GlycoMar

Marine biotechnology for human health, personal care, and the life sciences

Oligosaccharides in Drug Discovery

2012

Development of Oligosaccharides in drug discovery

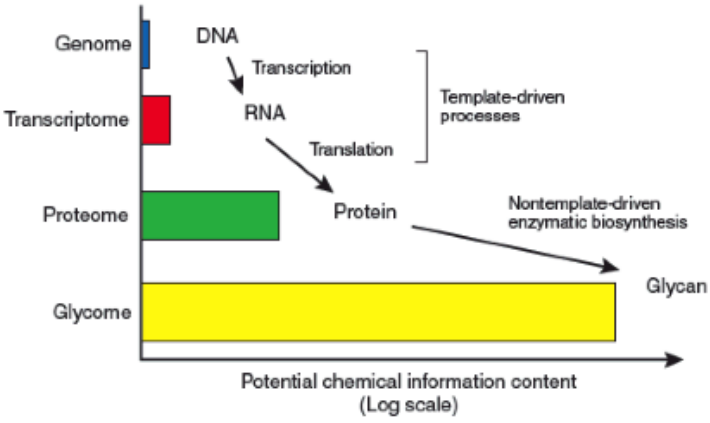
Introduction

Glycobiology is the branch of biology concerned with the study of structure, biosynthesis, and function of saccharides (sugar chains), which may exist purely or conjugated to other biological molecules to form glycoconjugates. The study of such molecules is technically challenging as no sequencing tool, such as that used in proteomics or genomics, is available. However, following on from genomics and proteomics, there is increasing recognition of the importance of carbohydrate-based molecules in basic cellular processes. This has resulted in more extensive glycomic studies in the areas of glycosylation of therapeutic proteins, glycosylation patterns in cell recognition, cellular glycoprofiling studies in cancer and other diseases, correlation between activity and sulphation patterns in glycosaminoglycans, and the improved chemical analysis and synthesis of carbohydrate molecules.

Glycobiology offers enormous untapped potential in the discovery of new therapeutics derived from saccharides or other molecules which target the biosynthesis and function of saccharides.

Saccharides: multifunctional biological molecules

Saccharides offer potential chemical diversity orders of magnitude greater than their protein and nucleic acid counterparts[1]. For example, DNA can give 256 4-unit structures; amino acids can give 16000 4-unit structures, whereas the nine common monosaccharides have the theoretical ability to generate nearly 16 M 4-unit structures[2]. The level of chemical information encoded in saccharides is therefore unrivalled.



Turnbull & Field 2007 Nature Chemical Biology 3(2), pp74-77

Saccharides have multiple functions which makes them relevant to almost any area of biological research. They are ubiquitously present on cell surfaces, mediating the interaction of cells with other cells, with the extracellular matrix and with effector molecules. The glycosylation of protein molecules is also critical for their function, bioavailability and half-life. Polysaccharides and glycoconjugates also play a major structural role in all connective tissues. Oligosaccharides, which are short chains of sugars derived from larger polysaccharides or synthesised in their own right, are widely studied to identify functional groups within complex glycoconjugates or polysaccharides.

Oligosaccharide therapeutics:

The central role of saccharides in cellular interactions means that novel oligosaccharides are of value in R&D programmes addressing a wide range of therapeutic areas[3, 4], including:

- **Inflammation**
- **Immunity**
- **Oncology**
- **Neurodegenerative disease**
- **Infection**

Regulation of the immune system is a key area of interest to glycobiologists, due to the central roles of carbohydrate-based molecules such as glycoproteins and glycosaminoglycans in cell-cell recognition, cell signaling and infection. With increasing understanding of the inflammation process in a range of disorders including vascular disease (artherosclerosis, thrombosis, diabetes), neurodegeneration (Alzheimers, Multiple sclerosis), cancer and orthopedic illnesses (arthritis, Ankylosing spondylitis), there is wide scope for the further application of novel carbohydrate-based drugs.

Oligosaccharides in use as drugs or in development:

The use of carbohydrate-based drugs is in its infancy, although several are well known (see Table 1). In addition to 'monosaccharide-inspired' drugs such as influenza treatment Tamiflu (oseltamivir, Roche), two blockbuster drugs, Acarbose (Bayer) and heparin, stand out. Both oligosaccharides were isolated, and reached the clinic, before a detailed structure-activity relationship had been carried out. Heparin is the key example of a major carbohydrate-based molecule, which has been developed for medical use in anti-coagulant therapies. Low molecular weight heparins (eg. Certoparin, Dalteparin) and various derivatives (Fondaparinux – fully synthetic) have been developed to improve efficacy and half-live, and some are now being trialled for non-thrombotic/vascular applications (eg. Certoparin for inflammatory aspects of Alzheimers disease). It is only comparatively recently that the anti-inflammatory properties of heparin have been discovered.

Delivery and immunogenicity:

The drugs listed in Table 1 have overcome some of the perceived limitations of sugar-based molecules in terms of delivery, synthesis and immunogenicity. Although many still require intravenous delivery, several are available orally (eg. Pentosan polysulphate) and further research is targeting the improvement of oral availability by reducing compounds to their smallest active components, or by combining with other molecules (eg. sulodexide). Improvements in synthesis has meant that some compounds can be synthesised (eg. Fondaparinux), and small active components can be selected or modified to improve efficacy. No major problems have been reported with immunogenicity either in animal trials or as approved drugs, using synthetic or animal derived material, including that obtained from marine invertebrates.

