There's a Whole Lot of Nothing Going On

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If he was alive now, Sir Peter Medawar, the British immunologist, might well say of gene therapy (as he actually did of psychoanalysis), "Considered in its entirety, [it] won't do. It is an end product, moreover, like a dinosaur or a zeppelin: No better theory can be erected on its ruins. . . ." If gene therapy is ever to generate end products, it needs to turn back from its evolutionary dead-end, to come out of the clouds of its ambitions, and instead to build upward from its scientific base.

The air in the lofty aeries where the practitioners of gene therapy congregate is often thick with discussion. But oddly enough, the indignant chatter of late has been less of science, and more of intellectual property—a reflection, one suspects, of the relative abundance of the two in the field. The grit for most debate has been U.S. 5.399.346, the broad "*ex vivo*" gene therapy patent assigned to French Anderson, Michael Blaese, and Steven Rosenberg and licensed to Gene Therapy Inc. (Gaithersburg, MD). But some people in the field do find the whole patent debate annoying. Chairing a recent Keystone Conference on gene therapy, Savio Woo of Baylor (Texas) banned all talk of patents during the sessions. Needless to say, delegates resumed their discussions in the coffee break, though in deference to Woo, their tones were hushed and they spoke only of "the P-word."

At present at least, any discussion of ownership in gene therapy patents is not just tiresome, it is also largely irrelevant. Who owns what matters little when the chattel has no value. Ownership may be an incentive to make something work (and nonownership a disincentive). But what is clear in gene therapy so far is that not much of what has been trialed (tried) does work. The only thing that gene therapists can say so far is that their techniques don't kill people.

How can that be so? Since 1990, over one hundred gene therapy trials have begun, and many have been completed. Surely, patients, investors, and researchers should have had some more encouraging news by now?

The reason they have not, I believe, is that gene therapy has been riding a merry-go-round. Gene therapy was a "good story" with a simple plot: patient gets sick, patient gets gene, patient gets well. Since it began, therefore, gene therapy has been busy. Lots of people have been doing something and it didn't much seem to matter what. In fact, as long as they were all doing something different from each other (and to this, perhaps, patents have contributed), there was a newsy niche for everyone.

There has been a strong commercial imperative to undertake spectacular clinical trials. It became a hallmark of gene therapy that a company would form one month, and enter clinical trials the next. The news flow encourages investors. Every other week there is (or was) a new vector, a new trial, a new company.

There has been a strong medical imperative, too. It is no accident that terminal cancer represents a hugely disproportionate fraction of gene therapy indications. When patients have but a few miserable months or weeks to live if untreated, then—for physician and patient alike—almost any kind of snake-oil will do. Not that gene therapy is snake-oil. But as long as the wheels of gene therapy are stuck in the rut of potentially risky retroviral vectors, only treating the most desperate of conditions is justified.

Unfortunately, what has been lost in the scramble is the science. For example, the average number of patients enrolled in each gene therapy trial is around six. What statistical test will find significance in those numbers? Consider, too, that most of the trials have had little scope for rigorous control groups of patients: What chance is there, therefore, for demonstrating efficacy? But, I hear you argue, most of the trials were only phase I studies and, therefore, not designed to show efficacy.

Strictly speaking, that is true enough. And yet, where it is patients rather than healthy volunteers that are in the phase I trials, and where the risk in those trials is being offset by whatever hope gene therapy might offer at the last, then some indication of efficacy surely must be sought. At the very least, one would have expected from the trials some information on the design of vectors, on the relative cost and safety of the various gene therapies, and on their underlying science. But in most cases, today's gene therapy cannot even offer that.

The combination of the commercial and medical imperatives has fragmented the field. Virtually every study is unique in vector design or in indication, or both. As a result, there is no "body of work" in gene therapy. Nobody asked whether the enterprise as a whole made sense scientifically. One of the leading lights in the field has publicly admonished even those who were doing more fundamental studies—such as tracing the delivery of marker genes—to "get on with it and get into clinical trials."

It is only now, when the clinical results are equivocal that the folly of that approach is clear. And it is only now, with the formation of the special National Institutes of Health (NIH) committee under Inder Verma (Salk Institute, La Jolla, CA) that the science underlying gene therapy is being properly scrutinized. In the meantime, gene therapy is the loser. The field seems to have little sense of direction. Thus, it is difficult to judge the value of any particular piece of intellectual property (but that doesn't stop the empty prattle while people try). And that will make it extremely difficult for any investor to reinvest in companies developing the technology. ///