



EUROPEAN SOCIETY OF GENE THERAPY

Position paper on social, ethical and public awareness issues in gene therapy

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The European Society of Gene Therapy (ESGT) is a professional society dedicated to the development of gene therapy, cell therapy and genetic vaccines (<http://www.esgt.org>). The mission of ESGT is to promote basic and clinical research in gene therapy, and education and information on the technology of gene transfer and its application to clinical medicine. A crucial part of the ESGT mission is to serve as a professional adviser to the scientific community, governments and regulatory bodies, and the general public in Europe. This position paper is meant to contribute to the social debate on gene therapy and the emerging technology of genetic and molecular medicine.

1. What is gene therapy?

Gene therapy is a technology by which genes or small DNA or RNA molecules are delivered to human cells, tissues or organs to correct a genetic defect, or to provide new therapeutic functions for the ultimate purpose of preventing or treating diseases. Although the term gene therapy is often associated to the concept of genetic modification or manipulation of the human genome, the most common use of this technology implies addition of new genetic information to human cells rather than alteration of their genome. The most comprehensive description of gene therapy is therefore the use of recombinant genetic material (DNA, RNA or hybrid molecules) under different forms or pharmaceutical preparations, as a therapeutic agent.

2. The technology of gene therapy

The delivery of genes (gene transfer) can take place directly into the patient's body (*in vivo* gene therapy), or in cells which are treated outside the body and then re-implanted or re-infused into the patient (*ex vivo* gene therapy).

In *in vivo* gene therapy, a therapeutic gene is administered to a specific tissue or organ for a defined application. The administration can take the form of particles derived from disabled viruses (viral vectors), artificial particles (synthetic vectors), or "naked" DNA. The route of administration can be intravenous, intramuscular, by inhalation, or by direct injection into the target organ.

In *ex vivo* gene therapy, the cells come either from the same patient (autologous treatment) or from a donor (allogeneic treatment). Gene transfer is carried out in culture by many different techniques, again involving viral or non-viral vectors. Due to limitations in growing, manipulating, and re-administering cells from many tissues and organs, *ex vivo* gene transfer is today essentially limited to blood, skin and liver cells, to cells of the immune system, or to tumor-derived cells used as cancer vaccines.

Both *in vivo* and *ex vivo* approaches have advantages and limitations. *In vivo* gene therapy may appear an ideal concept, due to its potential simplicity and similarity to traditional therapies. The currently available technology, however, is far from optimal in terms of efficacy, and in some of its applications also in terms of safety. The viral and non-viral vectors developed so far can efficiently target only a few organs (essentially, liver, brain, and respiratory airways), and do not normally allow permanent insertion of genes into the target cells. These factors limit the application of the *in vivo* technology to the treatment of cancer and a small number of genetic diseases, or to applications requiring short-term gene expression, such as genetic vaccination (the use of DNA as an immunizing agent). On the other hand, *ex vivo* technology is better controlled and more efficacious, and allows permanent integration of genes into the genomes of the target cells. However, it implies expensive and labor-intensive manipulation of cells and tissues, which at present are performed only in highly qualified centers, and may require more invasive procedures.

Despite these limitations, gene therapy has entered a phase of active clinical investigation in many areas of medicine. Human clinical trials have started for the

treatment of severe congenital immunodeficiencies, hemophilia, cystic fibrosis, familial hypercholesterolemia, Duchenne muscular dystrophy, AIDS, cardiovascular disorders, and many types of tumors (melanoma, leukemia/lymphoma, prostate, ovarian and lung cancer). Although it's probably too early to draw significant conclusions from the almost 400 running clinical trials, encouraging results have already been obtained, and useful lessons have been learned from successes and failures. Early enthusiasms about the enormous potential of gene therapy have certainly generated much hype and many unfounded expectations. ESGT is actively promoting a more balanced and realistic view of the potential risks and benefits of this technology, which is making slow but continuous progress and has recently showed its potential in the cure of at least two types of severe genetic immune deficiencies. As always in the history of medicine, the development of a completely new and potentially revolutionary therapeutic approach needs time, patience, and labor. The academic research community is actively working in this direction, while the biotechnology industry is providing the economic and human resources necessary to transform scientific knowledge into technology and products. It is this combined effort that will ultimately make human gene therapy a clinical reality.

3. Genetically modified cells and genetically modified organisms

There is a conceptual and substantial difference between the creation of genetically modified organisms, and the use of genes to modify the functions of cells or tissues in individual patients for therapeutic purposes. Examples of the former technology are the development of transgenic plants or animals. Examples of the latter include the development of genetically modified tissues or organs to produce therapeutic substances directly into the patient's body.

