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Review Article

Glycotherapeutics: Clinical Implications

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Abstract

Carbohydrates are the most abundant molecules present in nature. They are the structural building blocks and the fundamental constituents of every cell surface. Carbohydrates make an ideal therapeutic platform because they are known to be involved in various biological processes. Increased understanding of how glycobiology changes between the normal and the disease states has fueled interest in these molecules as excellent starting points for developing a multitude of new drugs and therapeutic approaches. Therefore, they play a major role in glycotherapeutics. As in other fields that have spawned successful new therapeutics, years of effort have been required to understand the unique challenges that are innately linked to carbohydrate-derived drugs and to develop the basic skills and the specific knowledge to move from the excitement of scientific discovery to the development of a new class of therapeutics. Glycans have potential therapeutic benefit as drugs themselves or as drug targets. Recognition of carbohydrates and related structures in biological systems represents a new line of research. Breakthroughs in this field may lead to the development of better drugs and effective vaccines.

Keywords: Carbohydrates, drugs, glycobiology, glycotherapeutics, vaccines.

INTRODUCTION

Carbohydrates are the most abundant naturally occurring molecules. They are the fundamental constituents of every cell surface and are involved in various biological processes (Table-1).

All cell surfaces are coated with complex carbohydrates where they act as vital cellular recognition molecules for other cells, functional molecules, and pathogens. They exist as chains of monosaccharides (glycans), which form a layer (glycocalyx), ranging from 10 to 100 nm in thickness.¹ Glycans are present in many different molecular forms, including glycoproteins, proteoglycans, glycolipids and glycosphosphatidyl inositol linked proteins. Their broad diversity originates from their basic assembly from a monosaccharide, which can be linked to each other at various positions on their pyranose or furanose rings. Each ring can establish several linkages.²

Finally, the structural complexity is further increased by the possibility of α and β isomers at the anomeric centre. This dense structural information is decoded by carbohydrate binding proteins. Glycoproteins are usually present on the cell surface, where they are recognized by bacteria, viruses, and other proteins,

such as lectins, in order to facilitate various important functions. Glycans are also involved in a variety of biological processes including protein folding and signalling events. Unlike DNA and proteins, however, monosaccharides may be linked to one or more other monosaccharides, to form a branched tree structure. Proteins called “lectins” have evolved three-dimensional domains [carbohydrate-recognition domains (CRD)] that can bind specific carbohydrate structures and thus decode the information.³

Glycotherapeutics

Carbohydrates make an ideal therapeutic platform because they are known to be involved in various biological processes. Increased understanding of how glycobiology changes between the normal and the disease states has fueled interest in these molecules as excellent starting points for developing new therapeutic approaches⁴ (glycotherapeutics).

Currently, over 80 carbohydrate binding proteins have been recognized. The binding specificities for many of them have been elucidated, and others are being screened on large glycoarrays to determine their glycan binding epitopes. These discoveries have

led to a new beginning in glycobiology. They also provide a continuous supply of carbohydrate related targets for the structure based design of new chemical entities that mimic bioactive carbohydrates, and form a novel class of therapeutics.² A good drug is a target-specific drug; its users can expect high efficiency and few, if any, side effects. Target specificity also means recognition, and this is where carbohydrates come in. While many drugs contain carbohydrates as part of their molecules, other drugs – lacking carbohydrates covalently bound to their molecules – can be guided by them.

Carbohydrate-derived drugs

Despite playing an essential part in numerous biological processes, carbohydrate and carbohydrate derived drugs cover only a limited area of the world of therapeutics. Many pathophysiological important carbohydrate–protein interactions have yet to be exploited as a source of new drug targets. One reason might be the pharmacokinetic drawbacks that are inherently linked to carbohydrates high polarity, precluding satisfactory oral availability, and fast renal excretion following parenteral administration.²

A few dozen US FDA-approved prescription drugs contain carbohydrate moieties as part of their structures. The removal of the sugar eliminates the therapeutic value of the drug. These drugs can be divided into five categories⁵ (Table-2):

Monosaccharide conjugates include, in turn, five groups of prescription drugs (Fig-1):

Monosaccharides

Glucose as dextrose solution is used as i.v.fluid. Glucose is also a component of oral rehydration solution (ORS) given in cases of dehydration. Mannitol is used in cerebral oedema to reduce intracranial tension.

