

Minireview

## The discovery, biology, and drug development of sialyl Le<sup>a</sup> and sialyl Le<sup>x</sup>

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Dedicated to the memory of Dr. Victor Ginsburg, a great mentor, pioneer, and creative force in science

### Abstract

The discoveries of sialylated, fucosylated lacto-, and neolacto-type carbohydrate structures were accomplished with the aid of analytical methods and monoclonal antibodies such as the immunostaining of thin layer chromatograms. Based on the use of such antibodies, these structures, notably sialyl Le<sup>a</sup> and sialyl Le<sup>x</sup>, were demonstrated to be highly expressed in many malignant cancers. A diagnostic assay using one of these antibodies (CA19-9) is now established as one of the more commonly used assays for pancreatic and gastrointestinal cancers worldwide. Upon further study, several laboratories have demonstrated that the level of expression of these carbohydrate tumor markers is also positively correlated with patient survival and is a prognostic indicator of metastatic disease. Concurrent with this finding, both sialyl Le<sup>a</sup> and sialyl Le<sup>x</sup> were shown to bind to a family of carbohydrate-binding proteins involved in the extravasation of cells from the bloodstream, called the selectins. Thus, sialyl Le<sup>a</sup> and sialyl Le<sup>x</sup> expressed on cell surfaces play functional roles in medical conditions that require extravasation of cells from the bloodstream which include a wide range of inflammatory diseases and cancer metastasis. Many studies have confirmed the function of sialyl Le<sup>a</sup> and sialyl Le<sup>x</sup> in animal models of these diseases and the inhibition of binding of sialyl Le<sup>a</sup> and sialyl Le<sup>x</sup> to the selectins is a validated drug target in the pharmaceutical industry. Thus, a new class of drugs, arising from the field of glycobiology, is based on the rational design of small molecule drugs that mimic the structures sialyl Le<sup>a</sup> and sialyl Le<sup>x</sup> and can potentially inhibit their functional binding to the selectins. © 2004 Published by Elsevier Inc.

### Background: the discoveries of sialyl Le<sup>a</sup> and sialyl Le<sup>x</sup>

#### *Sialyl Le<sup>a</sup>*

The advent of monoclonal antibodies made it possible to clearly and reproducibly identify specific molecules in biological samples. Koprowski et al. [1] used this technology to identify antigens present on a wide variety of adenocarcinomas, but absent in comparable normal tissues. A serum diagnostic assay was developed using one of these antibodies [2].

Dr. Ginsburg's laboratory at NIH had been pioneering highly sensitive methods to detect carbohydrate structures based on binding to protein receptors [3,4].

By immunostaining thin layer chromatograms of lipid extracts of colorectal carcinoma cell lines (SW1116) with antibody CA19-9, the tumor associated antigen was defined to be a monosialoganglioside [5]. Purification and structural characterization of this ganglioside by GC/mass spectroscopy resulted in the first description of the sialyl Le<sup>a</sup> epitope [6]. Further analysis of the molecular species carrying the sialyl Le<sup>a</sup> epitope detected by the CA19-9 diagnostic assay revealed the unusual discovery at that time, that the majority of sialyl Le<sup>a</sup> in cancer patient's sera resided in large molecular weight mucin-like molecules [7].

#### *Sialyl Le<sup>x</sup>*

Sialyl Le<sup>x</sup> is technically a misnomer, as this structure (IV3NeuAcIII3FucnLc4, sialylated lacto-*N*-fucopentaose III) is unrelated to the Lewis blood group antigens.

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The name is derived from  $\text{Le}^x$ , which was originally known as the X-structure [8], but is now regarded by the field as  $\text{Le}^x$ , since it is a positional isomer of the Lewis blood group structure,  $\text{Le}^a$  [9].

Sialyl  $\text{Le}^x$  was first described in ganglioside fraction of human kidney [10] and trace amounts were found in human milk [11]. Hakomori's laboratory developed a monoclonal antibody (FH6) to an extended Sialyl  $\text{Le}^x$  ganglioside that was found to accumulate in human colonic adenocarcinomas but was absent from normal colonic mucosa [12]. Sialyl  $\text{Le}^x$  was also indicated as a tumor-associated antigen by characterization using the monoclonal antibody CSLEX [13]. Shortly thereafter, Fukuda et al. [14] reported on the presence of the sialyl  $\text{Le}^x$  epitope in large lactosaminoglycans purified from human neutrophilic granulocytes.

