Gene Therapy – Where Do We Go?

Amos Etzioni MD

Meyer Children's Hospital, Haifa, Israel
Affiliated to Technion Faculty of Medicine, Haifa, Israel

Key words: gene therapy, severe combined immunodeficiency, leukemia

IMAJ 2003;5:883–884

Gene therapy, a notion once considered fantastical, is today a very real part of modern medicine. However, as clinical trials began, complications were encountered that cast doubt on the excitement. The extraordinary progress of human genetic research during the past three decades has led to the characterization of most common single gene disorders as well as many uncommon ones. As soon as the first single gene defects were defined, the notion of gene therapy was proposed. Namely, if a normal wild-type gene could be effectively delivered to the right cells, then the disease, which is due to a single gene defect, can be cured [1]. Unfortunately, the first attempt at gene therapy, undertaken 20 years ago, where the β globin gene was injected into a patient with β-thalassemia, failed because it was not based on an understanding of gene regulation.

It soon became clear that identifying a gene sequence and a disease-causing mutation was not a sufficient basis for gene therapy. Understanding gene regulation and maintaining its activity are crucial for successful gene therapy. One of the main obstacles was the location of effective vectors that can enter the desired cell. The target cell can either be in culture, thereby allowing *ex vivo* gene transfer, or it can reside in organs or tumors, which would require *in vivo* gene transfer [2]. A major setback to the *in vivo* trials occurred in 1999 when an 18 year old boy with ornitine transcarbamylase deficiency died from hepatic failure several days after an adenovirus vector was used to deliver potentially therapeutic DNA to the liver [3].

Selected mammalian viruses have been engineered as viral vectors to treat human diseases. These fall into two classes: those that persist in the host and are therefore best suited for long-term gene replacement therapies, and viruses that are solely lytic in nature and thus provide powerful tools for the "hit and run" application for vaccination or tumor destruction [4].

In this issue of *IMAJ*, Touraine and colleagues [5] describe the use of gene therapy as an option to control human immunodeficiency virus infection. Although these are preliminary animal data, it seems reasonable to believe that such an approach may be feasible in the future in human subjects as well. Gene therapy is an attractive option for inherited blood-borne diseases since gene transfer into hematopoietic stem cells with self-renewal capacity should lead to cure. In such trials the corrective gene can be packaged into modified retroviruses, which can incorporate themselves into the host cells' DNA. These retroviruses are stripped of most of their viral genes to prevent them from causing dangerous infections. Initial clinical trials using retroviral vectors to treat severe combined immunodeficiency and other inherited immunodeficiency syndromes, including leukocyte adhesion deficiency and chronic granulomatous disease, were hampered by very low levels of gene transfer into the hematopoeitic stem cells [6]. Advances in the technology – such as using cytokines during the *ex vivo* infection phase or using different culture medium and manipulating the retrovirus vector – enabled the French group led by Alain Fischer to conduct the first successful gene therapy in 11 children with SCID due to a common α-chain defect [7]. Recently, a combined effort from Milan and Jerusalem cured two children with SCID due to adenosine deaminase deficiency. In order to enhance engraftment of the transduced CD34 stem cells these investigators also administered a small amount of chemotherapy just before the treatment [8].

Still, gene therapists cannot control where retroviral vectors insert themselves. One of the main problems is that a vector could disrupt important genes through "insertional mutagenesis" and, if the gene involved is one that normally regulates cell growth and division, cancer could result. Indeed, almost 3 years after therapy was completed, with normal immune reconstitution, leukemia developed in two patients from the French trial [9]. Significantly elevated leukocyte counts were detected during routine examination, and further investigation showed the development of clonal T cell proliferation. In both cases, the leukemia cells contained a single intact copy of the retroviral vector that had integrated into chromosome 11, near the promoter of the proto-oncogene LMO2, triggering the patients' leukemia [4]. The two patients are currently well and alive 2 years after cession of chemotherapy therapy [10]. Notably, in more than a decade, leukemia has not developed in any patients enrolled in other trials that involved retroviral transduction of stem cells. Better insight into leukemia pathogenesis is required in order to assess and ultimately minimize the relative risk of this complication in patients who receive gene therapy for blood cell diseases [11].

SCID = severe combined immunodeficiency

These two cases raised enormous concern about the future of gene therapy. Many editorials [12] were written and several committees were formed to deal with the future of gene therapy. Of interest is the opinion of parents of children with SCID, a fatal disease if not treated. If a suitable donor for bone marrow transplantation exists, gene therapy should not be considered. When there is no identical donor, parents feel strongly that having the option to make an informed choice is better than having no choice at all.

In the United States, the Federal Drug Administration put the trials that use retroviruses for gene therapy for primary treatment of SCID on temporary hold. Investigators were informed that in order to resume trials they need to modify their consent forms to reflect the real (not just hypothetical) risk of leukemia. They also need to provide monitoring plans for such adverse events. To date, no new case of SCID has been enrolled in such a study (J. Puck, personal communication). However, the FDA has not shut down any trials completely and has invited researchers to submit plans to proceed with their protocols on a case by case basis, weighing risks and benefits. Non-retroviral trials were not affected by the French experience and many are ongoing, especially in cancer, neurologic and cardiovascular areas.

To put the issue into perspective, we must remember that chemotherapy, tissue transplantation and many surgical procedures raised similar issues regarding risk to benefit assessment. We have also always to remember Robert Ingersol's words [9]: "In nature there are no rewards or punishments, there are consequences."

References

1. Verma IM, Somia N. Gene therapy – promises problems and prospects. *Nature* 1997;3890:239–42.
2. Fischer A, Hacein-Bay S, LeDeist F, Saint Basile G, Cavazzano-Calvo M. Gene therapy of human severe combined immunodeficiency. *IMAJ* 2002;4:51–4.
3. Lehrman S. Virus treatment questioned after gene therapy death. *Nature* 1999;401:517–18.
4. Kohn DB, Sadelain M, Glorioso JC. Occurrence of leukemia following gene therapy of X-linked SCID. *Nat Rev Cancer* 2003;3:477–88.
5. Touraine J-L, Sanhadji K, Sembeil R. Gene therapy for human immunodeficiency virus infection in the humanized SCID mouse model. *IMAJ* 2003;5:863–7.
6. Goebel WS, Kume A, Dinauer MC. Gene therapy for chronic granulomatous disease and leukocyte adhesion deficiency. *Int J Pediatr Hematol/Oncol* 2001;7:359–72.
7. Cavazzano-Calvo M, Hacein-Bey S, Saint Basile G, et al. Gene therapy of human severe combined immunodeficiency (SCID) – X1 disease. *Nature* 2000;288:669–72.
8. Aiuti A, Slavin S, Aker M, et al. Correction of ADA-SCID by stem cell gene therapy combined with non-myeloablative conditioning. *Science* 2002;296:2410–13.
9. Check E. A tragic setback. *Nature* 2002;420:116–18.
10. Hacei-Bey-Abina S, Von Kalle C, Schmidt M, et al. LMO2 associated clonal T cell proliferation in two patients after gene therapy for SCID-X1. *Science* 2003;302:415–19.
11. Noguchi P. Risks and benefits of gene therapy. *N Engl J Med* 2003;348:193–4.
12. Juengst ET. What next for human gene therapy? *Br Med J* 2003;326:1410–11.

Correspondence: Dr. A. Etzioni, Meyer Meyer Children's Hospital, Bat-Galim, Haifa 31096, Israel.
Phone: (972-4) 864-2646
Fax: (972-4) 854-2441
email: etzioni@rambam.health.gov.il