**Synthetic Studies Toward Lewis Y Glycoconjugates**

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**Introduction**

Lewis Y (Le^a^) is a tumour-associated, tetrasaccharide antigen expressed on the surface of various tumour cells. The antigen is a target of therapeutic monoclonal antibodies (BR96) and is proposed as a glycoconjugate cancer vaccine. Active research on synthetic cancer vaccines has yet to establish the optimal structure for the presentation of synthetic carbohydrate antigens to the immune system.

As a step towards understanding the effect of antigen size on vaccine immunogenicity, two extended Le^a^ epitopes have been synthesized and will be conjugated to BSA (1 and 2). By incorporating portions of lactose and a truncated ceramide, the extended antigen approximates the Le^a^ epitope as it occurs in glycolipids (Fig. 1) on the surface of tumor cells (Fig. 2).

**Figure 1. Natural Le^a^ Glycolipid**

**Figure 2. Target Glycoconjugates**

**Discussion**

The two Le^a^ oligosaccharides were synthesized first as TMS ethyl glycosides (Scheme 2). Conversion of the TMS ethyl glycosides to trichloroacetimidate donors was followed by glycosidation with a truncated azidosphingosine acceptor. Reduction of the azide followed by N-acetylation furnished the desired ceramide analog. This reaction provides a ceramide functionalized for coupling to protein but also permits the selection of N-acyl groups of different chain length. Since glycosylation of ceramide derivatives is a notoriously low-yielding reaction, truncated azido sphingosines conserve valuable oligosaccharide intermediates.

Protein conjugation experiments have been carried out on a lactose ceramide (Scheme 1). An amino functionality was introduced into the glycolipid analog by radical addition of cysteamine hydrochloride to the alkene. The amino-derivatized sugar was then coupled to the thioltated protein carrier (BSA) using a heterobifunctional cross-linker. The synthetic Le^a^ glycoconjugates 1 and 2 will be evaluated in mice.

**Scheme 1. Protein Conjugation Studies With A Disaccharide Sphingolipid Analog**

**Scheme 2. Synthesis of the Penta- and Hexasaccharide Sphingolipid Analogs**

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**Acknowledgements**

We thank Dr. P. Zhang and C. Nychoi for supplying the truncated azidosphingosine acceptor. This work was supported by a NSERC Research Grant and a postgraduate studentship.