The structures of the sialyl  $\text{Le}^a$  and sialyl  $\text{Le}^x$  epitopes are shown in Fig. 1. While they are positional isomers, antibodies to sialyl  $\text{Le}^a$  were generally unreactive with sialyl  $\text{Le}^x$  and vice versa.

### Sialyl $\text{Le}^a$ and Sialyl $\text{Le}^x$ are tumor markers

The structure of sialyl  $\text{Le}^a$  was originally discovered as a tumor marker defined by a monoclonal antibody [6]. Numerous reports over the years [15–31] have described high expression of the sialyl  $\text{Le}^a$  carbohydrate epitope in association with neoplastic transformation and cancer. In fact, sialyl  $\text{Le}^a$  has been demonstrated to be a prognostic indicator of metastatic disease, which will be addressed in more detail in a later section.

The CA19-9 antibody which binds sialyl  $\text{Le}^a$  detects the presence of this antigen in the sera of patients with gastrointestinal and pancreatic cancers. The sialyl  $\text{Le}^a$  antigen in sera is mainly expressed on large mucin-like molecules [7] that contain a high content by weight of carbohydrate and many sialyl  $\text{Le}^a$  epitopes per molecule. These large multivalent mucin-like molecules are optimally suited for detection by standard sandwich-type immunoassay techniques. A serum-based cancer diagnostic assay was commercialized using the CA19-9 antibody. This product is now one of the top cancer

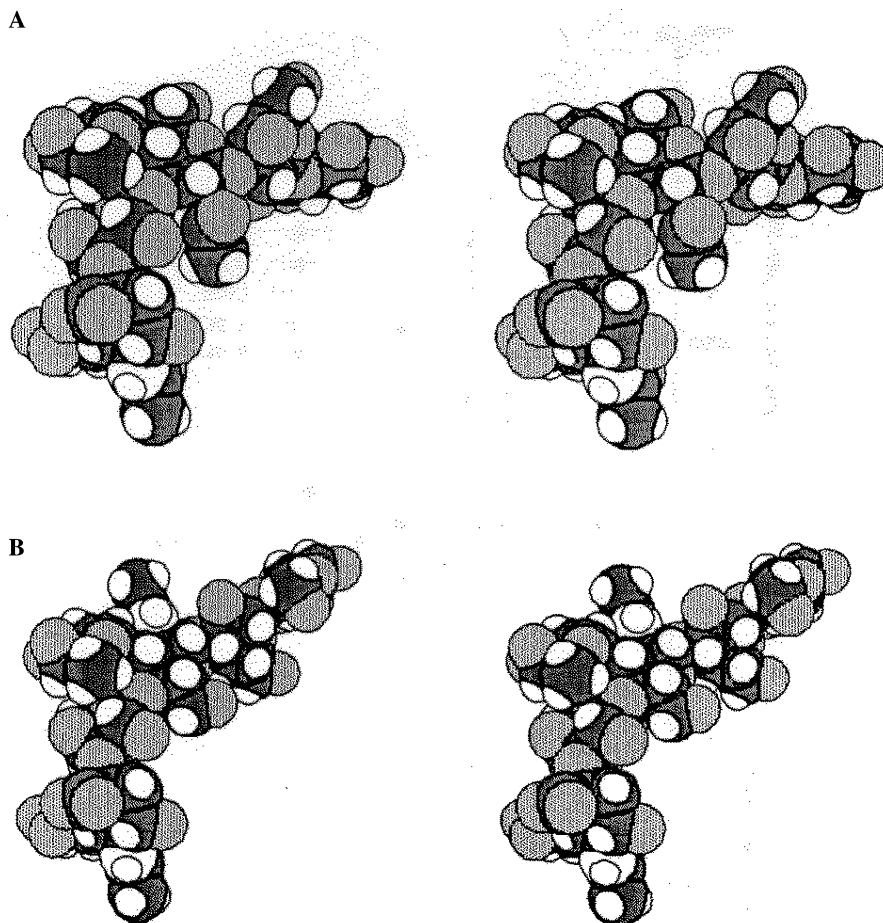


Fig. 1. Stereo pairs of sialyl  $\text{Le}^a$  (A) and sialyl  $\text{Le}^x$  (B). The lower portion of the molecule is the sialic acid (non-reducing end) and the fucose juts out from the plane of the image. The molecules share a common trisaccharide domain, but the molecule twists at the GlcNAc towards the reducing end.

diagnostic assays for detecting gastrointestinal and pancreatic cancers worldwide with approval for use in Japan, Europe, and more recently granted FDA-approval for use in the US.