Gene therapy does not imply the permanent modification of the inheritable genome of a patient, but only a permanent or transient modification of the genetic information of specific cells (somatic cells). Germ line (sperm or ovary) cell modification to permanently alter the genome of a human being and its progeny is not an available technology at the moment, and is considered undesirable and unethical in the European Union, the United States and the vast majority of the economically and scientifically developed countries. As an organization of professionals directly involved in the development of gene transfer technology, ESGT shares these ethical and social concerns and does not support germ line gene therapy.

4. Why do we need gene therapy?

Despite the high standard of today's medical treatments and the number of available drugs, most human diseases do not have a cure yet. The molecular basis of many genetic disorders, such as hemophilia, cystic fibrosis or muscular dystrophy, has been elucidated by the discovery of the affected genes. In many forms of cancer, genetic predisposition plays a role, as important as environmental factors, in tumor growth and malignancy. Genetic research is therefore progressively changing our diagnostic tools and our view of preventive medicine.

In order to have an impact on treatment, genetic knowledge has to be translated into therapeutic strategies. Gene therapy may provide a curative rather than a symptomatic approach to diseases, by directly treating a genetic defect through the transfer of new genetic information into the affected cells or organs. Therefore, gene therapy may become the treatment of choice for many chronic, life-threatening, and so far incurable diseases, including cancer, diabetes and cardiovascular disorders. Compared to traditional pharmacology, gene-based biotechnology shows a number of potential advantages, including safety (most gene products are natural human substances), efficacy (genes will treat the cause, not the symptoms, of a disease), faster development, and a modest impact on the environment. Genes introduced in tissues and organs for transplantation may reduce the risk of rejection with lower toxicity and less side effects than the current immunosuppressive drugs. Development of artificial organs made by autologous, genetically-modified cells may allow to overcome the severe organ shortage currently limiting the use of transplantation, and extend the availability of an organ replacement therapy for common diseases such as diabetes. In addition, the use of DNA as a vaccine may provide new therapeutic opportunities for developing countries. DNA is inexpensive to manufacture, ship, and store in a stable and standardized form, and might therefore boost vaccination programs for infectious diseases (malaria, AIDS) or some forms of endemic cancer (Burkitt's lymphoma) in areas of the world where lack of resources limit the diffusion of preventive medicine and comprehensive care.

5. Is gene therapy safe?

In the last fifteen years, gene transfer technology has been the subject of thorough and in-depth research with particular emphasis on its safety aspects. Pre-clinical

investigation carried out in animal models for many years and in many different countries has provided little evidence that the use of genes or gene-carrying vectors is more harmful or dangerous than conventional drugs or therapies, supporting the initiation of clinical trials in human patients. Gene therapy entered the era of clinical applications in 1991, and since then the number of clinical trials has steadily increased. As of September 2001, there are more than 600 gene therapy clinical trials worldwide, involving more than 3,500 patients mainly affected by cancer (63 %), genetic (13 %), cardiovascular (8 %) or infectious (6 %) diseases (source: the Journal of Gene Medicine Clinical Trial Database at <http://www.wiley.co.uk/genetherapy/clinical/>). Most of these trials (98 % of trials and 93 % of patients) are in so-called phase I/II of clinical development, and have therefore specifically addressed the issue of safety and toxicity of the vector and of the expression of the transferred gene. In general, no specific risk factor has been associated to the use of genes, gene transfer vectors or gene transfer procedures. Much effort has been put in testing the possibility that the introduction of new genetic material into cells may disrupt or functionally inactivate normal genes, or worse, activate cancer-related genes (oncogenes). The available evidence indicates that the likelihood of either phenomena is extremely low, although a lymphoproliferative disorder has been recently observed in a patient undergoing gene therapy for a severe immunodeficiency. The origin of this severe adverse event is at present unknown, but it has been suggested that a fortuitous integration of the gene transfer vector into an oncogene might have contributed in causing the malignant transformation. In 1999, an *in vivo* gene therapy trial for a rare genetic disease in the United States resulted in the unfortunate, sudden death of one patient. This is the worst adverse effect directly caused by a gene therapy procedure, reportedly due to acute toxicity of an extremely high dose of a specific type of vector (an adenoviral vector). Although loss of lives is always an unacceptable consequence of any medical intervention, it must be emphasized that gene therapy has so far demonstrated a safety record comparable to, or better than, any other therapy for life-threatening disorders.

An additional concern about *in vivo* gene therapy is the fortuitous insertion of genes into germ line cells that might be propagated to the patient's progeny. Therefore, both pre-clinical and clinical testing of gene transfer vectors for *in vivo* gene therapy includes monitoring the biodistribution of the vector, particularly in the reproductive organs.