Anthracycline Antibiotics and Agents

The second group is represented by cytotoxic anthracycline antibiotics of microbial origin (**Doxorubicin** and **Daunorubicin**) or their semi-synthetic derivatives (**Epirubicin** and **Idarubicin**). These are potent anti-neoplastic agents consisting of a naphthacenequinone nucleus linked through a glycosidic bond at ring atom 7 to an amine sugar, daunosamine. The planar anthracycline nucleus interactions with the DNA double helix, between nucleotide base pairs, with consequent inhibition of nucleic acids (DNA and RNA) and protein synthesis. They stabilize the DNA-topoisomerase II complex, by inhibiting topoisomerase II activity, thus blocking the ligation-religation reaction. All of these drugs show the

cytotoxic effect on malignant cells and – as side effects – on various organs. These drugs induce apoptosis, which may be an integral part of the cellular action related to antitumor therapeutic effects as well as toxicities. Another doxorubicin derivative is its conjugate with a polymeric galactomannan, which has cytotoxicity some 20 to 90 times lower than that of doxorubicin. 5-FU and GM CT-01 apparently show synergism in entering a malignant tumor, and the same two compounds interfere with each other when entering the liver. This might explain how the combination might show a better antitumor activity and lower toxicity toward healthy cells and organs.

Nucleotides and Nucleosides and Their Analogs

Among them are:

Fludarabine Phosphate (fluorinated arabinofuranosyladenine 5-monophosphate), whose metabolic product inhibits DNA synthesis. It is indicated for the treatment of B-cell chronic lymphocytic leukemia. Another such agent **Gemcitabine** (2'-deoxy-2, 2'-difluorocytidine), is a nucleoside analogue that inhibits DNA synthesis and exhibits antitumor activity.

Stavudine, a synthetic thymidine nucleoside analog, is active against the human immunodeficiency virus (HIV).

Adenosine (6-amino-9- -D-ribofuranosyl-9-Hypurine), present in all cells of the body and activates purine receptors (cell-surface adenosine receptors) causing relaxation of vascular smooth muscle, therefore indicated in patients with paroxysmal supraventricular tachycardia.

The first synthetic, non-interferon type antiviral drug **Ribavirin** (ribofuranosyl-triazole derivative), a nucleoside analog, active against respiratory syncytial virus (RSV).

A cardioprotective agent **Acadesine**, a ribofuranosyl-imidazole derivative and a purine nucleoside analog, which is employed in coronary artery bypass graft surgery.

Polyenes

The fourth group, polyenes, is exemplified by **Amphotericin B**, which is an antifungal antibiotic of microbial origin. It is a 3-Amino-3,6-dideoxy- -D-mannopyranosyl derivative of an octahydroxypolyene. It binds to cell membrane sterols and thus changes the cell membrane permeability of susceptible fungi which leads to leakage of intracellular content – and, as a consequence, cell death. Liposomal amphotericin B is even more effective and less toxic.

Other Agents

The fifth group of monosaccharide drugs contains a number of assorted compounds, such as:

The cancer chemotherapeutic agent **Etoposide**, a semi-synthetic β -D-glucopyranoside derivative of podophyllotoxin.

An antibacterial antibiotic of microbial origin **Lincomycin**, a derivative of 1-thio-D-erythro- β -D-galacto-octopyranoside.

A semisynthetic antibiotic, **Clindamycin**, a derivative of 1-thio-L-threo- β -D-galacto-octopyranoside and produced from Lincomycin.

An antitumor drug, **Pentostatin**, a direct inhibitor of adenosine deaminase and ribonucleotide reductase, particularly in cells of the lymphoid system.

