GENE THERAPY

Gene therapy utilizes gene formulations containing the DNA sequences encoding the protein of therapeutic interest and has been known in clinical medicine for over 20 years (1). At the core of the development of gene therapy lies evidence of drugs that are targeted to the cause of the disease, and not just the symptoms. The emergence of a European Pharmacopoeia monograph describing gene preparations (2), and most recently the introduction of genes for the treatment of patients suffering from lipoprotein lipase deficiency (LPLD) (3) were examples of progress in the field of gene therapy. The gene drug (termed Glybera) was cloned based on the recombinant viral vector AAV (adeno-associated virus), serotype 1 and was registered by the corresponding European and American agencies (3). Glybera has been approved for the treatment of a very rare inherited disease, LPLD. It has proved the AAV vector as a very suitable gene vehicle for the correction of LPLD. The introduction of the gene product to the treatment reflects the huge progress in biomedical sciences and documented clinical need for innovative medicine.

At present, the development of gene therapy is firstly inextricably linked with the molecular study of genes that may be important for medicine/therapy. Secondly, the development of gene therapy is focused on new, powerful systems to introduce genes into cells (4). Recently, great attention has also been paid to the studies of biological properties of inducible stem cells. Research is conducted mainly towards the use of the therapeutic (regenerative) potential of stem cells in medicine (5). The studies of the gene carriers, which are often called vectors, extend primarily in the design and cloning genes that could be delivered into the targeted cells. Most attention is drawn to the potential of infectious viruses, in particular lentviruses, adenoviruses and adeno-associated virus (AAV), hence most cloned recombinant viral vectors are constructed based on the genomes of the mentioned viruses (4, 6). For the purposes of scientists involved in developing vectors - the ideal gene vector is introduced into a selected cell, lead to a transgene expression that is efficient and regulated by external factors and is well tolerated by the patient (no side effects) (4, 6). At the present stage of development of gene therapy primary focus is put on cloning vectors with high infectious potential. The laboratory of gene engineering allows for relatively easy manipulation of the DNA sequences of vectors. The situation is that on the one hand the natural properties of the virus to infect cells is used, while on the other hand engineering tools allow modifications in the structure of the native gene particles. Intensive work is carried out in the direction of cloning vectors equipped with regulated promoter sequences, or the chemically modified capsid proteins (4, 6). Basic research performed on the cells of appropriate cell lines or in laboratory animals is indicating that recombinant viral vectors quite efficiently introduce transgenes into many types of cells and tissues. The time of transgene expression is dependent on the promoter used, the structure of the capsid and the form of the vector, as well as the type of infected cells and immune response. Encouraging clinical results are obtained based on adenovirus and lentivirus vectors (4). As reported in the world literature data many clinical trials of gene therapy are conducted in cancer patients (4). Although the first clinical trials were focused on monogenic diseases (1, 4), now mainly because of the global nature of cancer and still unsatisfactory treatment and side effects of treatment, most studies are based on cancer. A variety of therapeutic strategies are used in terms of cancer gene therapy. The mechanism of many gene formulations is based on inhibiting the activity of oncogenes or inducing overexpression of tumor suppressor genes. Work is also carried out on the use of preparations that inhibit tumor angiogenesis, or with immunostimulatory properties (4). The suicide gene strategy is also often used (4). The latest studies also show a variety of clinical efficacy due to a combination therapy based on the use of conventional cytostatic drugs and innovative formulations of siRNA (4, 7). It is well known that the effective treatment of patients always depends on the form of administration of the medicinal product. While conventional drugs can be divided into various pharmaceutical forms, for example injectable solutions, tablets, in the case of therapeutic genes primarily only injection forms are known. Gene preparations are administered in clinical trials into various organs but injection forms still dominate. For example, the mentioned gene product Glybera is administered via a one-time series of small intramuscular injections in the patients’ legs.
Many studies are performed on the development of new formulations which could definitely widen the clinical applicability of gene preparations. The development of new pharmaceutical forms for therapeutic genes, can provide gene preparations for a larger number of patients. Progress in the field of pharmaceutical technology could also lead to a wider registration of gene drugs and could stimulate their incidence in pharmacies. The legitimacy of the gene therapy concept is reflected in clinical trials and that number is steadily increasing. The development of gene therapy strategies is conducive to huge progress in the methodology of gene engineering and pharmaceutical technology. However, the need to introduce new and effective life-saving medicines seems to be the most important inducer of gene therapy progress.

REFERENCES


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