Controlled Release | Targeted Delivery | **Solubility Enhancement**

PROTEIN PEGYLATION

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Introduction

Therapeutic proteins and other biopharmaceuticals, such as peptides and oligonucleotides, are often potent drugs that comprise an established and fast growing segment of the pharmaceuticals market. Unfortunately, proteins are prone to aggregation and misfolding, making them difficult to formulate and use. In addition, most proteins are cleared rapidly from the bloodstream upon administration. Although therapeutic protein metabolism and pharmacokinetics (PK) are complex,[1] rapid clearance can result in dose dumping, the lack of a therapeutic dose between each administration and the need for higher cumulative and more frequent dosing. Frequent dosing can result in increased occurrence of side-effects, increased risk for immunogenicity, and suboptimal efficacy. Often there is the need to extend the half-life of biopharmaceuticals in the blood to maximize clinical safety and efficacy.

Many strategies[2] have been developed and studied to optimize the pharmacokinetic properties of proteins, including hyperglycosylation,[3] fusion to an antibody Fc or to albumin, non-covalent association to albumin, and encapsulation or association with particulates.[1a,1b,4] PEGylation has been the most clinically successful strategy and involves the covalent conjugation of poly(ethylene glycol) (PEG) to the biopharmaceutical of interest (**Figure 1**). Many different proteins, peptides, and oligonucleotides have been PEGylated for use in a wide range of medical indications.[5]

Protein PEGylation was first described by Frank Davis et al. in 1977.[6] The first therapeutic PEGylated products (PEG-enzymes) appeared in the early 1990s and PEGylated cytokines were registered for clinical use by the early 2000s. The field developed rapidly thereafter. Currently, there are at least 12 innovative PEGylated biopharmaceuticals registered for clinical use, with many more in development. The most recent of these is Plegridy® (2014).[7] A number of PEGylated products have been developed from essentially the same parent protein, and several PEGylated proteins including PEGylated interferon-a2 (Pegasys® and PegIntron®) and PEGylated GCSF (Neulasta® and Lonquex™) have been developed as first-line treatments. PEGylation is also now a viable strategy for the life-cycle management of unmodified proteins in order to develop improved or biobetter versions of existing therapeutics. With the expiration of patents on the first PEGylated products about to occur, biosimilar versions are rapidly being developed, along with the required development of international standards[8] to govern this new type of generic therapeutic. The PEGylation of many other molecules (peptides, oligonucleotides, and low molecular-weight chemical entities) is also an active area of research.[5b,9]

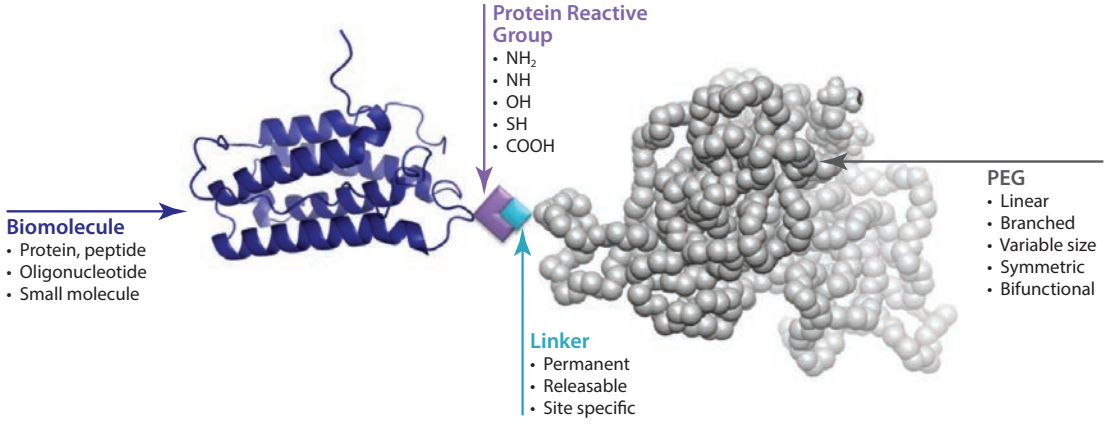

Figure 1. Schematic of a PEGylated biopharmaceutical. (Image courtesy of Dr. Karolina Peciak.)