

PROTEIN THERAPY

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ABSTRACT

Protein therapy is a method of therapy that delivers a healing level of protein that would otherwise be absent in amount in individuals with an illness. Protein therapy delivers protein to the body in specific amounts, as would be ordinarily present, to help repair illness, treat pain or remake structures. It is a medical treatment showing much promise that is still in mostly investigatory stages which has wide reaching healing possibilities currently being developed in many fields such as cancer, diabetes etc.

KEYWORDS: Protein therapeutics - benefits - limitation –
classification of protein therapy.

INTRODUCTION

Proteins have most dynamic & diverse role in our body. They are essential nutrients for human body. A disease may result when one or more proteins undergo mutations or present in an abnormally high or low concentration. Proteins which are engineered in laboratory for pharmaceutical use is known as protein therapy. It is similar to gene therapy, but unlike gene therapy, protein therapy delivers protein to the body in specific amounts, for treatment of diseases. Modern protein therapeutics is produced by using recombinant DNA technology. Insulin was the first therapeutic protein to treat diabetes, in 1920.^[8]

Advantages^[9]

- Proteins often serve a highly specific & complex set of functions that cannot be mimicked by simple chemical compounds.
- It is highly specific in action. Fewer side effects.
- Less likely to elicit immune response.

Benefits of Protein therapy^[4]

- Curing chronic pain conditions.
- Arresting an illness that causes degradation of tissues, restoring or rebuilding tissue.
- Treatment of: Hemophilia, anemia, multiple sclerosis, hepatitis B/C, cancer, diabetes.

Limitations of protein therapy^[2, 5, 6]

1. They are very expensive reflective, high production cost.
2. They are denatured and or proteolysed in the gut and are thus not orally bioavailable.
Protein therapeutics is limited to cell surface or extracellular targets.
3. Less patient acceptability & clinical application.

FUNCTIONAL CLASSIFICATION OF PROTEIN THERAPEUTICS^[1]

Protein therapeutics is organized by function and therapeutic application.

Group I: protein therapeutics with enzymatic or regulatory activity

- Group Ia: Replacing a protein that is deficient or abnormal.
- Group Ib: Augmenting an existing pathway.
- Group Ic: Providing a novel function or activity.

Protein therapeutics in this group function by a classic paradigm in which a specific endogenous protein is deficient, & the deficit is then remedied by treatment with exogenous protein.

GROUP Ia is used to replace a particular activity in case of protein deficiency or abnormal protein production. A classic example is the use of **insulin** for the treatment of diabetes. Patients with cystic fibrosis are often treated with a combination of pancreatic enzyme isolated from pigs—including **lipases, amylases and proteases**—that allow the digestion of lipids, sugars and proteins. Patients who have had their pancreas removed or who suffer from chronic pancreatitis can also benefit from this therapy.

GROUP Ib proteins are administered to enhance the magnitude or timing of a particular protein activity. Recombinant proteins in this category have been immensely successfully in treating hematopoietic defects. The most prominent eg: is recombinant **erythropoietin** a protein hormone secreted by the kidney that stimulates erythrocyte production in the bone marrow. In the patients with chemotherapy- induced anemia recombinant erythropoietin is used to increase erythrocyte production & thereby

ameliorate the anemia. In patients with chronic kidney disease, whose levels of endogenous erythropoietin are below normal, recombinant protein is administered to correct this. A variety of other disease states are also treated with Group Ib proteins. Type II diabetes is treated with the recently approved incretin mimetic **exenatide**.

GROUP Ic are proteins including both foreign proteins with novel functions & endogenous proteins that act at a novel time or place in the body. **Papain** is a protease purified from the *Carica papaya* fruit. This protein is used therapeutically to degrade proteinaceous debris in wounds. **Collagenase**, obtained from fermentation by *Clostridium histolyticum*, can be used to digest collagen in the necrotic base of wounds. The protein-mediated debridement or removal of necrotic tissue is helpful in the treatment of burns, pressure ulcers, postoperative wounds, carbuncles & other types of wounds.

Group II: protein therapeutics with special targeting activity

- **Ila:** Interfering with a molecule or organism by binding to it & thereby blocking its function or targeting it for degradation.
- **Ilb:** Stimulating a signaling pathway.
- **Ilc:** Delivering other compounds or proteins.

GROUP Ila proteins, also known as immunoadhesins, use the antigen recognition sites of immunoglobulin molecules to guide the body's immune system to destroy specifically targeted molecules or cells. Other immunoadhesins neutralize molecules by simple physical occupation of a functionally important region of the molecule. Immunoadhesins combine the antigen recognition sites of known immunoglobulins with Fc region of the same or a related immunoglobulin. The Fc region can target a soluble molecule for destruction because cells of the immune system, endocytose the attached molecule, and break down the molecule chemically & enzymatically. Cell killing can be mediated by macrophages, by other immune cells, or by complement fixation.

Infliximab is a Group Ila protein. This recombinantly produced monoclonal antibody binds TNF – alpha & is used to neutralize the action of TNF - alpha in inflammatory condition such as rheumatoid arthritis & inflammatory bowel disease. Another example of the use of a Group Ila protein is the prevention of severe infection by respiratory

syncytial virus (RSV) which is one of the leading causes of hospital admissions for pediatric respiratory illness.

GROUP IIb targeting proteins can activate cell signaling pathways and profoundly affect cell function. Outcomes range from cell death to down– regulation of cell division to increased cell proliferation. Although it has been difficult to prove that a particular target- binding protein mediates an in vivo effect through the modulation of a particular signaling pathway, in vitro evidence suggests that this type of modulation is the mechanism of action of certain therapeutic proteins.

