Medical-ethical guidelines for somatic gene therapy in humans

1. PREAMBLE

These Guidelines are addressed to all ethical committees and medical persons who are confronted with projects in the field of *gene therapy*[1]. *Somatic* gene therapy in humans is understood to mean interventions into the *genes* of somatic *cells* (a more precise description is given in Chapter 2 "Area of Application"). Article 24[novies] of the Federal Constitution makes the important restriction that direct intervention into the genes of the *germinal* cells, i.e. changes made with the aim of passing these on to future generations, is forbidden. Unintentional modifications to the germinal cells, such as can occur in accepted forms of therapy (*chemotherapy*, *radiation therapy*) are excluded from this restriction. The following considerations relate exclusively to somatic gene therapy.

Considerable expectations are being placed in the use of gene therapy in areas that up till now have not been readily accessible to medicine, or only unsatisfactorily so: *hereditary diseases*, *AIDS*, *cancer*. There is at present intense medical activity, worldwide, aimed at determining the possible application and the limitations of gene therapy. At the same time, certain groups in society categorically reject any form of *genetic engineering*. The greatest fear is that gene therapy could be misused for the genetic "improvement" or "redesign" of the human being.

In order to make a judgment regarding gene therapy, particular consideration has to be given to the following aspects: the development of gene therapy requires major investments. Already at an early stage, the concept and the setting of priorities for *clinical trials* are determined by material interests. The promotion of health requires not only the assurance of continued research, but also the protection of the individuals concerned against abuse in the interest of third parties. The risk of an unintentional modification of the germinal cells or of a possible threat to the environment has to be thoroughly evaluated - which requires long-term follow-up, always taking into account the demand for confidentiality. Furthermore, gene therapy, as a technologically highly developed field of medicine, raises difficult questions of equity.

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[1] The words in italics are explained in the Glossary.

2. AREA OF APPLICATION

We understand gene therapy in *human medicine* to mean a modification to the *genetic programme* of cells, undertaken for the purpose of therapy or *prophylaxis*. This can be done either by specifically changing the structure or the function of individual genes in the human body in the long term, or by introducing into the human body *nucleic acid sequences* created by means of genetic engineering. With somatic gene therapy, hereditary transmission of the altered genes is neither intended nor desirable. Hence every effort must be made to prevent any changes to the germinal cells; in principle, the consequences of gene therapy must be restricted to the individual treated.

The following interventions do not belong to somatic gene therapy:

a) organ, tissue and cell transplantations, provided no genetic changes were made to the donor tissue before transplantation;
b) radiotherapy, cytostatic therapy and treatment with nucleoside analogues;
c) treatment with drugs manufactured by means of genetic engineering;
d) *therapeutic* modulation of gene expression.

3. PRINCIPLES

Gene therapy is only admissible under the following conditions:

3.1 The guidelines of the Swiss Academy of Medical Sciences on experimental research in humans are observed.

3.2 The Federal Committee for Biological Safety (EFBS/CFSB) has appraised and approved the proposed procedure from the scientific and technological points of view. The result of this appraisal and its justification must be made available, in an appropriate form, to all those entitled to have access to it.

3.3 Confidentiality of the *genetic data* of the persons treated is guaranteed.

3.4 The long-term follow-up of the consequences of the treatment by a central authority is guaranteed, according to the Federal Law for the Protection of Personal Data (Datenschutz-Gesetz, state 1.1.1995).

3.5 There must be a *medical indication* for the treatment. Gene therapy is only to be advocated if it is at least comparable to conventional procedures in regard to prognosis, risks and quality of life, and if it can be expected to provide clear benefits in the future.

3.6 The risks must be reasonably justifiable in relation to the chances of cure or alleviation and the severity of the disease. In particular, the risk of an unintentional modification

of the germinal cells, as a side effect, must be kept to the minimum and weighted appropriately.