Disaccharides and Disaccharide Conjugates

These are represented by the following medications:

An antipeptic and ulcer-protective drug, **Sucralfate**, a β -D-fructofuranosyl- β -D-glucopyranoside basic aluminum sucrose sulfate complex. It accelerates healing of peptic ulcers.

A synthetic colonic acidifier **Lactulose** (4-O- β -D-galactosyl-D-fructose) which promotes laxation.

A microbial amphoteric tricyclic glycopeptide antibiotic, **Vancomycin**, which inhibits bacterial cell-wall biosynthesis.

Trisaccharides

These are represented by the following two prescription drugs:

An antibacterial aminoglycoside antibiotic of microbial origin, **Tobramycin**, a derivative of an aminoglucofuranosyl-ribohexopyranosyl-L-streptomine. The drug acts primarily by disrupting protein synthesis through altering cell membrane permeability; thereby breaching the cell envelope and causing eventual cell death. It is indicated for the management of cystic fibrosis.

A cardiac glycoside, **Digoxin**, that belongs to a closely related group of drugs of plant origin and that contains a sugar and a cardenolide; the sugar part consists of (O-2,6-dideoxy- β -D-ribo-hexapyranosyl). Digoxin inhibits sodium-potassium ATPase leading to an increase in the intracellular concentration of calcium. It is useful in the treatment of cardiac failure.

Oligosaccharides and Polysaccharides

Prescription drugs made of oligosaccharides and polysaccharides include three principal groups:

- ❖ *Glycoaminoglycans*
- ❖ *Heparin like saccharides* (Heparin, Enoxaparin, Tinzaparin, Dalteparin, Danaparoid, Pentosan polysulfate).

- ❖ *Complex oligosaccharides* (Streptomycin, Neomycin, Acarbose).

Glycoaminoglycans (GAGs) are unbranched, polydisperse, acidic polysaccharides, often covalently linked to a protein core to form proteoglycans (PGs).⁶ GAGs are characterized (with the exception of keratin sulfate) by a repeating core disaccharide structure comprised of uronic acid and hexosamine residues. The most common GAGs are heparin, heparin sulfate (HS), hyaluronic acid (HA), chondroitin sulfate (CS), dermatan sulfate (DS), and keratin sulfate (KS). The PG family consists of 30 members, which display a broad range of biological functions.⁷

Heparin and Heparin-like Saccharides

In 1916, heparin was discovered by McLean, working under the directions of William Howell at John Hopkins University. To ascertain the origin of a substance causing blood coagulation, McLean isolated fractions from mammalian tissues. These, however, instead of clotting blood, prevented its coagulation. Howell recognized the importance of his student's discovery, suggesting heparin's therapeutic use to treat coagulation disorders.⁸

Heparin is a polydisperse, highly sulfated, linear polysaccharide made up of repeating 1-4 linked uronic acid and glucosamine residues.⁹ For the past 70 years, heparin has been used clinically as an anticoagulant, but its precise structure remains unknown. It is short-lived, as it is immediately processed by a β -glucuronidase to form a number of smaller polysaccharide chains (only one of which, corresponding to the original site of attachment to the core protein, should contain peptide) called GAG heparin.¹⁰ Heparin sulfate (HS) is primarily found in the extracellular matrix and in cell membranes,¹¹ while heparin is only intracellular. Although having structural similarity, HS and heparin have different ratios of N-acetyl to O-sulfo groups and can be often distinguished by differences in their sensitivity to heparin lyases.

Heparin is synthesized in connective tissue type mast cells, as part of the serglycin PG.⁶ HS is produced by most animal cells and is bound to a variety of core proteins, corresponding to syndecan, glypican, perlecan, and agrin PGs.¹² PG heparin is primarily found in the granules of mast cells. When mast cells degranulate, heparin is released as GAG heparin.¹³ Heparin is the most commonly used anticoagulant. Since orally administered heparin is inactive and also has a low bioavailability when administered subcutaneously¹⁴, so it is usually injected intravenously. The success of low molecular weight heparin (LMW) heparins is primarily because of their

high subcutaneous bioavailability.¹⁵ LMW heparins are prepared by the controlled chemical or enzymatic depolymerization of heparin. Their clinical use has recently surpassed the use of heparin in the US. In addition to heparin's anticoagulant activity, it has a wide variety of other activities (Table-3).

