Oncology Issues

ISSN: 1046-3356 (Print) 2573-1777 (Online) Journal homepage: https://www.tandfonline.com/loi/uacc20

Gene Therapy: An Infant Science Shows Great Promise

Lilian Delmonte

To cite this article: Lilian Delmonte (1998) Gene Therapy: An Infant Science Shows Great Promise, Oncology Issues, 13:6, 19-40, DOI: 10.1080/10463356.1998.11904789

To link to this article: https://doi.org/10.1080/10463356.1998.11904789

Published online: 18 Oct 2017.

Gene Therapy: An Infant Science Shows Great Promise

by Lilian Delmonte, D.Sc.

Gene therapy has come of age, as shown by the enthusiastic crowd of 2,000 specialists who attended the inaugural May 1998 meeting of the American Society of Gene Therapy (ASGT) in Seattle, Wash. Nearly 800 presentations and posters spanned every biomedical discipline at this well-attended gathering.

At a press briefing, gene therapy pioneers W. French Anderson, M.D., of the University of Southern California and Inder Verma, Ph.D., of the Salk Institute discussed the clinical promise of this emerging discipline.

"The general consensus clearly is that gene therapy will have a major impact on health in the coming century," said Verma. "Usually we think of gene therapy in terms of human genetic diseases, of which there are at least 500. At least 10 percent of the defective genes responsible for these diseases have been identified and sequenced, and are potential targets of gene therapy."

In actuality, Anderson pointed out, only about two-thirds of the more than 300 gene therapy protocols ongoing or approved in the United States and abroad target genetic diseases. Of the more than 3,000 patients currently participating in the trials, 65 percent are being treated for cancer; the remainder are being treated for neurologic, cardiovascular, pulmonary, or infectious diseases.

"Gene therapy probably could be used to treat every conceivable disease, but it is not going to be a panacea," said Anderson. "The reason is that the human organism is too complex. Our genome contains approximately 100,000 genes that interact with each other and with the environment in ways we do not yet understand. Let us take supercomputers as an example: You cannot just go in and change a few lines of code without messing up the overall program. You can improve the genetic 'program' of the human body, but you cannot redesign the human genome by putting in a dozen or so genes. There are many diseases that one can ameliorate by boosting this or that gene, but in some instances this might risk causing a defect in an adjacent normal gene. You can't do all things at all times in all parts."

A number of vectors (delivery systems) are being explored for introducing transgenes (foreign genes) into cells that express defective genes or gene products that cause a disease. These vectors include: altered viruses, naked DNA, antisense sequences, ribozymes, and liposomes. At this stage of the art, viruses are the most common vectors used.

VIRAL VECTORS

"Two years ago," said Verma, "we in our lab realized that after fifteen years of efforts by hundreds of investigators, gene therapy was in a mid-life crisis. The retroviral vector most of us were using (Moloney virus) had a serious flaw: It had to be inserted into the target cell in the laboratory and reintroduced into the patient. The consensus of virologists and gene therapists [was] that we must develop vectors capable of delivering a gene directly to the target tissue to overcome this flaw."

Here the Salk group and others came up against a major obstacle: the immune system. Although intramuscular injection of as little as one milliliter of a viral vector carrying a human gene (about a billion viral particles) resulted in long-term expression of the human gene product in genetically immune-incompetent mice, gene expression persisted for only five days in immune-competent mice.

"We found an entirely unexpected ally to solve this problem," said Verma. "HIV, the AIDS virus."

Over the past two years, his team has succeeded in debilitating the HIV virus to the point that more than 90 percent of the wild-type HIV genome, including genes coding for pathogenicity and virulence, have been eliminated from the vector. The 'gutted' HIV vector is of major importance since, unlike previous retroviral vectors, it can successfully infect nondividing end cells, such as the neuron, muscle, and lung cells, or predominately resting stem cell populations, such as the hematopoietic stem cell. Moreover, the vector is capable of transfecting and replicating in a wide variety of cell types (e.g., brain, liver, lung, pancreatic islets, muscle, blood stem cells), but is not pathogenic or immunogenic and does not cause significant side effects. Numerous studies have demonstrated that HIV vector preparations are totally free of contamination with wild-type HIV, long a major concern impeding FDA approval of clinical trials.

EARLY CLINICAL STUDIES USING VIRAL VECTORS

Where are we with respect to clinical applications of gene therapy? Some of the early clinical results presented at the ASGT meeting suggest that gene therapy may prove beneficial as an adjunct to conventional therapies for difficult-to-treat diseases such as multiply recurrent head and neck cancers, among others.

In an ongoing, nonrandomized Phase II trial, David H. Kirn,

continued on page 40

Lilian Delmonte, D.Sc., is a medical writer in New York City.

continued from page 19

M.D., and colleagues at Onyx Pharmaceuticals treated twenty-six patients with multiply recurrent head and neck tumors refractory to conventional therapies with five-day courses of an intratumorally injected vector (ONYX-015), given either alone or in combination with intravenous chemotherapy (conventional therapy: 5-fluorouracil and cisplatin), repeated at three-week intervals. The ONYX-015 adenoviral vector, by virtue of missing a gene called E1B 55kd, is lethal to cancer cells that have a dysfunctional p53 gene or gene product (i.e., 80 to 90 percent of all cancers). The vector does not damage normal cells whose wild-type p53 gene acts as a security alarm that blocks adenoviral replication.

Six of fifteen chemotherapy-refractory patients who received ONYX-015 alone had objective response (two complete tumor regression, four partial) in vector-injected tumors but no change in carrier-injected tumors. Six others had stable disease. Ten of eleven conventional therapy-naïve patients had objective response (two complete tumor regression, eight partial) of the vector-injected tumors after 2 to 4.5 months on combined ONYX-015/conventional therapy; another had minor response. "This is impressive, since historically only 30 to 40 percent of patients with this type of tumor achieve objective response and with conventional therapy alone," said Kirn.

OTHER VECTORS

"Viruses represent just one type of vector," said Verma. "The important thing to remember is that there is no 'right' vector for everything. For example, if you want to make a vaccine, you can simply take naked DNA and inject it into a muscle, and it will make enough protein to immunize the organism. But if you want to make enough protein to treat hemophilia, it would take hundreds upon hundreds of injections of naked DNA to make the required amount of protein."

Regulation of gene expression is an important issue that remains to be resolved, since overproduction of a therapeutic gene product could be almost as undesirable as underproduction. Verma said that a variety of systems that have the ability to turn a specific gene on or off are being investigated.

"What I think is exciting about gene therapy is that we have the ability to actually influence the outcome of what I call acquired diseases—cancer, cardiovascular disease, neurologic disease, infectious disease," said Verma. "The concept that we can exploit the ability of a gene to either alleviate a defect, slow down the progression of disease, or completely ameliorate a disease is spectacular. You might well ask: If the concept is so simple, how come none of the ongoing clinical trials have resulted in a resounding success? The crux of the matter is that we do not yet have efficient methods of gene delivery."

However, Verma continued, "I would not be surprised if by the year 2003, we will have successfully treated patients with monogenic (single cell defect) diseases such as hemophilia, which is caused by a factor VIII or factor IX gene deficiency, and will be able to say: 'We no longer need exogenous protein therapy for this disease. Our body can behave like that of a normal person.'"