3.7 The individuals concerned or their legal representatives are adequately informed of the nature of the proposed therapy and of the possible risks and have, in full knowledge of the implications, freely given their consent to the treatment.

4. COMMENTARY

re 1. Preamble:

For the time being, only a small section of the world population will be able to benefit from gene therapy. In order to avoid discrimination against developing countries steps could be taken to promote research into less costly procedures. Future developments in this field promise, for example, to provide cheap vaccines resistant to tropical conditions. In this as in other areas there is no other practicable way to gradually close the gap between industrialised and developing countries.

re 2. Area of application:

It is difficult to give a clear, unequivocal definition of gene therapy, as on the one hand one would like to include in it all conceivable developments in this field, while on the other one would not wish to introduce new regulations for long-established procedures.

- For example, certain *live vaccines* (e.g. *poliomyelitis*, yellow fever) cause a modification of the genetic programme of cells, although one cannot classify this type of vaccination, which has been practised for 40 years, as gene therapy. On the other hand, vaccinations with pure *DNA*, which lead to temporary *reprogramming* of certain somatic cells, have to be considered as gene therapy.

- Genes, like *hormones* or *cytokines*, can be activated or neutralised by drugs, a process that one would not wish to classify as gene therapy, whereas the use of chemically modified *RNA*, such as *anti-sense RNA*, for example, should be considered as gene therapy.

- The *implantation* of cells or organs that have been genetically altered falls within the definition of gene therapy, even if the patient's own cells are not subjected to genetic modification.

- The genetic modification of cells of human origin "*in vitro*" is considered as gene therapy, provided the modified cells are implanted into a human organism.

re 3. Principles:

re 3.1 The success rate obtained with gene therapy is still modest. It can be expected that in the foreseeable future every gene therapy project will constitute a *research study in humans* and will thus be subject to the corresponding SAMS guidelines.

re 3.2 Even a purely technical study, designed to assess safety aspects only, will not be permitted without prior appraisal of risks in relation to benefits. It is therefore important that the responsible ethical committees and the persons who are directly involved (including the patients to be treated) are aware of the considerations that have led the EFBS to grant a safety certificate authorising the use of gene therapy in each individual case.

re 3.3 Genetic data require special protection, since they can have life-long consequences for the individual.

re 3.4 Possible consequences of gene therapy that do not become *clinically manifest* or detectable for several years could only be recognised if follow-up is guaranteed and if all gene-therapy studies carried out in humans are recorded and stored in a central registry for Switzerland. Follow-up controls with *eugenic purposes* in mind are not permitted.

re 3.5 This in itself normal requirement, which applies to all medical interventions, assumes particular importance here, because it can be envisaged that the indications for gene therapy will change in the course of time. In a first phase, gene therapy will be used only in certain serious diseases. Later, less serious diseases will also undoubtedly be considered, A threshold will be approached where it could be more a question of "improvement" than "cure" or "alleviation". This threshold should not be crossed. The ambition to use a new form of therapy must not lead either doctors or patients to wish to obtain a therapeutic success with gene therapy at any price, in cases where traditional procedures are available.

re 3.6 Even when the greatest care is taken, unwanted effects on the germinal cells cannot be entirely excluded. The mere possibility of a modification of the germinal cells, as a side effect, does not however in itself constitute an absolute obstacle to the ethical justifiability of a gene therapy. There are also recognised methods of treatment, e.g. radiation therapy or *cytotoxic* chemotherapy, in which the possibility of changes in germinal cells is accepted.

re 3.7 This, too, is a normal requirement to which particular weight has to be given, because gene therapy is new, unfamiliar and complex and is accompanied by equally exaggerated hopes and fears. Care must be taken to ensure that the persons concerned are aware of the decision as to what is to happen to them, so that they can give their informed consent.

These guidelines were approved by the Senate of the SAMS on June 3, 1998.

