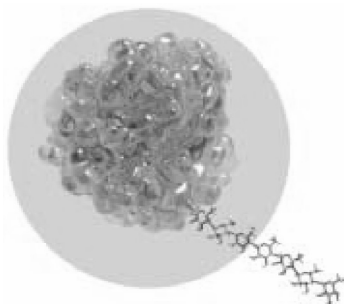


## SUGARS & ENZYMES

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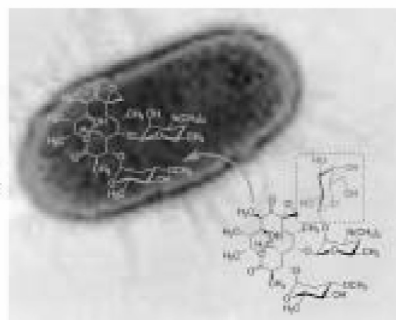
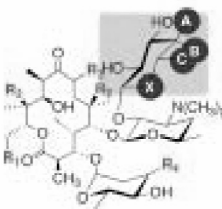
Sugars are critical biological markers that modulate the properties of proteins. Our work studies the interplay of proteins and sugars. This lecture will discuss recent developments our laboratory in two areas: (i) glycoconjugates and their use in potential therapy; and (ii) carbohydrate-processing enzyme mechanism—the engineering and study of glycosidases & glycosyltransferases and the synthesis of probes of their mechanism.



(i) Glycoconjugate synthesis: To explore the key properties of glycosylated macromolecules e.g. proteins, there is a continuing need for methods that not only allow preparation of pure glycosylated proteins, but will also allow the preparation of non-natural variants for e.g. structure-activity relationships (SARs).[1] We have developed methods for precise protein glycosylation[2] that allowed the effects of protein glycosylation to be explored precisely for the first time.[3] Glycosylated enzymes can be used in • preparative biocatalysis[4] • drug delivery[5] and • selective protein degradation[6].

A new class of glycoconjugate, the *glycodendriprotein*[7] acts as a powerful nanomolar inhibitor of bacterial interactions. Newly developed *glycoviruses* allow targeted gene transfer.[8]

(ii) Carbohydrate-Processing Enzymes: These enzymes are powerful tools not only for use in glycoside synthesis but also as potential targets for therapeutic intervention. Many elegant studies have made significant advances towards understanding the reactive catalytic mechanisms of these enzymes. However, the mechanism



by which substrate specificity is determined is still largely unclear. We have begun to explore the underlying basis of these catalysts[9] and methods to enhance their synthetic utility. For example, through the use of a novel high throughput mass spectrometric screening system[10] we have identified enzymes capable of remodelling macrolide antibiotics to enhance function. Secondly, we have developed methods for the ready construction of arrays of inhibitors as probes of carbohydrate-processing enzymes and which have allowed the identification of novel inhibitors.[11] These include novel stereodynamic aza-sugar strategies that have allowed the first synthesis of naturally occurring hydrophobically modified aza sugar, Adenophorine[12] & creation of targeted libraries of antivirals.[13]

[1] B.G. Davis, *Chem. Rev.* 2002, 102, 579; [2] D.P. Gamblin et al *Angew. Chem. Int. Ed.* 2004, 43, 827. [3] B.G. Davis et al *Bioorg. Med. Chem.* 2000, 8, 1527. [4] K. Matsumoto et al, *Chem. Commun.* 2001, 903; K. Matsumoto et al *Chem. Eur. J.* 2002, 4129. [5] M.A. Robinson, B.G. Davis, *Curr. Opin. Drug Disc. Devel.* 2002, 5, 279; M.A. Robinson et al *Proc. Natl. Acad. Sci. USA* 2004, 101, 14527; [6] B.G. Davis et al, *ChemBioChem* 2003, 4, 533. [7] B.G. Davis, *Chem. Commun.* 2001, 351-352; P.M. Rendle et al, *J. Am. Chem. Soc.*, 2004, 126, 4750-4751; [8] O.M.T. Pearce et al *Angew. Chem. Int. Ed.* 2005, 44, 1057. [9] K. Corbett et al *FEBS Lett.* 2001, 509, 355; [10] M. Yang et al *ChemBioChem* 2005, 6, 346; [11] B.G. Davis et al. *Org. Lett.*, 2002, 4, 103; T.M. Chapman et al *Chem. Eur. J.*, 2003, 9, 3397; [12] M.A.T. Maughan et al *Angew. Chem. Intl Ed.* 2003, 42, 3788. [13] T.M. Chapman et al *J. Am. Chem. Soc.* 2005, 127, 506-507.