Gene Therapy in Neurology

Departments of Neurology and Pediatrics, Kennedy Krieger Institute, Johns Hopkins University, Baltimore, Md., USA

Hugo W. Moser, MD, Departments of Neurology and Pediatrics, Kennedy Krieger Institute, Johns Hopkins University, 707 North Broadway, Baltimore, MD 21205 (USA)

The topic of gene therapy is of profound significance for the neurologist because hundreds if not thousands of genetic disorders that affect the nervous system exist, and therapy is available for only a small proportion. Recently it has seemed as though each week brings the discovery of the molecular basis of yet another neurological disorder. As a neurologist looking after children with genetic disorders of the nervous system and working with their families, I note that these discoveries are met with hope and excitement, but that these positive feelings may be followed by impatience and even disillusion because this new knowledge cannot as yet produce immediate benefit. An appraisal of the current status and future prospects of gene therapy is therefore highly desirable.

Which Neurological Disorders Are Targets for Consideration in Gene Therapy?

At this time the genetic disorders due to single enzyme defects are the most promising targets, provided the following conditions apply:

- The gene has been isolated. The natural history and pathogenesis of the disorder has been defined. The disorder causes serious disability, cannot be treated with existing methods, and can be diagnosed before significant damage has occurred.
- The defect involves a gene the activity of which does not require delicate control, and which is normally present in excess, so that replacement of a fraction of normal activity can be of benefit.
- A ‘surrogate marker’, such as an enzyme assay or biochemical assay, permits timely assessment of the activity of the inserted gene.
- Disorders that respond to bone marrow transplantation are particularly promising candidates at this time.
- The availability of an animal model is desirable but not absolutely essential.

Disorders that fit these criteria include the mucopolysaccharidoses, metachromatic leukodystrophy, adreno-leukodystrophy, Duchenne muscular dystrophy [1], and the Lesch-Nyhan syndrome.

Methods of Delivery

At this time the greatest success has been achieved with retroviral vectors. Retrovirally induced transgenes have been expressed stably to correct genetic defects in fibroblasts, bone marrow stem and progenitor cells, hepatocytes and other cell types [2]. Two years ago this technique was applied successfully in two sisters with adenosine deaminase deficiency and these patients are now able to lead normal lives. Another highly promising approach is the use of replication-deficient adenoviruses [3]. These can deliver the cystic fibrosis gene to airway cells and show potential for directing genes into the liver, skeletal muscle, and even the central nervous system. Methods to deliver genes to the central nervous system are under intensive investigation. Anderson et al. [4] have used a herpes simplex virus to introduce a gene into the adult rat caudate nucleus with persistence of the gene for at least 30 days.

Considering the availability of an animal model is desirable but not absolutely essential.

Methods of Delivery

At this time the greatest success has been achieved with retroviral vectors. Retrovirally induced transgenes have been expressed stably to correct genetic defects in fibroblasts, bone marrow stem and progenitor cells, hepatocytes and other cell types [2]. Two years ago this technique was applied successfully in two sisters with adenosine deaminase deficiency and these patients are now able to lead normal lives. Another highly promising approach is the use of replication-deficient adenoviruses [3]. These can deliver the cystic fibrosis gene to airway cells and show potential for directing genes into the liver, skeletal muscle, and even the central nervous system. Methods to deliver genes to the central nervous system are under intensive investigation. Anderson et al. [4] have used a herpes simplex virus to introduce a gene into the adult rat caudate nucleus with persistence of the gene for at least 30 days.

Consideration of Gene Therapy for Adrenoleukodystrophy as an Illustration of Current Scientific and Ethical Issues

Adrenoleukodystrophy (ALD) fulfills some but not all of the criteria specified above. The gene has been isolated [5], but it has not yet been demonstrated that the gene corrects the biochemical defect in an in vitro system. The disorder is serious, it can be diagnosed years before neurological damage occurs, and existing methods of therapy, including the much publicized ‘Lorenzo’s oil’, are not sufficiently effective [6]. Bone marrow transplantation, provided it is offered under carefully selected conditions [7, 8], shows promise, suggesting that replacement of only a fraction of normal enzyme activity is helpful. An animal model of ALD is not available, but may become so with a ‘knockout’ approach in transgenic mice.

In spite of these favorable features several additional questions must be resolved before gene therapy of ALD is ethically permissible. One consideration relates to the natural history of the disease. Less than half of the patients with the biochemical defect of ALD develop the severe childhood form of the disease. Half of the patients develop the milder adult form which is compatible with a productive life and at times with survival to the 70s. Segregation analysis suggests the presence of an autosomal modifier locus that determines whether an asymptomatic boy present in excess, so that replacement of a fraction of normal activity can be of benefit.

a a ‘surrogate marker’, such as an enzyme assay or biochemical assay, permits timely assessment of the activity of the inserted gene.

b Disorders that respond to bone marrow transplantation are particularly promising candidates at this time.

c The defect involves a gene the activity of which does not require delicate control, and which is normally present in excess, so that replacement of a fraction of normal activity can be of benefit.

d The disorder causes serious disability, cannot be treated with existing methods, and can be diagnosed before significant damage has occurred.

e Disorders that fit these criteria include the mucopolysaccharidoses, metachromatic leukodystrophy, adreno-leukodystrophy, Duchenne muscular dystrophy [1], and the Lesch-Nyhan syndrome.

f Disorders that fit these criteria include the mucopolysaccharidoses, metachromatic leukodystrophy, adreno-leukodystrophy, Duchenne muscular dystrophy [1], and the Lesch-Nyhan syndrome.