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Glycosylation targets for drug design

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One of the main reasons for understanding the conformations of oligosaccharides is to study their interaction with carbohydrate binding proteins or antibodies in order to design vaccines or inhibitors of pathological processes. The oligosaccharides can be part of protein or lipid glycosylation, the proteoglycans and bacterial capsular polysaccharides (CPS). The earliest emergence of glycobiology was in the understanding of the blood group ABO system and the characterisation of the receptor destroying enzyme (RDE) of influenza virus. These have now turned into potential multi-million dollar therapeutics via blood group-related sequences as ligands for selectins and as oncodevelopmental antigens and the sialidase inhibitors for treatment of influenza and possibly other infections [1]. The other great potential realised several years ago is in anti-bacterial (CPS) vaccines and in inhibitors of bacterial toxins that bind to host gangliosides (sialylated glycolipids). Most recently other lipid–oligosaccharide conjugates have received attention, i.e. the glycosylphosphatidylinositol (GPI) anchors and related glycanphospholipids, both in designing strategies for inhibition of microbial and parasite infection (e.g. see Ref. [2]) and the role of the former in mammalian cell interactions [3]. The physico-chemical methods of analysis include X-ray crystallography, NMR, surface plasmon resonance [4], microcalorimetry (discussed at the last polysaccharide conformation satellite), and molecular dynamics. X-ray crystallographic data are now available of antibody–carbohydrate antigen interactions [5,6] and plant [7–10] and mammalian lectins [11,12] and more recently oligosaccharide ligands themselves [13]. There is still a place for dynamic studies based on NMR and molecular modelling, for example in the area of glycolipids [14,15]. At the La Thuile meeting Dr P.-G. Nyholm described molecular modelling of complexes of verotoxin with glycolipids of the globo series. This talk was followed up by Dr L. Raimondi with a computational model of the complex between ganglioside GMI and the heat-labile enterotoxin of *Escherichia coli*. Dr C. Hervé du Penhoat described the Forssman oligosaccharide sequence of glycolipids and its interaction with antibodies. Dr A. Imberty described how antibodies and lectins recognise histo-blood group oligosaccharides using a 3D QSAR approach (Quantitative Structure/Activity Relationship). I reported on Thy-1 and the modelling of this GPI-anchored glycoprotein within a simulated lipid monolayer. This is a good example of a multidomain molecule with various interactions, which need to be modelled: its protein domain has two probable functions, one to bind extracellular matrix proteoglycans and two, as yet unknown interactions via its flexible loops; the GPI glycan, which affects the loop conformation [16], and maybe interacts with other molecules in the membrane [3]; and three N-glycans, which can also be thought of as domains (of similar size to the single immunoglobulin superfamily protein domain in Thy-1), the functions of which are likely to hinge on their flexibility and solution dynamics.

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