In general, most antibodies that bind sialyl Le<sup>a</sup> will not bind its positional isomer, sialyl Le<sup>x</sup>. One exception is the antibody HECA-452, which will be addressed later. Many monoclonal antibodies selected for strongly binding to cancer cells recognize sialylated and/or fucosylated polylactosamine structures [32–35] such as Le<sup>x</sup> and sialyl Le<sup>x</sup>. These carbohydrate structures were also found to be surface markers for the myeloid cell lineage in normal blood [36] with high expression on granulocytes and neutrophils [12,37,38]. Since these reports, many laboratories have described the association of sialyl Le<sup>x</sup> expression with neoplastic transformation and cancer in humans [22,39–44]. Given the expression of sialyl Le<sup>x</sup>, care must be taken in such studies to identify sialyl Le<sup>x</sup> expression directly on cancer cells and not from infiltrating inflammatory cells such as neutrophils at the tumor site.

### Biosynthesis of sialyl Le<sup>a</sup> and sialyl Le<sup>x</sup>

As stated earlier, sialyl Le<sup>a</sup> is related to the Lewis blood group system, while sialyl Le<sup>x</sup> is not. This car-

bohydrate was originally described as the X-hapten and was later designated Le<sup>x</sup> due to its structure being a positional isomer of the Lewis antigen, Le<sup>a</sup> (Fig. 1).

The biosynthesis of sialyl Le<sup>a</sup> was elucidated in Zopf's laboratory at NIH [45] and is shown in Fig. 2. As sialyl Le<sup>a</sup> is related to the Lewis blood group antigens, its expression depends on the Lewis status. Individuals who are Lewis negative (Le<sup>a-b-</sup>) lack the Lewis fucosyltransferase (FT3), and are unable to synthesize and express sialyl Le<sup>a</sup>. Individuals who are strong Lewis b secretors will fucosylate the precursor structure Gal $\beta$ 1-4GlcNAc thereby producing lower levels of sialyl Le<sup>a</sup> than found in Le<sup>a</sup> non-secretors. These genetic differences in the ability to express sialyl Le<sup>a</sup> must be considered when evaluating the use of the CA19-9 diagnostic assay as a screen in the general population [46,47]. Likewise, we originally hypothesized that these genetic differences may, in fact, impact the occurrence of pancreatic cancer in different blood type populations [48], which was recently supported and will be described in a later section.

The biosynthesis of sialyl Le<sup>x</sup> and extended sialyl Le<sup>x</sup> structures that bind the antibody FH6 was originally reported by Holmes et al. [49] to be similar to sialyl Le<sup>a</sup> synthesis in that sialylation must precede fucosylation of internal GlcNAc residues. More recently, Grabenhurst

