Targeting glycosylation with chemical tools

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Glycosyltransferases (GTs) are Nature's glycosylation reagents: enzymes that catalyse the transfer of a mono- or oligosaccharide from a glycosyl donor to a suitable acceptor, e.g. a glycan, peptide, protein or lipid. Glycosylation is one of the most important posttranslational protein modifications, and GTs play a key role in many fundamental biological processes underpinning human health and disease, such as bacterial cell wall biosynthesis and cell adhesion. Individual GTs have been identified as promising therapeutic targets in infection, inflammation and cancer [1]. Inhibitors and chemical probes for GTs are therefore of considerable scientific interest for drug discovery and chemical biology. Potent, selective and cellularly active GT inhibitors would be powerful tools for glycoengineering, and to dissect complex glycosylation networks in living cells.

The Wagner group has a long-standing interest in the development of chemical inhibitors and probes for glycosyltransferases. Recent examples include the discovery of a novel type of allosteric GT inhibitor [2], the development of fluorescent probes for mammalian and bacterial galactosyltransferases [3], and the identification of drug-like inhibitors for mannosyltransferases from the human parasite *T. brucei* [4]. In this presentation, a brief introduction will be given to the biological and therapeutic relevance of GTs. This will be followed by selected examples from ongoing research in the Wagner group into the discovery and biological application of GT inhibitors, including results from structural biology studies and assay development.

References

[1] for a recent review see e.g. G. K. Wagner & T. Pesnot "Glycosyltransferases and their assays". *ChemBioChem* **2010**, *11,* 1939-1949

[2] (a) *Nature Chem. Biol.* **2010**, 6, 321-323; (b) *J. Med. Chem.* **2012**, *55*, 2015-2024; (c) *Chem. Commun.* **2012**, in press.

[3] (a) *ChemBioChem* **2010**, *11*, 1392-1398; (b) *Org. Biomol. Chem.* **2011**, *9*, 1855-1863

[4] (a) *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1749-1752; (b) *Org. Biomol. Chem.* **2010**, *8*, 3488-3499

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