Enoxaparin, Tinzaparin and Dalteparin are all prepared by controlled depolymerization of heparin or its derivatives, accomplished by alkaline degradation, enzymatic hydrolysis, and nitrous acid fragmentation, respectively. **Danaparoid** is a complex glycosaminoglycuronan whose active components are heparan sulfate, dermatan sulfate, and chondroitin sulfate. Finally, **Pentosan Polysulfate** is a semi-synthetic sulfated heparin-like oligomer. Composed of -D-xylopyranose residues, it shows anticoagulant and fibrinolytic effects.

The antithrombotic action of heparin is due mainly to its ATIII-mediated anticoagulant activity. ATIII, a serine proteinase inhibitor (SERPIN), is an anionic glycoprotein which forms tight, irreversible, equimolar complexes with its target enzymes (thrombin, factor Xa, etc.).¹⁰

When heparin is administered intravenously, lipoprotein lipase (LPL) is mobilized from the vascular endothelial surface into the blood. This may result in increased triglyceride lipolysis in the bloodstream, lowering the concentration of cholesterol-rich remnant particles in contact with the arterial wall.¹⁶ Heparin's application as an anti-sclerotic agent is limited by its primary activity as an anticoagulant and its lack of oral bioavailability.¹⁷

Heparin may also act as an anti-inflammatory agent through its interaction with selectins and chemokines.¹⁸ Selectins are a family of transmembrane glycoproteins found on endothelium, platelets and leukocytes. Although the putative ligand on the endothelium responsible for leukocyte interaction with selectins is sialyl Lewis X, HS plays a role in this interaction.¹⁹

Heparin may play a variety of roles in angiogenesis. Immediately before capillary ingrowth, mast cells accumulate at the site of the tumor²⁰ and release heparin that can stimulate endothelial cell migration. Protamine and the chemokine platelet factor 4, both of which bind and inactivate heparin, can inhibit angiogenesis.²¹ Heparin can localize, activate, stabilize, and stimulate angiogenic growth factors such as fibroblast growth factor and endothelial cell growth factor.²²

Because of its anticoagulant function, heparin can inhibit thrombin and fibrin formation induced by cancer cells. Heparin may therefore potentially inhibit intravascular arrest of cancer cells and thus

promote metastasis. Moreover, heparin in mast cells also binds pathogens and may target them to dendritic or phagocytic cells.²⁰

Dermatan and Chondroitin sulfates

Dermatan sulfate (DS) and chondroitin sulfate (CS) make up a second GAG family, called galactosaminoglycans. CS is the most abundant GAG in the body, and occurs in both skeletal and soft tissue.¹⁰ CS consists of repeating units of glucuronic acid and GalNpAc. The two most common isomers contain O-sulfo groups at positions 4 (CS-A) or 6 (CS-C) of the galactosyl residue. DS, found mainly in mucosa and skin, is a polydisperse micro heterogeneous sulfated copolymer of D-GalpNAc and primarily L-IdoAp acid.²³ Thrombomodulin is a PG found on the luminal surface of the vascular endothelium and on underlying smooth muscle cells. DS may also play a role in lipid metabolism by binding and releasing endothelial lipoprotein lipase into the circulation.²⁴ The compositions of the endothelial cell surface HS and DS PGs change during atherogenesis.²⁵ Like HS, DS is a relatively weak anticoagulant. Other applications for DS include the preparation of medical devices and artificial tissues. Small arterial prostheses composed of a microporous polyurethane tube coated with a gel containing a mixture of type I collagen and DS have been designed.¹⁰

