

## Protein Therapy vs. Gene Therapy

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by Dr. Thomas J. Stegmann

Proteins are the most important molecules inside every living cell, tissue, organ—and inside the human body. Proteins do everything: They control our thinking, they regulate all our physiological reactions, they metabolize carbohydrates and fats that our body use, they defend our bodies against bacteria and viruses, they work as enzymes, exquisitely potent hormones, antibodies, cytokines and signaling peptides that transmit information into cells—they do everything.

Most human diseases are related to the malfunctioning of particular proteins, either systemically or locally. Today, a variety of human proteins can be produced with relative ease by means of genetic engineering and recombinant DNA technology. Large quantities of the desired protein can be made in mammalian cells, yeast or bacteria. Novel protein expression systems, including phage technology process, allow biologically active, properly folded, engineered proteins to be manufactured and purified in high yield at a very reasonable cost. Therapeutic proteins can be used as highly effective medical treatments (protein therapy) for a wide array of diseases in which the protein is either lacking or deficient (growth hormone and insulin), or the therapeutic protein is used to inhibit a biological process (antibodies that block blood supply to tumors).

Gene therapy can actually be considered a form of protein therapy. However, instead of the therapeutic usage of the protein itself, gene therapy works by placing into a cell a defined gene to either replace a defective gene or to increase the amount of a specific gene in a targeted cell/tissue in order to produce a higher amount of the desired protein (for example, angiogenic growth factors to stimulate blood vessel growth in ischemic tissue).

To deliver the therapeutic gene to the patient's target cells, either a carrier (vector DNA) must be used (examples include retroviruses, adenoviruses, adeno-associated viruses, and Herpes simplex viruses) or the therapeutic DNA must be introduced as "naked" DNA, most often as plasmid DNA, into the target cells. The latter approach is limited in its application because it can be used only in certain tissues and requires large amounts of DNA.

There are still serious, unsolved problems related to gene therapy including: 1. Difficulty integrating the therapeutic DNA (gene) into the genome of target cells; 2. Risk of an undesired immune response; 3. Potential toxicity, immunogenicity, inflammatory responses and oncogenesis related to the viral vectors; and 4. The most commonly occurring disorders in humans such as heart disease, high blood pressure, diabetes, Alzheimer's disease are most likely caused by the combined effects of variations in many genes, and thus injecting a single gene will not be beneficial in these diseases.

In contrast, protein therapy uses well defined, precisely structured proteins, with previously defined optimal doses of the individual protein for disease states, and with well-known biological effects. On the other hand, an obstacle of protein therapy is the mode of delivery: oral, intravenous, intra-arterial, or intramuscular routes of the protein's administration are not always as effective as desired; the therapeutic protein can be metabolized or cleared before it can enter the target tissue.

The FDA has not yet approved any human gene therapy product for sale. A total of 401 FDA authorized clinical trials exploring gene therapy are currently underway, most of them addressing advanced tumor stages (only 23 addressing cardiovascular disease). In contrast, a total of 764 authorized protein therapy studies are ongoing, most of them, too, addressing malignancies, with only 29 designed to treat various forms of cardiovascular disease (CVD).

CVD is the number one killer in the United States. According to the American Heart Association, nearly 2,500 Americans die each day from CVD. That's one death every 35 seconds. In 1998, we introduced—for the first time in humans—protein therapy into the therapeutic arsenal of treatment modalities for coronary heart disease (CHD). Since then, three human clinical trials were successfully performed using the human protein fibroblast growth factor (FGF-1)—which is capable of initiating the growth of new arteries and capillaries—angiogenesis—inside the myocardium of patients suffering from a lack of adequate blood flow in the heart.

This new type of treatment is a good example how to use the benefits of protein therapy: Using a human protein with no immunogenic response, no need for viral vectors, localized effect at the target tissue, and

predictability of dose.

It seems that protein therapy will become the treatment modality of choice for many disorders for at least the next 10 years—at least until further research has resolved the hurdles and risks related to gene therapy.

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