



Glycoprotein Synthesis and Remodeling by Enzymatic Transglycosylation

The Challenge: Glycoproteins play an important role in many biological processes and belong to the largest group of protein-based drugs. Post-translational modification by glycosylation is a crucial step in preparation of effective protein-based drugs. One system used for production of glycoproteins is mammalian cell culture. This system, however, has several disadvantages. These include high cost, long cycle times and, importantly, limited control over glycosylation, which is the basis for structural heterogeneity of glycoproteins. Therefore, natural and recombinant glycoproteins are typically produced as a mixture of glycoforms that differ only in the structure of the pendent sugar. The attached sugar chains can have profound effects on protein folding, stability, pharmacokinetics, and serum half-life. However, while some of the effects are beneficial, others are detrimental. For example, it often happens that more active glycosylation states are present only in small amounts or minor fractions. Notably, some glycoforms can cause allergy problems and can induce adverse immune responses. Based on all this, it is obvious that there is a need for a well controlled and consistent glycosylation system that would allow development of glycoprotein therapeutic agents that comply with government regulations for market approval.

UMBI Solution: A UMBI scientist has developed a new chemoenzymatic method for the preparation of homogeneous glycoproteins or glycopeptides. This method describes the synthesis of a glycopeptide or glycoprotein where a well-defined sugar chain is synthesized separately. It is then added to an N-acetylglucosamine (GlcNAc)-protein by transglycosylation to form any desired glycopeptide or glycoprotein with the specific sugar chains of choice. The donor substrate includes a synthetic oligosaccharide oxazoline. The (sugar chain) transfer occurs in the presence of a catalyst comprising endoglycosidase (ENGase). This process enables glycoprotein drugs to be modified for prolonged half-life in vivo, reduced immunogenicity, enhanced in vivo activity, specific targeting and drug delivery.

Commercial Applications:

- Synthesis of therapeutic glycoprotein hormones and cytokines, and antibodies such as monoclonal antibodies

Advantages:

- Prolonged half life
- Less immunogenic
- Enhanced in vivo activity
- Targeted drug delivery

Stage of Development: Preclinical

Patent Status: Pending PCT patent application

Licensing Potential: UMBI is seeking non-exclusive and exclusive licensees to all or part of this technology. The inventors would welcome the opportunity to work with any licensee to further refine or extend the capabilities of this invention.

Inventor & UMBI Reference: Wang, 06-002

Relevant Publications:

1. Wei, Y., Li, C., Huang, W., Li, B., Strome, S. E., Wang, L. X., “Glyco-engineering of human IgG1-Fc through combined yeast expression and *in vitro* chemoenzymatic glycosylation”, *Biochemistry*, in press (2008).
2. Wang, L. X., “Chemoenzymatic synthesis of glycopeptides and glycoproteins through endoglycosidase-catalyzed transglycosylation”, *Carbohydr. Res.*, *343*, 1509-22 (2008).
3. Li, H, Li, B., Song, H., Breydo, L., Baskakov, I. V., Wang, L. X. “Chemoenzymatic synthesis of HIV-1 V3 domain glycopeptides carrying two N-glycans and effects of glycosylation on the peptide’s domain”. *J. Org. Chem.*, *70*, 9990-9996 (2005).
4. Li, B., Zeng, Y., Hauser, S., Song, H., Wang, L. X. “Highly efficient endoglycosidase-catalyzed synthesis of glycopeptides using oligosaccharide oxazolines as donor substrates”. *J. Am. Chem. Soc.*, *127*, 9692-9693 (2005).

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