CS has been widely used as a nutraceutical for the treatment of osteoarthritis.²⁶ CS from human milk has also been found to inhibit HIV glycoprotein gp120 binding to its host cell CD4 receptor *in vitro*. CS-C has been used as a component of artificial skin.²⁷

Hyaluronan

Hyaluronan (HA) is a polyanionic natural polymer occurring as linear polysaccharide composed of glucuronic acid and N-acetylglucosamine repeats via a -1,4 linkage.²⁸ It is mainly found in the extracellular space, where it accumulates, but can also be bound to the cell surface or be located intracellularly around the nucleus and in the lysosomes.²⁹ The largest storage of HA in humans is in the skin (50% of the body's HA).³⁰

One important function of HA is its ability to immobilize specific proteins (agrecan, versican, neurocan, brevican, CD44) in desired locations within the body.³¹ HA is produced at high levels during cell proliferation, especially during mitosis. HA may help the cells to detach from the matrix, making it easier for them to divide, while some cell surface receptors (i.e., CD44 and RHAMM) bind HA, immobilizing them in the desired location.³² Cancer cells are often enriched with HA, and intense

intracellular staining for HA is a weak prognostic indicator for cancer therapy.³³ During inflammation, the HA production is increased, and the viscous solutions seem to inhibit cell activities.

The high water-binding capacity and viscoelasticity give HA a unique profile among biological materials. One of the most successful medical applications of HA is the intra-articular use of sodium hyaluronate for the treatment of osteoarthritis. In cataract surgery “viscosurgery”, viscoelastic materials such as NaHA are used to maintain operative space and to protect the endothelial layer of the cornea or other tissues from physical damage. HA has been mixed with other materials with desirable physicochemical, mechanical, and biocompatible properties. These include combinations with polyvinylalcohol for ophthalmic use, and with carboxymethylcellulose (carbodiimide crosslinked) to produce a bioseparable film for prevention of postsurgical adhesions, for wound-healing applications (with collagen) and for preparing stealth liposomes.³⁴

Conversion of the carboxylic groups of HA to N-acylhydrazides affords derivatives useful for controlled drug release. HA esters have been prepared and fabricated into hydrophobic gauzes and microspheres, for use in transmucosal drug delivery. Cross-linked, biocompatible HA hydrogels allow covalent attachment of therapeutic molecules.³⁵

Acharan Sulfate

N-sulfoacharan sulfate, a chemically modified acharan sulfate, is a moderately active inhibitor of thrombin³⁶ and shows heparin-like effect on basic fibroblast growth factor-2 mitogenicity but at a greatly reduced level.³⁷

Fucoidins

Fucoidin is a complex sulfated polysaccharide, derived from marine brown algae, the jelly coat from sea urchin eggs, and the sea cucumber body wall. Fucoidins are primarily composed of α -(1 \rightarrow 3)-linked units of 4-sulfo-L-fucose with branching or a second sulfo group at position 3. *Fucus* fucoidan has anticoagulant activity, and is a potent activator of both ATIII and HCII. Fucoidan inhibits both the initial binding of sperm and subsequent recognition, prevents infection of human cell lines by several enveloped viruses, blocks cell-cell binding mediated by P- or L-selectin (but not by E-selectin) and also exhibits differential binding to interleukins and the hepatocyte growth factor. It may be useful as an anticoagulant, antiviral, anti-inflammatory, or contraceptive agent. On oral administration fucoidans have been effective in healing and preventing gastric ulcers in animal models.¹⁰

Carrageenans

Carrageenans are sulfated polysaccharides derived from various species of red algae. Carrageenan (Irish moss) has been used as a cough medicine³⁸, and a degraded κ -carrageenan is marketed in Europe as an anti-ulcer preparation.³⁹ Carrageenan activates Hageman factor, and has cardiotoxic activity. On oral administration in animals, both κ - and λ -carrageenan show anti-tumor activity.⁴⁰

Sulfated chitins

Chitin poly-2-acetamido-2-deoxy-D-glucopyranose), is the main structural element of cuticles of crab, shrimp, and insects, and fungal cell walls.⁴¹ Chitosan derivatives show anticoagulant activity related to their degree of sulfation. Carboxymethylated sulfochitosan inhibits thrombin activity through ATIII to almost the same degree as heparin.

