Understanding Neuropathy Pathogenesis: Synthesis of Ganglioside BSA Glycoconjugates and Immobilization on Sepharose Gel.

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Introduction

Guillain Barré syndrome (GBS), an acute autoimmune neuropathy syndrome and its variant, Miller Fisher syndrome (MFS), are characterized by circulating antibodies that react with ganglioside epitopes on nerve cells. GBS is the foremost cause of neuromuscular paralysis worldwide and can led to total paralysis within 48 hours and often leaves the patient with long-term or permanent disability. The disease is highly associated with antibodies to gangliosides, GM_1, GD_{1a}, GM_{1b} and GalNAc-GD_{1a}, and in MFS, GQ_{1b} ganglioside.[1,2]

The onset of GBS follows an infection, where there is a transient presence of anti-ganglioside antibodies, causing demyelination and/or axonal degeneration. The source of the anti-ganglioside response, is thought to arise from a primary immune response to an infection, most often the bacteria *Campylobacter jejuni*. Since there is a striking structural homology between gangliosides and the outer core oligosaccharides (OS) of lipopolysaccharides (LPS) in certain *C. jejuni* serotypes, it is proposed that antibodies generated against OS cross-react with the neuronal gangliosides – this cross-reactivity is sometimes called molecular mimicry.

(GM_1) Gal(β1-3)GalNAc(β1-4)Gal(β1-3)Hep(α1-3)Hep
NeuNAc(α2-3)

(GD_{1a}) NeuNAc(α2-3)Gal(β1-3)GalNAc(β1-4)Gal(β1-3)Hep(α1-3)Hep
NeuNAc(α2-3)

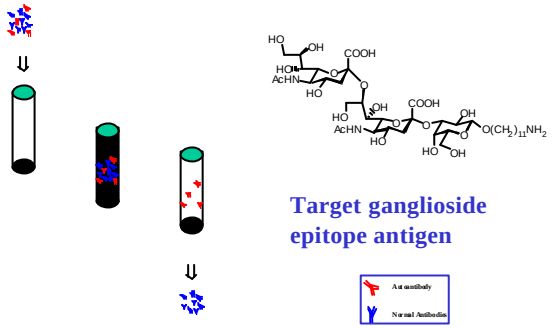
(GT_{1a}) NeuNAc(α2-8)NeuNAc(α2-3)Gal(β1-3)GalNAc(β1-4)Gal(β1-3)Hep(α1-3)Hep
NeuNAc(α2-3)

(GD_3) NeuNAc(α2-8)NeuNAc(α2-3)Gal(β1-3)Hep(α1-3)Hep

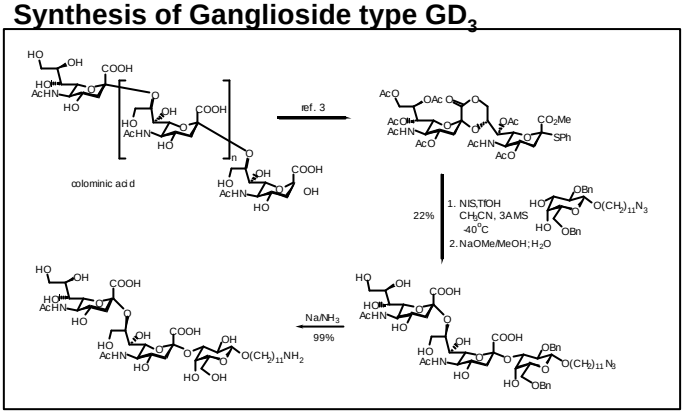
Structural homology of *C. jejuni* LPS with gangliosides marked in blue.

Plasma exchange and intravenous immunoglobulin are the only available therapies for GBS and both have serious long term risks. Specific removal of autoantibody by immobilized ganglioside antigen is a targeted approach that returns other blood components to patients.

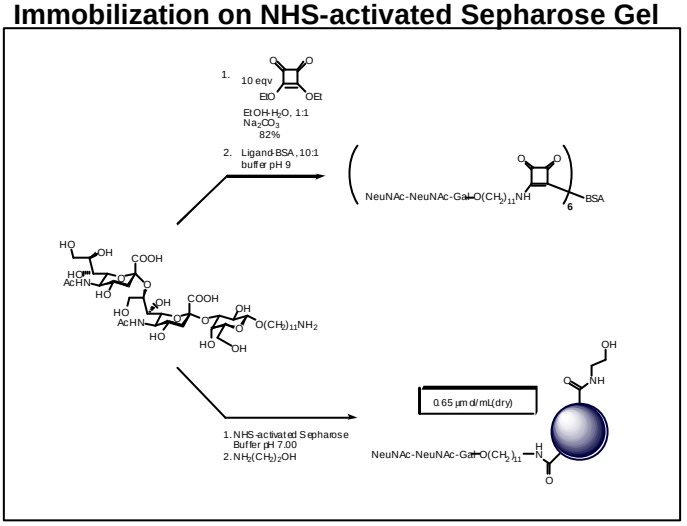
To identify appropriate ganglioside epitopes, we have begun the synthesis of several, NeuNAc(α2→8)NeuNAc(α2→3)Gal being one of them. To facilitate the immobilisation we attached an aliphatic chain containing a primary amine to the reducing sugar. For ELISA screening of patient sera we also prepared the corresponding BSA glycoconjugate.



Synthesis of Ganglioside type GD_3



Preparation of BSA Glycoconjugate and Immobilization on NHS-activated Sepharose Gel



Biological results

The GD_3 type disialylgalactose trisaccharide epitope conjugated to BSA binds to serum IgG antibodies in 54% of Miller Fisher syndrome sera that contain anti-GQ1b IgG antibodies and to serum IgM antibodies in 60% of chronic ataxic neuropathy sera that contain anti-disialosyl IgM antibodies. Consistent with this, the affinity column showed clearance of disialylgalactose-binding anti-GQ1b IgG antibodies from plasma of MFS patients.

This data supports the concept that oligosaccharide specific immunadsorption might be applicable as therapy for diseases such as GBS that are characterized by circulating anti-ganglioside antibodies.

References

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Acknowledgements

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