Opinion on the use of somatic gene therapyprocedures. Report.

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Opinion

Somatic gene therapy can be defined as the use of genes as medication for treating hereditary or acquired disease, without modifying the patient's heredity.

The treatment can be applied to cells taken from the patient, cultured outside the organism (ex vivo), and into which a gene with a hopefully therapeutic effect is introduced. These " genetically modified" cells are then retransplanted into the patient. It is for this type of gene therapy that the National Consultative Ethics Committee gave a favourable Opinion, on December 13th 1990, indicating, however, that it is advisable " *to 1imit the possibilities of gene therapy exclusively to somatic cells, and formally to prohibit any deliberate attempt to modify the genome of germinal cells, and any gene therapy involving the risk of such modification. In the same spirit, it is advisable to prohibit the transfer of genes by viral vectors into the human embryo, given the associated risk of affecting germinal cells. In the domain of hereditary disease, gene therapy research should be envisaged only for diseases resulting from an anomaly involving a single gene (monogenic disease), and leading to particularly severe pathology* " .

However, many diseases cannot be treated by this approach of autotransplantation of ex vivo genetically modified cells, because in these cases the cells to be affected are disseminated throughout the body, and cannot be sampled and/or cultured. Then the only possibility is to introduce the therapeutic gene directly into the organism (in vivo), by means of viral or inert vectors.

When applied after birth to patients with severe morbidity, these in vivo somatic gene therapy protocols do not seem to raise problems that are fundamentally new with respect to therapeutic trials in general, whose rules they must follow, in particular those defined by the law of December 20th 1988 on the protection of persons engaged in biomedical research. The committees constituted by this law (Consultative Committees for the Protection of Subjects in Biomedical Research - CCPPRB) must, of course, be consulted systematically. Moreover, whenever the use of genetic engineering methods is involved, the trial protocols must also conform with the provisions of the law, dated July 13th 1992, on the use of genetically modified organisms, and be submitted to the commissions constituted by that law.

In so far as the National Consultative Ethics Committee is concerned it recalls that any intervention with the objective, in the absence of severe disease, of changing an individual's general physical or mental characteristics is to be excluded.

- It considers that somatic gene therapy trials must be preceded by *prior animal experimentation* sufficient to specify the possible effectiveness and the probable innocuity of the techniques in question.

- It believes that such trials should be considered only in patients *whose morbid condition has no effective available treatment* , and with a sufficiently severe prognosis to justify the potential risks involved in the application of a treatment that is still largely experimental.

In this particularly important area, with future applications possibly having a broad scope, it is absolutely necessary that there be *careful monitoring of the results of these trials* , by a technically and scientifically competent evaluation commission, and by the National Consultative Ethics Committee in so far as general developments in the area are concerned.

One important ethical aspect of gene therapy trials is the information given to the families concerned, and to the public at large, about current experimental work. In an area as sensitive as serious genetic children's diseases, for example, parents cling to every ray of therapeutic hope. Any *information* on the progress of research, and the announcement of possible consequences for the treatment of these diseases *must therefore be imbued with objectivity, restraint, moderation and realism* , with particular stress on the long lead time needed for optimal development of these types of treatment, and for evaluation of their effectiveness and of their possible side effects.

Report

The National Consultative Ethics Committee published an Opinion on gene therapy on December 13th 1990.

Since that date, our knowledge about experimental models has progressed quite far, but applications to man are still very limited, and much time-consuming work needs to be done before we achieve convincing evaluation of the effectiveness and promise of these techniques.

Taking recent progress and new possibilities into consideration, it is opportune to flesh out some of the points made in the first Opinion.

It is first necessary to recall the ethical considerations of the Opinion dated December 13th 1990.

- Only the correction of a specific genetic defect leading to severe symptoms in the patient should be considered, and any intervention should be formally prohibited, when the objective would be, to the exclusion of any therapeutic indication, to change an individual's general physical or mental characteristics.

- Any attempt at germinal gene therapy is to be excluded. Germinal gene therapy is a procedure that affects reproductive cells, that is, male and female gametes (spermatoids and oocytes), and therefore involves transmission of the resulting genetic modification to the patient's progeny. In the present state of our knowledge and techniques, it would imply the transfer of a gene to a very early, unicellular embryo, resulting in a " transgenic" man or woman, possessing the supplementary " transgene" in all cells, and notably in his or her germinal cells. Transgenesis is commonly used in the animal and plant kingdoms, to endow the organism with characteristics that are " advantageous" for farmers, producers or industrialists.