Dextran sulfate

Dextran, a (1 \rightarrow 4)- β -D-(1 \rightarrow 3)- β -D-branched Glc polymer, can be chemically sulfonated to prepare dextran sulfate. Dextran is a plasma expander. Dextran sulfate has low anticoagulant activity with high LPL-releasing activity, used as a heparin replacement in anticoagulation and has been immobilized on plastic tubes to prepare non-thrombogenic surfaces. It is an inhibitor of HIV binding to T-lymphocytes, but its low oral bioavailability has precluded its use in the treatment of AIDS.⁴²

Alginates

Alginate, a commercially important component of brown seaweeds, consists of D-mannuronic acid and L-glucuronic acid. Alginates have been used to treat wounds, gastric ulcers and reflux esophagitis. It also decreases the plasma cholesterol level, and strongly inhibits hyaluronidase and mast cell degranulation, involved in allergic reactions.¹⁰

Small sulfonated molecules

Suramin was the first heparin analogue used clinically in a broad range of applications⁴³, including its activity as an anti-helminthic, anti-protozoal, and anti-neoplastic, and an anti-viral agent. However, suramin has a very long half-life in the body and exhibits a wide range of toxic effects.

Naphthalene sulfonates show potent anti-HIV activity, but limited toxicological data are currently available. A series of simple aliphatic disulfates and disulfonates have been tested for their ability to arrest amyloidosis *in vivo* as potential agents for the treatment of Alzheimer's disease.⁴⁴

Sulfated cyclodextrins such as α -cyclodextrin tetradecasulfate have anticancer activity; probably through an anti-angiogenic mechanism.⁴⁵ They also inhibit complement activation.⁴⁶

Phosphosulfomannan (PI-88) is a sulfonated phosphomannan oligosaccharide mixture derived from the yeast *Pichia holstii*. It is a promising inhibitor of tumor cell growth and metastasis currently undergoing Phase I clinical trials, believed to interfere in HS interaction with FGF and FGFR and prevents metastasis by inhibiting heparanase, thus blocking the breakdown of extracellular matrix. PI-88 also shows substantial antithrombotic activity through its catalysis of HCII-mediated inhibition of thrombin.¹⁰

Pentosan, a linear Xylp polymer extracted from the bark of the birch tree *Fagus sylvatica*, when sulfonated and partially depolymerized, is an anti-coagulant with one tenth of heparin's activity on a weight basis.⁴⁷ Its primary anti-IIa activity has been postulated to be HCII-mediated.⁴⁸ Trestatin A, a pseudo-nonasaccharide obtained from strains of *Streptomyces dimorphogenes*, is a potent α -amylase inhibitor. A highly sulfated maltotriosyl trehalose pentasaccharide chemically modified from the Trestatin substructure has an antiproliferative activity comparable to that of heparin.⁴⁹ Sulfated lactobionic acid, prepared through the chemical sulfonation of lactose dimer, is an antithrombotic agent in animal models. It acts primarily through HCII but showed some toxicity precluding its clinical use.⁵⁰

GAG-based (and potentially other carbohydrate-based) agents have unique properties – such as high specificity, delocalized binding sites, low antigenicity, and multivalency- difficult to replicate with other classes of molecules. Their biological functions might be enhanced by administration of exogenous GAGs, modified GAGs, GAG oligosaccharides, or GAG analogues.

