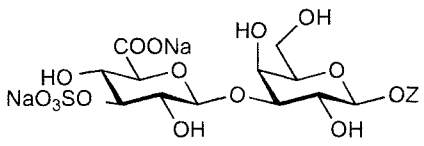
of its molecular weight is contributed by heterogeneous *N*-linked oligosaccharides. All of the potential eight *N*-glycosylation sites of MAG can carry the HNK-1 epitope. The two glycolipids (SGPG, SGLPG) carrying the HNK-1 epitope contain 3-*O*-sulfoglucuronic acid (SO_3-3GlcA) as a specific hallmark (T. Ariga et al., J Biol Chem 1987, 262:848-853). Interestingly, the HNK-1 epitope structure of bovine glycoprotein P0 also contains this characteristic feature. The similarity between the three elucidated structures is restricted to the terminal trisaccharide. Consequently the HNK-1 epitope was defined as SO_3-3-GlcA(β1-3)Gal(β1-4)Glc*N*Ac-OH.

The precise carbohydrate epitope recognized by IgM antibodies remains unclear. A study with SGPG derivatives showed that the IgM antibodies place different importance on the carboxyl and the sulfate group. Whereas "intact" SGPG, containing both negatively charged groups, was reported as optimal epitope for antibody binding (A.A. Ilyas et al., J Neurochemistry 1990, 55:594-601), other studies emphasize the importance of the length of the carbohydrate chain for antibody recognition. Furthermore, the SO_3-3-GlcA(β1-3)Gal disaccharide epitope seems to be the minimum requirement for binding (A. Tokuda et al., J. Carbohydrate Chemistry 1998, 17:535-546).

Summary of the invention

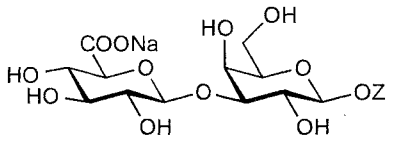
The invention relates to carbohydrate ligands that bind to anti-MAG IgM antibodies, and their use in diagnosis as well as for the treatment of anti-MAG neuropathy.

In ~~particular~~one aspect, the invention relates to disaccharides of formula (**I**)



(**I**)

and of formula (**II**)



(**II**)

wherein Z is optionally substituted phenyl, heteroaryl, arylcarbonyl, or heteroarylmethyl.

~~Furthermore~~In a further aspect, the invention relates to therapeutically acceptable polymers comprising a multitude of substituents of formula (**I**) and/or formula (**II**), wherein Z is a linker connecting said substituent to the polymer backbone.

~~The invention relates~~ Aalso disclosed herein are ~~to~~ pharmaceutical compositions comprising these compounds, diagnostic kits containing these, and to the use of these compounds for the diagnosis and therapy of anti-MAG neuropathy. Thus, in one aspect, there is provided a pharmaceutical composition comprising a compound of formula (**I**) or (**II**) according to the present invention or a polymer according to the present invention. In another aspect, there is provided a diagnostic kit comprising a compound of formula (**I**) or (**II**) according to the present invention or a polymer according to the present invention. In a further aspect, there is provided the compound of formula (**I**) or (**II**) according to the present invention or the polymer according to the present invention for use in the diagnosis of anti-MAG neuropathy. In yet a further aspect, there is provided the use of the compound of formula (**I**) or (**II**) according to the present invention or the polymer according to the present invention in the manufacture of a medicament for the treatment of anti-MAG neuropathy in a warm-blooded animal.

Brief Description of the Figures

Figure 1. Schematic representation of a competitive binding assay

(a) Incubation of MAG-coated plates with anti-MAG IgM (patient sera) and polymer **25**. (b) Wash step. (c) Incubation with anti-human IgM antibody coupled to horseradish peroxidase. (d) Wash step. (e) Addition of tetramethylbenzidin (TMB) substrate. (f) Addition of acidic stop solution and measurement of the optical density.

Figure 2. Binding curves for compounds **1**, **2** and **25**

2(a) The MAG-coated wells were co-incubated with compound **1** (50 mM highest concentration) and the four patient sera **MK**, **DP**, **KH** and **SJ** (%ab = % IgM antibody binding to MAG).
2(b) Co-incubation of MAG-coated wells with compound **2** (50 mM highest concentration) together with patient sera **MK** and **SJ**.

2(c) Co-incubation with compound **25** (15 µM highest concentration) together with patient sera **MK**, **KH** and **SJ**. Compound **25** is a polylysine polymer with a defined percentage of lysine residues coupled to the minimal HNK-1 epitope (**1**). The general abbreviation used is as follows: PL(minHNK-1)$_x$ with x defining the percentage of epitope loading in %. In this case the polymer is PL(minHNK-1)$_{44}$.

2(d) Co-incubation with patient serum **KH** together with the polymers PL(minHNK-1)$_x$ with x being 10, 25, 31 and 44% (0.5 mM highest concentration).

9. The polymer according to claim 6 wherein the polymer backbone is poly-lysine.

10. The polymer according to claim 7 wherein the molecular weight of the polymer backbone is 1'000 kD to 300'000 kD.

11. The polymer according to any one of claims 6 to 10, wherein the linker Z is aryl, heteroaryl, aryl-lower alkyl, arylcarbonyl, or heteroarylmethyl, wherein aryl or heteroaryl is substituted by alkylene with 3 to 25 carbon atoms connecting to the polymer wherein optionally
(a) one or more carbon atoms of alkylene are replaced by nitrogen carrying a hydrogen atom, and one of the adjacent carbon atoms is substituted by oxo, representing an amide function –NH–CO–; and/or
(b) one or more carbon atoms of alkylene are replaced by oxygen;
(c) one or more carbon atoms of alkylene are replaced by sulphur; and/or
(d1) the terminal carbon atom connecting to the polymer is substituted by oxo; or
(d2) the terminal carbon atom connecting to the polymer is replaced –NH–.

12. The polymer according to any one of claims 6 to 11, wherein the relative molecular weight of polymer backbone to disaccharide of formula (**I**) and/or (**II**) is between 10:1 and 1:1.5.

13. A pharmaceutical composition comprising a compound of formula (**I**) or (**II**) according to any one of claims 1 to 5 or a polymer according to any one of claims 6 to 12.

14. A diagnostic kit comprising a compound of formula (**I**) or (**II**) according to any one of claims 1 to 5 or a polymer according to any one of claims 6 to 12.

15. The~~Use of a~~ compound of formula (**I**) or (**II**) according to any one of claims 1 to 5 or the~~a~~ polymer according to any one of claims 6 to 12 for use in the diagnosis of anti-MAG neuropathy.

16. ~~A method of treatment of anti-MAG neuropathy, which comprises administering a~~The use of the compound of formula (**I**) or (**II**) according to any one of claims 1 to 5 or the~~a~~ polymer according to any one of claims 6 to 12 in the manufacture of a medicament for the treatment of anti-MAG neuropathy in ~~in a quantity effective against said disease, to~~ a warm-blooded animal~~ requiring such treatment~~.