A real assessment of all the risks associated to the many different gene transfer technologies in all potential applications will come only from extensive clinical trials

involving large number of patients. In this regards, gene therapy should not be considered different from any other novel surgical or pharmacological treatment.

6. The ethics of gene therapy

The development of genetic engineering and gene transfer technology has had a fundamental impact on both medicine and the ethics of medicine. The lengthy and thorough examination process that gene therapy underwent before, during, and after its first clinical application, including an extensive public debate, is unprecedented in the history of medicine. As a result of this process, gene therapy has been considered a mature technology, ready for clinical application. The ethical implications of gene therapy do not substantially differ from those of any other form of experimental medicine, as long as the human genome is not altered in an inheritable way. Gene therapy is practiced with the goal of curing patients, and possibly increasing their quality of life. These issues are covered by the basic principles of medical ethics, which essentially demand a careful evaluation of the risks and benefits of any therapeutic intervention for any disease. The questions raised by introduction of new genetic information into a human being are comparable, under many respects, to those raised by organ transplantation. Because of their novelty, and their still limited clinical record, the main issues raised by the use of new gene transfer vectors are of regulatory nature.

The most significant ethical issue is the establishment of solid criteria to judge if, and when, application of a specific gene transfer technology is mature for clinical application and justified by a specific clinical need. This is a critical issue, since many of the clinical trials proposed in the last years suffered from poor design and lacked convincing proof of efficacy due to insufficient pre-clinical data (see the conclusions of the ad hoc Committees on gene therapy established by the NIH Director in 1995 and 2000 at <http://www.nih.gov/news/panelrep.html>, and <http://www.nih.gov/about/director/07122000.htm>). ESGT recognizes the need of appropriate pre-clinical investigation in all gene therapy trials, including more basic research in the development of efficient and safe gene transfer vectors. At the same time, ESGT recognizes that there is no real substitute for clinical investigation, and that a correct assessment of the risk/benefit ratio for every patient involved in a clinical trial is the first and most important ethical criterion, for gene therapy as for any other medical treatment.

The position of ESGT is that clinical trials in gene therapy should not start before the results of pre-clinical investigation fully justify human experimentation. However, any unnecessary delay in applying a mature technology would prevent it from showing its therapeutic potential, postpone its development into effective therapeutic products, and ultimately affect the right of patients to have access to an effective treatment in due time. As such, delays would be as unethical as rushed or ill-conceived experimentation.

Although it is the most important, safety should not be considered the only ethical criterion in evaluating the opportunity of a gene therapy clinical trial. In many cases, the design of a trial is just as important as the safety of the procedure involved. Gene transfer, both in vivo and ex vivo, is a complex and relatively young technology that poses unprecedented problems in the establishment of its biological and clinical efficacy. The performance of gene transfer vectors is often unpredictable on the basis of pre-clinical investigation, and the complex biological interactions between the patient's body and the vectors and/or the genetically modified cells require complex monitoring procedures and careful definition of clinical endpoints. For these reasons, a gene therapy clinical trial should be designed with the goal of providing indications on the potential efficacy of a procedure as much as on the reasons of a its failure, should this occur.

ESGT recognizes the role of the many European ethical committees and review boards in overseeing the development of gene therapy trials in a controlled and unbiased fashion. In this regard, harmonization of criteria and reviewing procedures among the European states would greatly facilitate the development of common ethical rules, and increase public trust in the regulatory authorities as well as in the operators in the field.

7. Social and economic issues

If successful, gene therapy will have a significant impact on the social and economic cost of treating patients affected by many severe and otherwise untreatable diseases. The majority of so-called rare diseases are of genetic origin, and many are caused by mutation of known genes. More than 5,000 rare disorders have been identified worldwide, and Europe, with its great variety of population groups, is home to a large number of them. For most of these diseases, there is at present no definitive therapy, and the overall cost for European countries of the currently available long-term, symptomatic treatments is very high and frustratingly ineffective. Gene therapy might

eventually provide a definitive treatment at lower cost for the European public health systems, with a significant impact on the quality of life of patients and their families.

