

linked DNA to produce a protein that links the protein for TNF receptor 2 to the protein for IgG1 Fc.

The fusion of two relatively large proteins each being over 50 kDa raises the question whether this would impact the functionality of either protein. While there is a possible potential variance, the existing science reveals no significant impact. This comment is important as in the future, the regulatory authorities may raise this question.

The utility of pegylation is well understood and appreciated, as the popular products like Neulasta (pegylated granulocyte-colony stimulating factor) have established their safety and effectiveness while prolonging their disposition half-life. The two polyethylene glycol molecules protect the molecule from degradation in the body as well as reduce the immunogenicity.

1.5 Posttranslational modification

Biological products are complex structures, not only because of their basic protein structure, but also because of other modifications that they undergo during their maturation, generating a final form that is not a single and monomolecular entity (as could be expected of a chemical molecule with 99.9% purity) but rather a complex mix of the same protein molecule under various structurally close isoforms.

A protein is characterized by its primary to the quaternary structures as we often see and also by its additional characteristics acquired *during* the cellular process of protein synthesis. These are called post-translational modifications, due to the fact that they occur once the gene (nucleic acid sequence) has been translated into the corresponding protein sequence (the amino acid chain). These modifications are also designated as the *maturation phase* essential before the release/

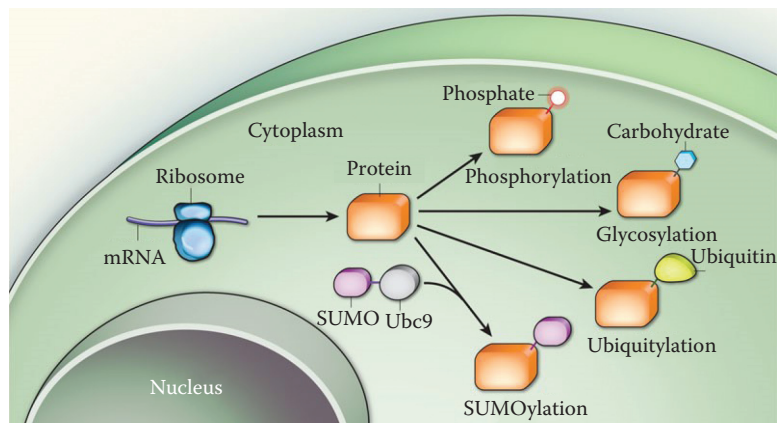


Figure 1.9 PTM of proteins.