, maintenance of sinus rhythm remains poor, even with

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