A large number of gene therapy trials are currently directed to the therapy of diseases with an enormous social impact, such as cancer, diabetes, cardiovascular disorders and AIDS. In all these fields genetic medicine, in combination with high-resolution diagnostics, conventional drugs and modern surgery, might provide new forms of treatments directed to currently unmet clinical needs and with a better impact on the patients' quality of life

The technology on which gene therapy is based is sophisticated and of high added value, and is expected to bring significant benefits to European countries in terms of technological and industrial development, increased employment opportunities for a highly-educated work force, and general improvement of the competitiveness of the European biomedical industry. Efficient technology transfer from academic laboratories to biotechnology and pharmaceutical companies is crucial for the competitive development of this technology. Cooperation between university and industry is particularly important in this early, high-risk phase of development, and should be promoted and supported by governments, institutions, and funding agencies. ESGT urges European states to take action to re-qualify the scientific careers in universities and research institutes, and to remove the existing obstacles to a more extensive and bi-directional exchange of human resources between academia and industry in the biomedical sector. ESGT believes that public funds, from both national and European agencies, must support primarily academic, open-ended basic research, which is the driving force of true innovation. However, governments should actively promote technology transfer and licensing activities from public institutions to industry, by providing funds or incentives to protect intellectual property rights, and remove legal obstacles for public employees – most European academic scientists – to start, or own shares of, spin-off industrial activities. At the same time, European guidelines and rules governing academia-industry collaborations and disclosure of potential conflict of interests by scientists and clinicians involved in privately funded research and clinical activities should be established and enforced.

8. The regulation of gene therapy

ESGT recognizes the role of the European Medical Evaluation Agency (EMA) and the many European government agencies in promoting the development of gene therapy in its many regulatory aspects. ESGT supports the establishment of guidelines and legislation for the design and approval of gene therapy clinical trials, for the development and manufacturing of gene therapy products, and for appropriate reporting and monitoring of clinical data. ESGT is prepared and committed to work with governments, academia, patients' groups and industry associations to implement an acceptable regulatory framework for the development and the appropriate use of gene therapy. The regulation has to insure that patients benefit in full from the development of new treatments by assessing efficacy, minimizing risks, and promoting commercialization of high-quality products. Since it involves the use of genetically modified organisms, gene therapy is covered across the EU by a complex body of legislation which is differently interpreted and implemented by the single member states (consult the EMA (<http://www.ema.eu.int/>) European State agencies (<http://heads.medagencies.org>) and ESGT (<http://www.esgt.org>) web sites for information and links). This leads to an undesirable high degree of heterogeneity, and creates unnecessary obstacles to a safe and timely development of this technology, particularly for the industry involved in the development of large clinical trials aimed at the registration and commercialization of gene therapy products. The current fragmentation of rules governing clinical trials, and the lack of a single European agency authorizing and overlooking early clinical experimentation (phase I/II trials) cause uncertainty and imposes an unnecessary bureaucratic burden on biotechnology and pharmaceutical companies involved in developing cell or gene therapy, and ultimately discourages the use of European clinical centers for this activity. Harmonization of criteria, legislation and procedures among the European member states, and between Europe and the rest of the world, is in the best interest of patients and the society at large, and would greatly facilitate the development of reliable clinical research and a competitive biotechnology industry in the EU. ESGT therefore urges the EU authorities to work on harmonization of legislation with top priority.

From a regulatory point of view, gene therapy products are currently regarded by most European countries as medicinal products, and are therefore subjected to the same regulation as conventional drugs for production and clinical experimentation. The main regulatory criteria are therefore safety, efficacy and quality, and clinical trials are regulated by the four-phase scheme used for registration and commercialization of any pharmaceutical product. However, concepts such as toxicity and efficacy, on which phase I/II trials are based, should be revised and adapted to the specific nature of gene

therapeutics and gene therapy clinical trials. ESGT actively promotes adaptation of existing legislation to the gene therapy reality, the adoption of scientific and flexible criteria for the establishment and implementation of regulation, and the development of a proactive and collaborative approach between regulators and operators. In this regard, Europe should acknowledge the role of the Food and Drug Administration as a major player in governing, stabilizing, and ultimately promoting development of new therapies in the US, and accelerate the establishment of EMEA as its European counterpart.

9. Information and public awareness

ESGT recognizes the importance of information and public awareness early in the development of novel medical technology such as gene therapy. ESGT is aware of the issues, the public concerns, and the ongoing debate on this technology, and believes that European citizens deserve access to reliable information in order to develop a balanced attitude towards gene therapy, which takes the benefits as well as the risks into consideration. ESGT is committed to participate to the public debate involving all stakeholders (legislators, academia, industry, patients' groups) by providing, through its Annual Meeting, its web site, and other institutional activities, high-quality information based on solid scientific knowledge. As the most representative association of the European gene therapy scientific community, ESGT will actively promote public discussion and the diffusion of balanced, qualified, and easily accessible information on the many aspects of gene therapy, and on its relevance for the future of the European Union and its citizens.