Table 1. Examples of carbohydrate-based drugs in use or in development			
Company	Compound	Activity / disorder	Development
Numerous	Heparin and derivatives: in particular low molecular weight forms	Anti-coagulants	Since 1940's
Astellas	Auranofin (Ridaura)	Anti-rheumatic	1983
GSK	Zanamivir (Relenza)	Anti-influenza	1992
Johnson & Johnson	Topiramate (Topamax)	Anti-epileptic	1987
Bayer	Acarbose (Glucobay) (Pseudo-oligosaccharide)	Type II diabetes Alpha-glucosidase, alpha-amylase inhibitor.	1990
Ortho-McNeil Janssen Pharmaceutical	Elmiron (Pentosan polysulphate)	Cystitis (interest in development for CJD)	1996
Alfa Wassermann	Sulodexide (Vessel™)	Various cardiovascular indications	Marketed since 1980's
Merion Pharmaceuticals	MER-102	Oral uLMW heparin for DVT	Phase IIa
Sanofi Aventis	idrabiotaparinux	Biotinylated idraparinux for the treatment DVT and pulmonary embolism	Phase III
Paringenix	PGX100	*O*-desulphated heparin for cardiac ischemia-reperfusion injury, COPD	Phase I
Hunter Fleming (now Newron)	HF0420 – low molecular weight oligosaccharide	Prevention of anti-cancer induced neuropathy (neuroprotective)	Phase I
Progen (Australia)	PI-88 (Phosphomannopentaose sulphate)	Heparan sulphate mimetics – Anti-angiogenic/anti-metastatic. Adjuvant therapy for post-resection hepatocellular carcinoma	Phase III
	PG500 series	Heparan sulphate mimetics – Anti-angiogenic/anti-metastatic.	Preclinical
Endotis Pharma	EP80061 – synthetic oligsaccharide	Anti-metastatic, heparanase inhibitor	Preclinical
	EP80031 – synthetic oligosaccharide	Hematopoietic stem cell mobilization	Preclinical
	EP37151 – oral fondaparinux	Anticoagulant	Preclinical
	EP217609 – biotinylated thrombin inhibitor coupled to pentasaccharide	Indirect factor Xa and direct thrombin (Factor IIa) inhibitor that can be neutralized quickly and effectively without rebound effect by a specific antidote: avidin	Phase I
Biotec Pharmacon	Beta-glucan	Various	Preclinical
Marinova	Fucoidan	Ostearthritis	Phase I & II
GlycoMar / Verona Pharma	GLY145 – fucosylated dermatan sulphate	Anti-inflammatory	Preclinical

Oligosaccharide libraries for drug discovery research

Native glycoconjugates and polysaccharides have limited value in drug discovery research due to their large size (MW 10 – 1000 kDa) and structural heterogeneity, although heparin is a notable historical exception which has been used in its native form (manufactured form bovine lung or porcine gastric mucosa). Oligosaccharides generated from native molecules offer the opportunity to identify active functional subunits and of revealing cryptic activity. Heparin provides an example of a blockbuster saccharide that has progressed from unfractionated polysaccharide, to low molecular weight polysaccharide, and now synthetic oligosaccharide, through the application of glycomic tools.

Oligosaccharide libraries clearly have value for drug discovery research in a wide range of diseases[5]. Limited numbers of such libraries currently exist and they are largely based on mammalian polysaccharides and glycoconjugates. The unique structures and sulphation patterns of marine derived sugars are being increasingly recognised and investigated[6]. Several compounds are already in use as nutraceuticals, with others having been tested in preclinical trials. Depolymerised and low molecular weight forms have also been investigated, with oral delivery and no reported problems with immunogenicity.

Marinova (Australia) are involved in the development of fucoidan-based products from seaweeds[7], using in-house modulation of sulphation and acetylation. They are investigating applications in cardiovascular, infection, oncology and inflammation areas, as are several other research and commercial labs. This parallels the activity by IFREMER, France.

Other compounds have been brought forward by academic research groups, in particular a Brazilian team from Rio de Janeiro, often in association with industrial partners eg. Sanofi-Aventis (sea squirt heparin).

Table 2. Examples of marine-derived carbohydrate-based therapeutic molecules

Compound	Source	Activity	Status
Chondroitan sulphates	Mussels	Joint repair / maintenance	Nutraceutical
Galactofucan sulphate (GFS)	Seaweed Marinova, Australia	Attenutates herpes virus infections. Improved mobilization of hematopoetic stem cells	Nutraceutical / Clinical
Fucosylated chondroitan sulphate	Sea cucumber	P-selectin mediated anti-inflammatory effects / unique anti-coagulant properties	Preclinical
Invertebrate Heparin	Sea squirt	Arterial thrombosis	Preclinical

Marine oligosaccharide libraries for drug discovery

GlycoMar is a biopharmaceutical company uniquely focused on the development of novel therapies based on saccharide molecules from marine organisms. The company has developed a unique library of *N*-glycans and *O*-glycans derived from a wide range of marine organisms.

GlycoMar can offer polysaccharides and oligosaccharides which meet a wide range of chemical and functional characteristics. These compounds provide a unique set of properties for drug discovery and are being developed by GlycoMar for inflammatory disease indications.

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GlycoMar is a biotechnology company, located at the European Centre for Marine Biotechnology in Scotland, UK. The company has created a unique combination of marine biology, glycobiology, and drug discovery.

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