Complex Oligosaccharides

The complex oligosaccharide group contains two fundamentally different kinds of prescription drugs. The first are bactericidal aminoglycoside antibiotics of microbial origin, **Streptomycin** and **Neomycin**, which interfere with protein synthesis. Streptomycin also forms a part of anti-tuberculosis regime. The second kind of complex oligosaccharide **Acarbose**, also of microbial origin, inhibits α -glucosidase and delays the digestion of ingested carbohydrates (beneficial in type 2 diabetes mellitus).⁵

Carbohydrate based antibacterial vaccines

Natural polysaccharides conjugated to carrier proteins are made as vaccines against *N. meningitidis*,

S. pneumoniae, *H. influenzae type b* (Hib) and other synthetic oligosaccharide epitopes offer opportunities for vaccination against HIV, *P. falciparum*, *V. cholerae*, *C. neoformans*, *S. pneumoniae*, Shiga toxin, *B. anthracis* and *C. albicans*.

Carbohydrate based anticancer vaccines

Cancer cells often display alterations in their glycan repertoire on the cell surface, referred to as tumor-associated carbohydrate antigens (TACAs). A three-component vaccine composed of a TLR2 agonist, a promiscuous peptide T-helper epitope and a tumor-associated glycopeptides demonstrated promising anticancer activity in mice.⁵¹

Monosaccharide mimics

Prominent examples are the inhibition of α -glycosidases for the treatment of diabetes by voglibose, miglitol, and the prevention of influenza virus infection by zanamivir and oseltamivir. Promising results have also been recently obtained in the treatment of cystic fibrosis with miglustat. Topiramate is an anticonvulsant drug.

Oligosaccharide mimics

Validamycin A, the major active ingredient of the fermentation culture of *Streptomyces hygroscopicus* subspecies *limoneus* is an agricultural antifungal antibiotic.

Several carbohydrate-based drugs are currently on the market. This list includes BG Medicine Inc.'s lead product, BGM Galectin-3, a blood test for clinical use in chronic heart failure. La Jolla Pharmaceuticals' lead drug, GSC100 (formerly known as GBC590), is a complex polysaccharide that binds to and block the effects of galectin-3. Additionally, Galectin Therapeutics' two lead drugs—GM-CT-01 for cancer immunotherapy and GM-MD-02 for fibrosis—are both based on carbohydrate chemistry.

Macrolides

The fifth and final subcategory of prescription carbohydrate drugs is represented by macrolides. The first, **Erythromycin**, is of microbial origin; it inhibits protein synthesis. The other three—**Dirithromycin**,

Clarithromycin and **Azithromycin** – are semi-synthetic macrolide antibiotics derived from Erythromycin.

Rational design: challenges and solutions

Years of effort have been required to understand the unique challenges (Table-4) that are inherently linked to carbohydrate derived drugs and to develop the

basic skills and the specific knowledge to move from the excitement of scientific discovery to the development of a new class of therapeutics. Although animal lectins usually show a high degree of specificity for glycan structures, their single site binding affinities are typically low. In biological systems, functional affinity is often attained by the oligovalent presentation of CRDs, either in an oligomeric protein (e.g., cholera toxin) or through clustering at cell surfaces (e.g., asialoglycoprotein receptor). Additionally, the pharmacokinetic properties of carbohydrates, such as bioavailability or plasma half life, are typically unsatisfactory. Finally, although tremendously improved novel glycosylation protocols and solid phase approaches have become available, oligosaccharides are still only manufactured by cumbersome multistep syntheses. Therefore, the challenge is to mimic the structural information of a functional carbohydrate with a compound that has drug-like characteristics. The first step in this process is to understand the structure-activity relationships of a carbohydrate lead, specifically the contribution made by each functional group to binding as well as the three dimensional presentation of the pharmacophores. Based on this information, it is possible to identify glycomimetics that are preorganized in their bioactive conformation, i.e., which will adopt their bound conformation in solution. In addition, the mimics should show improved pharmacokinetic properties while minimizing toxicity and cost of synthesis. In the past, the development of carbohydrate derived drugs was often not entirely focused on simultaneously solving all of the above requirements and some high profile failures resulted, notably in the field of selectin

antagonists. Nevertheless, rationally designed glycomimetics have the potential to gather the rewards of a relatively untapped source of novel therapeutics for wide ranging and important biological and medical applications.

