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Editorial

Glycotherapeutics: Emerging Trends in Pharmaceutical Sciences

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Glycans (sugars) have a pivotal role are in controlling many vital processes relevant to health and a broad range of diseases. Glycans or Carbohydrates are ubiquitous and represent the most abundant class of molecules in nature. Over 100 monosaccharides (sugars) occur in nature, ranging from 4-carbon erythrose and threose to 9-carbon sugars, such as the sialic acids, with complex functionality. The polyfunctional nature of carbohydrates enables their suitability in information transfer. Great structural diversity is possible when linking monosaccharide residues owing to the number of hydroxyl groups available and the possibility of creating either a α- or β-anomeric linkage (1). Calculations suggest that there are approximately 38,000 permutations possible for the linkage of three sugar residues. With a vocabulary of 20 carbohydrate residues there are 9 x 10^6 potential trisaccharides. The enormous dictionary of sugars also provides many targets for therapeutic interventions. Existing sugar-based therapeutics – "glycotherapeutics" - cover a wide range of applications. On cell surfaces, Glycans are attachment points for many disease pathogens, which has led to the development of drugs like Relenza (a neuraminidase enzyme inhibitor to treat influenza) and anti-bacterial vaccines such as Haemophilus influenzae type B (Hib vaccine) (2). One of the great success stories in glycopharmaceuticals is the recombinant human glycoprotein hormone erythropoietin (EPO) which is used as a treatment against anemia, where introducing more glycans carrying sialic acid greatly increased its biological half life (3).

Advances in the functional understanding of Glycan–protein interactions have enabled the development of a new class of small-molecule drugs, known as glycomimetics. These compounds mimic the bioactive function of carbohydrates and address the drawbacks of carbohydrate leads, namely their low activity and insufficient drug-like properties (4).

A few other successful application of sugar based therapy includes low molecular weight heparins, derived from animal tissue, and Fondaparinux (Arixtra; GlaxoSmithKline), which are used as anticoagulants. Inhibitors of α-glycosidase in the brush border of small intestine for the treatment of diabetes (by Voglibose (Basen/ Glustat/Volix; Takeda), Miglitol (Glyset; Pfizer) and Acarbose (Glucobay/Prandase/Precose; Bayer)) are also

some notable examples. Further, the inhibition of viral neuraminidases in the pharyngeal mucosa (by Zanamivir (Relenza; GlaxoSmithKline) for the treatment of influenza is also well known (5).

With the advent of novel technologies many promising glycodrug candidates have been reported. Selectins are perhaps the most intensely studied mammalian carbohydrate binding proteins, Expression of these Selectin ligands on the tumor cells of patients with gastric and colon cancers is significantly correlated with poor survival. Cimetidine (Tagamet; GlaxoSmithKline), a histamine receptor antagonist that also suppresses vascular expression of E Selectin, markedly and specifically improved survival of high risk patients identified by tumour expression of sLe^a and sLe^x, further supporting the usefulness of Selectins as therapeutic targets for cancer. Some examples of glycomimetic, small molecule antagonists of Selectins in clinical and preclinical trials are Bimosiamose (TBC-1269) (phase II a) for the treatment of Asthma and Psoriasis, OJ-R9188 (preclinical) for Allergic dermatitis, GMI-1070 (phase I) for treatment of Sickle cell crisis, PSI-697 (phase I) for the treatment of Athero–thrombotic and venous thrombotic diseases, Efomycin M (preclinical) for the treatment of Psoriasis (6).

Dendritic cell-specific ICAM3-grabbing non-integrin (DC-SIGN) important cell surface protein discovered on migrating dendritic cells with binding specificity to fucose and mannose residues were revealed to bind to a number of pathogens like HIV, Hepatitis C virus, Dengue virus, Ebola virus, Marburg virus, Coronavirus (which causes severe acute respiratory syndrome) and Cytomegalovirus, as well as bacteria such as *Mycobacterium tuberculosis* and *Helicobacter pylori* and yeast (*Candida albicans*) and even parasites such as *Leishmania* spp and *Schistosoma mansoni*. Thus, DC-SIGN is an interesting target for therapeutic intervention. Glycomimetic compounds that inhibit DC-SIGN have yielded promising results in combating Ebola infection (7).

Siglecs families of carbohydrate binding proteins with well known functions are also interesting therapeutic targets. Among Bacteria like *P. aeruginosa* virulence factors namely PA-IL and PA-IIL have also been demonstrated to be inhibited by carbohydrate inhibitors like D-galactose and L-fucose (8). Similarly, uropathogenic *Escherichia coli* have also been demonstrated to be inhibited by oligomannosides and aromatic αmannosides (9). Taken together, Glycans have potential therapeutic benefit as drug themselves or as drug targets. Breakthroughs in this field may lead to the development of effective vaccines and enhanced serodiagnostics to control infections. Glycotherapeutics offer a whole new and exciting field in pharmaceutics which definitely merit attention as it aims to address development of novel molecules with increased drug potency and efficacy (10).

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