ANNALES NESTLÉ

54 / 1

Gene Therapy

NESTLÉ NUTRITION SERVICES

Printed by Les Presses de la Venoge S.A., CH-1026 Denges, Switzerland.

The material contained in this issue was submitted as previously unpublished material, except in the instances in which credit has been given to the source from which some of the illustrative material was derived. Nestec Ltd. cannot be held responsible for errors or omissions, or for any consequences arising from the use of the information contained herein.

Indexed and abstracted in Excerpta-Medica database.

ISSN 0527-8606

Journal edited by
an international committee of paediatricians
and published by NESTEC LTD.

All correspondence should be sent to:
NESTEC LTD.
Avenue Nestlé 55
CH-1800 Vevey (Switzerland)

Contents

Editorial

The current knowledge in molecular biology has led for many years now to a concept that has focused on the goal of treating genetic disorders by influencing the genetic make-up of cells, organs and body systems such as the immune system. Widely performed research *in vitro* and in animals has progressed so much that we are just at the beginning of a completely new therapeutic regimen in medicine which has never existed before. Enough information has been gained to conclude that human gene transfer is possible and that it can evoke biological responses that are relevant to human disease [1].

Changing the genetic code in a living organism such as man will be applied to a variety of hereditary metabolic diseases particularly in childhood. Out of the about 2000 known disorders the most common are expected to profit from gene therapy in the next decades to come. Another challenge for intervention by gene therapy will be the treatment of various forms of cancer; specific targeting of harmful genes into cancer cells can modify these cells *in situ* leading to ultimate cell death and perhaps cure of the disease [2, 3]. Also, possibilities of drug delivery will be made possible by gene therapy when the patient's cells become able to release the product of a new gene which can act locally on neighboring cells or enter the circulation for delivery to distant cells [4].

Although the public has outspoken fear that the human genome is in danger of being adversely manipulated by these interventions, the only goal of such treatment is to have less suffering from a given disease. Under this definition, gene therapy is comparable to any other treatment in medicine.

In order to apply these new genetic tools the main challenge for research will be the targeting of new genes delivered into the appropriate organ. Certain strategies have been developed in recent years for introducing vectors containing appropriate genes into the genome of body cells. Here, Michael Strauss gives an overview over the current strategies involved and describes its implications as well as its limitations and difficulties. He shows the current approaches to this new treatment strategy and identifies the possible candidates for gene therapy. The basic understanding as to how viral and non-viral vectors can deliver their target genes is illustrated in his overview providing the perspectives for the future.

The most common autosomal recessive disorder in Caucasians with an incidence of about 1:2000 live births is cystic fibrosis. Although medical and surgical treatment including transplantation has improved considerably the life expectancy of these patients, gene therapy is considered the ultimate cure treatment. First attempts have been made in this disorder as described by Charles Coutelle. Again the correct targeting of retrovirus or adenovirus vectors are the challenges to overcome. Although some but limited clinical trials have been performed in this disorder, the overall outcome is still to be improved in cystic fibrosis. As all new therapy regimens it has its limitations as far as prognosis and pitfalls are concerned [5].

The most promising way of applying such techniques has shown to be the treatment of body cells *ex vivo* and reintroducing them back to the patient. Here the group of congenital immunodeficiencies are the group par excellence for such approaches. Alain Fischer and coworkers describe in detail the progress in this field and the success in treating children with adenosine deaminase (ADA) deficiency and other immunodeficiencies like X-linked severe combined immunodeficiency (SCID) and Wiskott-Aldrich syndrome by gene therapy.

Partial correction of affected cells in hereditary disorders such as lysosomal disease is another promising approach to help the affected patients and improve their suffering. Livia Poenaru outlines the possibilities of gene therapy in a variety of lysosomal disease including those with anomalies in the catabolism of glycolipids, glycoproteins and mucopolysaccharides. Similar approaches as described by Livia Poenaru are taken to treat paediatric lipid disorders [6].

This issue of *Annales Nestlé* intends to give an update on this exploding field of gene therapy concentrating on the goal that the use of sophisticated molecular biology techniques is on the edge of reality in medicine. It is therefore the aim of this issue to explain in simple terms what gene therapy is all about and what implication it will have in the future on patients where our standard therapy has its shortcomings.

References:

1. Crystal RG. Transfer of genes to humans: early lessons and obstacles to success. *Science* 1995;270:404-10.
2. Hart IR, Vile RG. Targeted gene therapy. *Br Med Bull* 1995;51:647-55.
3. Deonarain MP, Spooner RA, Epenetos AA. Genetic delivery of enzymes for cancer therapy. *Gene Ther* 1995;2:235-44.
4. Blau HM, Springer ML. Gene therapy – a novel form of drug delivery. *N Engl J Med* 1995;333:1204-7.
5. Leiden JM. Gene therapy – promise, pitfalls and prognosis. *N Engl J Med* 1995;333:871-3.
6. Humphries SE, Mailly F, Gudnason V, Talmud P. The molecular genetics of pediatric lipid disorders: recent progress and future research directions. *Pediatr Res* 1993;34:403-15.

Index of Abbreviations

A1AT	Alpha-1-antitrypsin gene
AAV	Adeno-associated virus
ACE	Angiotensin converting enzyme
AcNPV	An insect virus (baculovirus)
ADA	Adenosin deaminase
BMT	Bone marrow transplantation
btk	Bruton tyrosin kinase
cDNA	complementary DNA
CFTR	Cystic fibrosis transmembrane conductance regulator
CFTR-knockout mouse	Mouse in which the gene for CFTR is not expressed
CGD	Chronic granulmatous disease
CID	Combined immunodeficiency
CIITA	Class II transactivator
CNS	Central nervous system
DC-Chol/DOPE	3β [N-(N'N'-dimethylaminoethane-carbamoyl)] cholesterol/ dioleoyl phosphatidylethanolamin
DIMRIE	1,2-dimyristyloxypropyl-3-dimethylhydroxyethylammonium bromide
DOTAP	N-[1-(2,3-dioleyloxy)propyll-N,N,N-trimethylammonium methylsulphate
DOTMA	N-[1-(2,3.dioleyloxy)propyl]-N,N,N-trimetylammonium chloride
E1 gene	Essential gene of adenovirus for viral replication
EBV	Epstein-Barr virus
FDA	Food and Drug Administration
γc	γ chain of interleukin 2
Hex A	Hexosaminidase A
HIGM	Hyper IgM-syndrome
ICAM	Intercellular adhesion molecule
IL-2	Interleukin 2
Knockout mouse	An experimental mouse model in which a defined gene is not expressed
LAD	Leukocyte adhesion deficiency
LTC-IC	Long-term cultures initiating cells
LTR	Long terminal repeats, i.e. sequences of the viral genome which serve as control elements for replication
Man-6-P	Mannose-6-phosphate
MLD	Metachromatic leucodystrophy
MPS	Mucopolysaccharidosis
mRNA	messenger RNA

NK	Natural killer
OTC	Ornithine transcarbamylase
PAH	Phenylalanine hydroxylase
PCR	Polymerase chain reaction
PEG	Polyethyleneglycol
pfu	plaque forming units
PID	Primary immunodeficiency
RAC	Recombinant DNA Advisory Committee (USA)
Rb	Retinoblastoma suppresor gene
RT-PCR	Reverse transcriptase- PCR
SCID	Severe combined immunodeficiency
SMC	Smooth muscle cells
TCR	T-cell receptor
UTP	Uridine triphosphate
WAS	Wiskott-Aldrich syndrome
XID	X-linked immunodeficiency
XLA	X-linked agammaglobulinemia
YAC	Yeast artificial chromosome