Heparin and LMW heparins are heterogeneous mixtures. This complicates their application as drugs in a number of ways. Firstly, their must be controlled in order to obtain reproducible mixtures corresponding to those desired for the drug products. Secondly, analytical and quality control issues, while solvable, are more complicated than for homogenous products. Thirdly, biological evaluation of mixtures is more complicated than for a single entity. Fourthly, regulatory questions for drug mixtures can be formidable, making the drug approval process more difficult. Finally, a patent position is more difficult to establish for a mixture in which composition of matter is difficult to define. The new enzymatic approaches and solid-phase synthesis in carbohydrate synthesis might one day make complex synthetic carbohydrate based drugs economically viable. Indeed, the synthetic ATIII pentasaccharide is now clinically used as a highly specific anticoagulant agent in Europe.¹⁰

Conclusions and Future Perspectives

Glycans have potential therapeutic benefit as drugs themselves or as drug targets. Understanding the molecular details of protein-glycan interaction will provide the key to therapeutic targeting of this molecular encounter. Breakthroughs in this field may lead to the development of better drugs and effective vaccines.

Table 1: General Biological Functions of Carbohydrates

▪ Cell adhesion
▪ Cell activation
▪ Cell differentiation
▪ Fertilization
▪ Embryonic development
▪ Neural development
▪ Modulation of inflammation and immunity
▪ Modulation of cancer and metastasis

Table:2 Categories of Carbohydrate-based drugs	
>	Monosaccharide conjugates
>	Disaccharides and disaccharide conjugates
>	Trisaccharides
>	Oligosaccharides and polysaccharides
>	Macrolides

Table:3 Functions of Heparin	
▪	Anti-coagulant/anti-thrombotic
▪	Lipolysis
▪	Anti-inflammatory
▪	Angiogenesis regulation
▪	Immunomodulation
▪	Modulation of tumor growth

Table:4 Pitfalls in Carbohydrate-based Therapeutic Drug Development	
•	Target affinity
•	Protein binding
•	Half life and bioavailability
•	Solid phase synthesis
•	Analytical, pharmacokinetic, regulatory and patent issues of mixtures

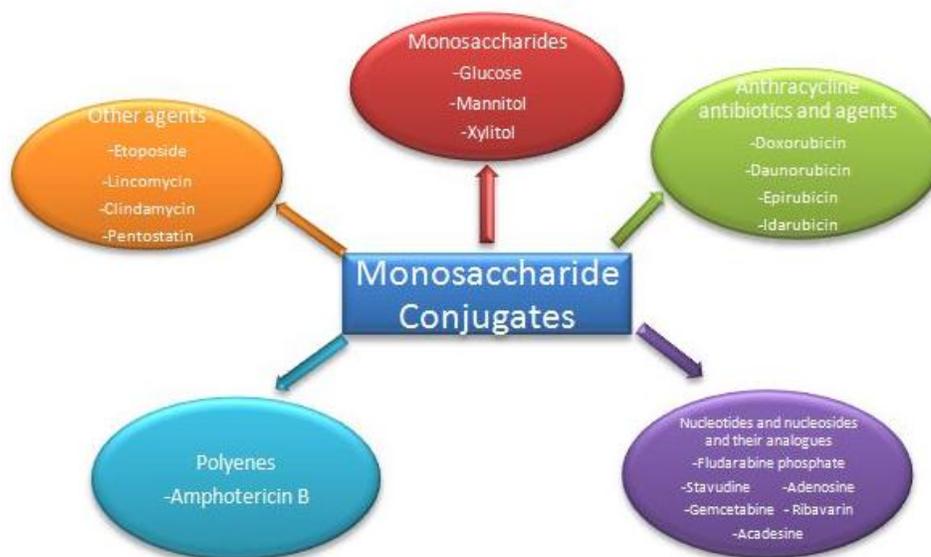


Fig 1
Monosaccharide Conjugate

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