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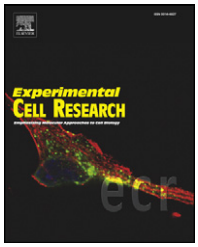

Review

# Introduction to current and future protein therapeutics: A protein engineering perspective

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ABSTRACT

Protein therapeutics and its enabling sister discipline, protein engineering, have emerged since the early 1980s. The first protein therapeutics were recombinant versions of natural proteins. Proteins purposefully modified to increase their clinical potential soon followed with enhancements derived from protein or glycoengineering, Fc fusion or conjugation to polyethylene glycol. Antibody-based drugs subsequently arose as the largest and fastest growing class of protein therapeutics. The rationale for developing better protein therapeutics with enhanced efficacy, greater safety, reduced immunogenicity or improved delivery comes from the convergence of clinical, scientific, technological and commercial drivers that have identified unmet needs and provided strategies to address them. Future protein drugs seem likely to be more extensively engineered to improve their performance, e.g., antibodies and Fc fusion proteins with enhanced effector functions or extended half-life. Two old concepts for improving antibodies, namely antibody-drug conjugates and bispecific antibodies, have advanced to the cusp of clinical success. As for newer protein therapeutic platform technologies, several engineered protein scaffolds are in early clinical development and offer differences and some potential advantages over antibodies.



## Contents



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*Abbreviations:* FDA, Food and Drug Administration; PEG, polyethylene glycol; TPO, thrombopoietin

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## Introduction

Since the early 1980s proteins have emerged as a major new class of pharmaceuticals with ~200 marketed products that are mainly therapeutics with a small number of diagnostics and vaccines [1]. Protein therapeutics can be classified based upon their pharmacologic activity as drugs that: i) replace a protein that is deficient or abnormal, ii) augment an existing pathway, iii) provide a novel function or activity, iv) interfere with a molecule or organism, or iv) deliver a payload such as a radionuclide, cytotoxic drug, or protein effector [2]. Alternatively, protein therapeutics can be grouped into molecular types that include: antibody-based drugs, anticoagulants, blood factors, bone morphogenetic proteins, engineered protein scaffolds, enzymes, Fc fusion proteins, growth factors, hormones, interferons, interleukins, and thrombolytics (Fig. 1) [1,3]. Antibody-based drugs are the largest and fastest growing class of protein therapeutics with 24 marketed antibody drugs in the USA [4] and over 240 more in clinical development [5].

This introductory article provides a brief history of protein therapeutics, offers a rationale for developing better protein drugs, and identifies some major future opportunities as well as emerging technologies that may meet them. The 30-year history of protein drugs is illustrated here with examples that pioneered their class or have high clinical or commercial significance. The rationale for creating better protein drugs, including antibodies [6], comes from the convergence of clinical, scientific, technological and commercial drivers that collectively have identified major unmet needs and provide strategies to address them. Major future opportunities for protein therapeutics, are improved efficacy, greater safety, reduced immunogenicity or improved delivery. A plethora of emerging technologies for the generation and optimization of protein therapeutics are anticipated to help address these opportunities. Space constraints limit examples here to a sampling of technologies of broad applicability — so called platform technologies. The interested reader is referred to many excellent articles on protein therapeutics including those in this special issue and others cited herein.

## Brief history of protein therapeutics

### *Protein therapeutics enabled by protein engineering*

Protein therapeutics and its enabling sister discipline, protein engineering, have emerged since the early 1980s. Protein engineering by rational design or molecular evolution allows the systemic dissection of protein structure–function relationships and the generation of novel proteins with modified activities or entirely new properties. Indeed, protein engineering has revolutionized protein therapeutics by providing the tools to customize existing proteins or to create novel proteins for specific clinical applications.

A brief history of protein therapeutics is provided here from a protein engineering perspective. The focus is on technologies with the greatest impact on current protein therapeutics — engineered versions of natural proteins, Fc fusion proteins, conjugation to the polymer, polyethylene glycol (PEG), and antibody therapeutics as the quintessential protein therapeutic platform.

### *Insulin — the first recombinant human protein therapeutic*

The first human protein therapeutic derived from recombinant DNA technology was human insulin (Humulin®) created at Genentech [7], developed by Eli Lilly, and approved by the US Food and Drug Administration (FDA) in 1982. Recombinant insulin

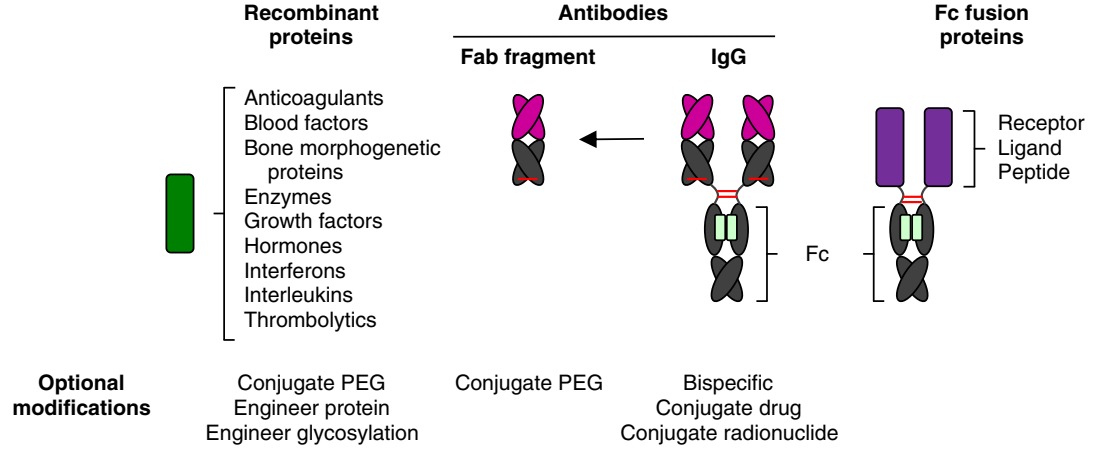


**Fig. 1 – Overview of currently marketed protein therapeutics from a protein engineering perspective.**