In man, one could envisage using this technique to correct a mutant gene responsible for a severe monogenic disease. The actual implementation of such a project would require, however, prior analysis of in vitro cultured embryos, in order to select those presenting the deficit one wished to correct. But this diagnosis would allow for simultaneous identification of embryos not presenting the deficit, and it would suffice to transfer them to achieve the birth of a healthy child, without recourse to the as yet uncertain method of transgenesis. In summary, since pre-implantation diagnosis of the morbid condition is indispensable, the

logical consequence should be embryo selection rather than gene therapy with uncertain results.

Scientific data on the methods of somatic gene therapy

The techniques for introducing a gene into a cell can be applied either outside the organism (ex vivo), or directly into the organism (in vivo).

The ex vivo techniques

They modify the genome of cells that are taken from the patient's organism, cultured and re-injected after introduction of the gene through a viral vector or by any other means. This amounts to autotransplantation of genetically modified cells.

These techniques can be applied:

- to circulating blood cells. This is the method currently being evaluated for gene therapy of ADA deficiency.

- to organ cells, for example, fibroblasts, hepatocytes, medullary stem cells or myoblasts, which, after introduction of the gene, are injected, in situ, into the tissue where the gene is normally expressed when it is not deficient, or at any other site, when the purpose is to produce a protein medication active within the circulation and/or in other cells.

It is also possible to introduce the gene into cells cultivated in a collagen fibrous bundle, constituting an " organoid" . When introduced into the organism, the organoid vascularizes and diffuses the protein that should normally be produced by the gene for which the recipient is deficient, or more generally, of which a therapeutic effect is expected.

In all these techniques, the important steps of cell genome modification take place ex vivo. It is possible to check for the quality of this modification, and for the absence of viral particles, before re-injection into the deficient organism.

However, there are many situations where such a method cannot be applied, for example, whenever the cells to be corrected are not precisely known, cannot be cultivated, or are spread throughout the organism.

The in vivo techniques

The last two years have seen the emergence of new techniques, allowing for the introduction of a gene into cells located within the organism. They open up the possibility of envisaging gene therapy application to situations, that cannot be tackled by autotransplantation of genetically modified cells.

Two types of methods are under study:

- introduction of copies of the gene associated with an inert medium, for example liposomes or lipid micro-vesicles, which are capable, upon introduction into the organism, of blending with cell membranes, thereby allowing for intracellular transfer of the gene.

- introduction into the organism of the gene within a viral, non-pathogenic vector, for example an adenovirus, that infects the target cells. This viral vector can be introduced directly by in situ injection, or indirectly by spraying (for tissues of the respiratory tree), or even by systemic administration (not yet considered to a great extent). These methods, with an adenovirus as the vector, are the object of substantial research, but raise problems connected with the introduction of a human virus into the organism, as well as difficult questions about the immediate reaction to the viral infection, the immune response,

possible recombination with wild viruses, the diffusion of the virus within the organism, and the possible risks of diffusion to the environment.

Nevertheless, somatic gene therapy does provide the first hope for treatment of and recovery from severe monogenic illnesses, not amenable to any existing therapeutic approach.

Ethical problems raised by somatic gene therapies

Somatic gene therapy trials in man do not give rise to essentially new ethical problems. Such trials must conform with general rules governing therapeutic trials, and in particular with the law of December 20th 1988 on the protection of persons engaged in biomedical research. The protocols of such trials must be submitted to the Consultative Committees for the Protection of Subjects in Biomedical Research (CCPPRB) constituted by this law.

Somatic gene therapy trials must be preceded by prior animal experimentation, sufficient to determine the possible effectiveness and probable innocuity of the proposed techniques.

Somatic gene therapy trials should be considered only for patients, whose morbid condition has no effective available treatment, and whose prognosis is sufficiently serious to justify the potential risks involved in the application of a largely experimental treatment.

In this particularly important area, whose future applications may be broad-ranging in scope, it is absolutely necessary that careful monitoring of the results of trials be provided for, although such monitoring is not envisaged by the law of December 20th 1988, and is not within the CCPPRB's competence.

Such monitoring should include both scientific evaluation by a competent evaluation commission, and general reflection by the National Consultative Ethics Committee on practical developments in the field.

Moreover, since these procedures draw on the methods of recombinant DNA and genetic engineering, the protocols of the trials must conform with European directives, and with the French law of July 13th 1992 on the use of genetically modified organisms.

One important ethical aspect of gene therapy trials is the information given to the public, and to the families involved, about current experimental work. In an area as sensitive as severe children's genetic diseases, parents cling to any ray of therapeutic hope.

Information about the progress of research, and the announcement of possible consequences for the treatment of these diseases must therefore be imbued with objectivity, restraint, moderation and realism, with particular stress on the long lead times needed for optimal development of these types of treatment, and for the evaluation of their effectiveness and their possible side effects.

The National Consultative Ethics Committee is already involved in more general thinking about how scientific information is conveyed to the public, about the role of the media, and about the behaviour of scientists in this respect.