EDITORIAL

Can we rely on gene therapy?

Genes are regions of DNA that code for proteins. Failure to supply normal levels of functional protein due to a defective gene may result in disorders like haemophilia B, cystic fibrosis, lysosomal storage disorders, lipoprotein lipase deficiency (LPLD) and a few cancers (1, 2).

Gene therapy is an experimental technique that focuses on the utilization of the therapeutic delivery of nucleic acids into a patient's cells as a drug to treat disease (3). Gene therapy is a way to fix a genetic problem at its source. This may involve delivering a copy of a healthy or therapeutic gene, repairing a faulty gene, and/or altering the degree to which a gene is turned 'on' and 'off'. Gene therapy can potentially be used to treat genetic disorders with one or few administrations instead of frequent dosing, improving quality of life and reducing the necessity for physician visits. Gene therapy also offers the potential to specifically target the affected tissues within the body (1, 4). It involves the introduction of one, or more foreign genes into an organism to treat hereditary or acquired genetic defects. The disease is treated with minimal toxicity, by the expression of the inserted DNA by the cell machinery**.**

Researchers are studying gene therapy for a variety of diseases, such as severe combined immune deficiencies, haemophilia, Parkinson's disease, cancer and even HIV, through different approaches. The delivery of DNA into cells are often accomplished by multiple methods. The two major classes are recombinant viruses (sometimes called biological nanoparticles or viral vectors) and naked DNA or DNA complexes (non-viral methods). Currently, the most common type of vectors are viruses that have been genetically altered to carry normal human DNA. Viruses have evolved a way of encapsulating and delivering their genes to human cells in a very pathogenic manner. Scientists have tried to harness this ability by manipulating the viral genome to get rid of disease-causing genes and insert therapeutic ones. Target cells such as the patient's liver or lung cells are infected with the vector. The vector then unloads its genetic material containing the therapeutic human gene into the target cell. The generation of a functional protein product from the therapeutic gene restores the target cell to a standard state. The technology is still in its infancy, but it has been used with little success (5).

Gene therapy may allow doctors to treat a disorder by inserting a gene into a patient's cells rather than using drugs or surgery. An article of Nature journal reports that researchers may have found a way to correct the chromosome defect that causes Down syndrome, though it will be years before it could be used as a therapy. Nevertheless, this approach can have very serious health risks, like toxicity, inflammation, and cancer. Because the techniques are relatively new, some of the risks may be unpredictable; however, medical researchers, institutions, and regulatory agencies are working to make sure that gene therapy research is as safe as possible.

Although over 200 clinical trials are launched within the United States that involve therapeutic approaches to cancer, nearly 30 of them involve correction of monogenic diseases such as cystic fibrosis, alpha1-antitrypsin deficiency and severe combined immunodeficiency (SCID). Most of the trials are phase I (safety) studies and the existing delivery systems do not have any major toxicity problems. So how far have we come since clinical trials began? The promises are still great, and the problems have been identified (and they are surmountable). Nevertheless, what are the prospects? In the upcoming future, gene therapy will become as routine a practice as heart transplants are today (6).

Gene therapy has suffered highs and lows in both the general public and scientific communities. Some speculated uses of gene therapy include gene doping where athletes might adopt gene therapy technologies to boost their performance (7) and human genetic engineering which not only cures diseases, but also to alter physical appearance, metabolism, and even improve physical capabilities and mental faculties like memory and intelligence. However, gene therapy also has its share of hurdles, which involves some

unsolved problems like short-lived nature, immune response, problems with viral vectors, multigene disorders and insertional mutagenesis (8).

In future, we need to concentrate on basic science behind gene therapy- particularly the three intertwined fields of vectors, immunology and cell biology. All of the available viral vectors arose from understanding the fundamental biology of the structure and replication of viruses. With respect to immunology, viruses still have many secrets to be unravelled. Viral systems that have evolved to escape immune surveillance may be incorporated into viral vectors. Some of these are being characterized; for instance, the adenoviral E3 protein, the herpes simplex ICP47 protein and the cytomegalovirus US11 protein (9). Cell biology is involved because, in many cases, the goal of gene therapy is to correct differentiated cells, like epithelial cells in cystic fibrosis and lymphoid cells in ADA deficiency.

The idea to use the genetic information obtained by sequencing of the human genome for the treatment of diseases is compelling. However, if scientists from different disciplines participate and garner as a team to tackle the obstacles, gene therapy will be added to our medicinal armada and the ever-expanding arsenal of new therapeutic modalities. Additionally, if researchers and clinicians continue to participate together then they can lead the nation in harnessing natural, biological processes to provide real therapeutic benefits during this unprecedented golden age of biomedical research (10).

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