Prof. W.H. Hitzig, Chairman of the Central Ethical Committee

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GLOSSARY

AIDS: Immunodeficiency caused by infection with *HIV*.

Anti-sense RNA: Ribonucleic acid (RNA), the nucleic-acid sequence of which is selected in such a way that it combines with an endogenous nucleic-acid sequence and in this way interferes with its function.

Cancer: Malignant cell proliferation which penetrates into the surrounding healthy tissue with a tendency to the formation of metastases.

Cell: The basic element of all living tissue. A cell consists of a cell membrane, a cell body and a nucleus. Cells multiply by cellular division.

Chemotherapy: Treatment by means of chemically defined, synthetically produced substances. This term is used mainly in connection with the treatment of cancer and infectious diseases.

Clinically manifest: Detectable on the basis of the signs and symptoms of a disease.

Clinical trial: The use of a diagnostic or therapeutic procedure carried out in humans with the aim of determining its effectiveness, safety and risks.

Cytokines: Substances produced by certain cells, which facilitate multiple interactions between them, as well as with other cell populations.

Cytotoxic: Toxic for certain cells. The aim of cytotoxic therapy is to destroy cells that are unhealthy, without too greatly affecting the other, healthy cells.

DNA: Desoxyribonucleic acid, one of the two forms of nucleic acid, which form the basis of all living organisms (with the exception of certain viruses).

Eugenic purpose: Intentional manipulation of human heredity with the aim of "improving" the human race or with other specific objectives.

Gene: Sequence of hereditary information. Genes are composed of nucleic acid. Genes are either "activated" or "inactivated". In the activated state they govern the formation of certain proteins.

Genetic data: List of the deviations or absence of deviations observed in the genes of an individual or a family.

Genetic engineering: All procedures by which genes can be introduced into cells, activated, inactivated, repaired or destroyed or by which their function can be altered.

Genetic programme: Regular course of the activation and inactivation of genes, which governs the development and the life of individual cells, tissues and organs and the complete organism.

Gene therapy: Treatment of diseases by means of the repair, introduction or inactivation of certain genes. A definition of the term "gene therapy" is proposed in Chapter 2 ("Area of Application") of these Guidelines.

Germinal cells: The entirety of the cells, of which the hereditary substance and the cytoplasm can be passed on to the descendants.

Hereditary diseases: Diseases that are passed on by parents to their descendants. In hereditary diseases, deviations from the norm are to be found in one or more genes.

HIV: Human immunodeficiency virus, the pathogen of AIDS.

Hormone: Messenger-substance produced by certain cells, which triggers certain reactions in other cells.

Human medicine: Medicine directed towards humans, in contrast to veterinary medicine.

Implantation: Introduction of cells, tissues or organs into an organism, in such a way that they continue to function in the new environment.

In vitro: Outside the body, in the test tube.

Live poliomyelitis vaccine: Vaccine for the prevention of infantile paralysis, with which a poliomyelitis virus that is weakened but is still capable of proliferation is administered.

Medical indication: Conclusion reached on the basis of medical examination to determine the suitability of a certain procedure for the alleviation, treatment or prevention of a disease or condition.

Nucleic acid: Important chemical building substance of life, from which the genes are derived. (See also "DNA" and "RNA").

Nucleic acid sequence: The sequence, in a specific nucleic acid, of the four basic elements from which all nucleic acids are formed.

Poliomyelitis: See Live poliomyelitis vaccine.

Prophylactic: In the sense of the prophylaxis or prevention of certain diseases.

Radiation therapy: Treatment by means of radiation, particularly x-rays.

Reprogramming: Modification of the genetic programme, for example after the introduction of a virus.

Research studies in humans: See Clinical trial.

RNA: Ribonucleic acid, one of the two forms of nucleic acid.

Somatic: Body components that do not belong to the germinal cells. Somatic cells and their descendants cannot develop into ova or spermatozoa.

Therapeutic: In the sense of medical treatment.

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