For example, the treatment of certain breast cancers, in which the malignant cells express the Her2/ Neu cell surface receptor, is enhanced by the addition of **trastuzumab**(an anti-Her2/ Neu monoclonal antibody) to the therapeutic regimen. Although trastuzumab contains an Fc region, it is unlikely that simple targeting of the immune system to breast cancer cells by trastuzumab is sufficient to mediate cell killing. This is because many other monoclonal antibodies, with similar abilities to target breast cancer cells, have failed to show efficacy in vivo.

Another example can be found in the treatment of CD20- positive follicular non-Hodgkin's Lymphoma. **Tositumomab**, a monoclonal antibody directed against CD20, is thought to inhibit this type of Lymphoma by signaling the cancer cells to undergo cell death via CD20- mediated apoptosis. Although few Group IIb proteins are currently in clinical use, more are in development and will likely be available in the coming years.

GROUP IIc proteins enable drug delivery to a specific site. Both examples are in the area of cancer therapeutics. **Gemtuzumabozogamicin** links the binding region of a monoclonal antibody directed against CD33 with calicheamicin, a small- molecule chemotherapeutic agent. By using this therapy, the toxic compound is selectively delivered to CD33- positive acute myeloid leukemia (AML) cells, resulting in the selective killing of these cells.

Similarly, refractory CD20- positive non- Hodgkin's lymphoma cells can be destroyed selectively by **I- 131 tositumomab**, a monoclonal antibody directed against CD20 and linked to the radioactive iodine isotope I- 131. Another challenging area of research

involves the delivery of proteins and other macromolecules to the **central nervous system (CNS)**.

Group III: Protein vaccines^[3]

- IIIa: Protecting against a deleterious foreign agent.
- IIIb: Treating an autoimmune disease.
- IIIc: Treating cancer.

Group III proteins have been successfully applied as prophylactic or therapeutic vaccines. For humans to develop effective immunity against foreign organisms or cancer cells, immune cells such as helper T cells must be activated. Immune cell activation is mediated by antigen- presenting cells, which display on their surface specific oligopeptides that are derived from proteins found in foreign organisms or cancer cells.

GROUP IIIa proteins are used to generate protection against infectious disease or toxins. One successful eg: is the **hepatitis B** vaccine. This vaccine was created by recombinant HBsAg protein, a noninfectious protein of the hepatitis B virus.

When immune competent humans are challenged & rechallenged with this protein, significant immunity results in the large majority of individuals. Similarly, the non infectious lipoprotein on the outer surface of *Borrelia burgdorferi* has been engineered into a vaccine for lyme disease (**OspA**).

GROUP IIIb proteins are used to treat patients with disorders that arise from autoimmune phenomenon. One eg:- is the use of **glatiramer acetate**, a short peptide of 4 amino acids. When administered to patients, this protein can improve the symptoms of certain forms of multiple sclerosis, an autoimmune disorder that targets the nervous system. Immunologic acceptance of a fetus during pregnancy represents a special situation with respect to vaccine use. Occasionally, a pregnant woman can reject a fetus after she has been immunized against certain antigens carried by a fetus from a previous pregnancy.

Administration of an **anti-Rh(D)immunoglobulin** prevents the sensitization of an Rh-negative mother at the time of delivery of an Rh-positive neonate. Because the woman fails to develop antibodies directed against the fetal Rh antigens, immune reactions &

pregnancy loss do not occur in subsequent pregnancies, even when the new fetus carries the Rh antigens.

GROUP IIIc proteins are used to vaccinate against some cancers. Although there are currently no FDA-approved recombinant anti-cancer vaccines, promising clinical trials employ patient-specific cancer vaccines. For eg: a vaccine for B-cell non-Hodgkin's lymphoma makes use of transgenic tobacco plants (*Nicotiana benthamiana*). Each patient with this type of lymphoma has a malignant proliferation of an antibody-producing B cell that displays a unique antibody on its surface. By sub cloning the idiotype region of this tumor-specific antibody and expressing the region recombinantly in tobacco plants, a tumor specific antigen is produced that can be used to vaccinate a patient. They are currently in clinical trials.

Group IV: Protein Diagnostics

GROUP IV proteins are not used to treat disease, purified & recombinant proteins used for medical diagnostics bear mentioning here because they are invaluable in the decision-making process that precedes the treatment & management of many diseases.

A classical eg: is the **purified protein derivative (PPD)** test, which determines whether an individual has been exposed to antigens from *Mycobacterium tuberculosis*. In this test, a non infectious protein component of the organism is injected under the skin of an immunocompetent individual. An active immune reaction is interpreted as evidence that the patient has been previously infected by *M. tuberculosis* or exposed to the antigens of these organisms.

CONCLUSION

Modern medicine stands at the edge of an entirely new pharmacology. For the first time in history, physicians seek to manage disease at the level of the genetic and protein information that underlies all biology. Protein-based therapies are playing an increasingly important role in the pharmacologic treatment of disease. The potential for new therapies is virtually endless, given the thousands of proteins produced by the human body and the many thousands of proteins produced by the human body and the many thousands of proteins produced by other organisms. Physicians and other medical researchers look to these studies with considerable hope, though it still could be years

before any one protein therapy treatment was approved for use by regulating agencies, or became widely used. Exciting new means of production are changing the scale, cost, and even route of administration of recombinant proteins therapies, and the large number of protein therapies both in current clinical use and in phase III clinical trials attests to the promise of this technology. It is likely that novel protein- based therapies will be available shortly for many types of cancer, autoimmune disorders, neurologic disease, graft rejection, microbial diseases, and vascular and hematologic regulation. Although the success of any particular protein therapy will depend on its pharmacodynamics pharmacokinetics & safety profiles, one can confidently predict that protein therapies will have an expanding role for years to come. Many scientists contend protein therapy is presently more advanced and easier to use. This therapy has a likely role in the future of medicine.

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