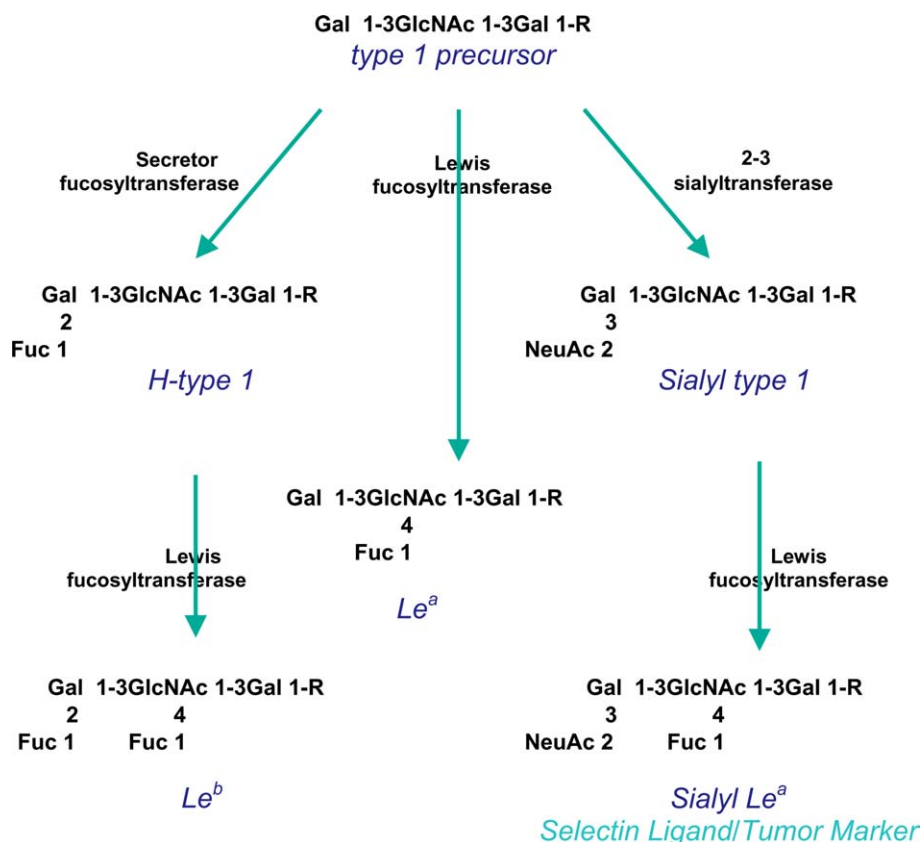


Fig. 2. Biosynthesis of sialyl Le<sup>a</sup>. The expression of sialyl Le<sup>a</sup> is influenced by the Lewis blood type of the individual. Lewis negative individuals (non-secretors, 5–10%) are incapable of synthesizing sialyl Le<sup>a</sup>, whereas, strong secretors (Le<sup>b</sup>) produce lower levels of sialyl Le<sup>a</sup> due to competition of the secretor fucosyltransferase with the  $\alpha$ 2–3 sialyltransferase for the type 1 precursor substrate.

et al. [50] carefully examined the ability of five different human fucosyltransferases (FT3 to FT7) to synthesize sialyl Le<sup>x</sup>. While a wider variety of fucosyltransferases fucosylate type 2 chain structures, these core structures must first be sialylated to result in sialyl Le<sup>x</sup> in the same order as sialyl Le<sup>a</sup> is synthesized. Sialyltransferase, ST3Gal-III, is required for sialylation of type 1 chains to produce sialyl Le<sup>a</sup> whereas ST3Gal-IV and VI can sialylate type 2 chains to produce sialyl Le<sup>x</sup> structures.

### Sialyl Le<sup>a</sup> and sialyl Le<sup>x</sup> function as receptors for the selectins

To optimize the detection of pathogens, lymphocytes constantly circulate and traverse through the vasculature system to the lymphatic compartment by binding and migrating through specialized endothelial cells in the high endothelial venules (HEV)<sup>1</sup>. A landmark paper by Gesner and Ginsburg [51] hypothesized the function of cell surface carbohydrates as recognition molecules during the normal trafficking of lymphocytes. Decades later, the binding of lymphocytes to HEV was shown to be dependent on the presence of sialic acid and calcium. Within a short period of time, three different calcium-dependent, carbohydrate-binding proteins called E-, P-, and L-selectins were identified as being responsible for the normal trafficking of lymphocytes and the extravasation of leukocytes during an inflammatory response. There is much homology among the three different selectins. Each contains a C-type lectin domain, an EGF-like domain, and similar complementary consensus repeat domains. L-selectin is expressed constitutively on neutrophils, monocytes, and lymphocyte subsets, whereas E-selectin and P-selectin are transiently expressed on endothelial cells upon activation and P-selectin is expressed on thrombin-activated platelets.

Sialyl Le<sup>x</sup> was first shown to bind directly to E-selectin [52,53]. Contrary to experience with most antibodies, E-selectin was also shown to bind Sialyl Le<sup>a</sup> [54,55]. At the same time, an unusual blocking antibody, HECA 452, also bound to both sialyl Le<sup>a</sup> and sialyl Le<sup>x</sup> [54]. Comparison of both structures in three dimensions revealed a common trisaccharide domain that is the minimal binding epitope for E-selectin [54]. L-selectin [56] and P-selectin [57] also bind both sialyl Le<sup>a</sup> and sialyl Le<sup>x</sup>, however, specificity is achieved with secondary binding sites. For optimal binding, P-selectin requires binding to an additional sulfated peptide sequence in its native glycoprotein receptor, PSGL-1 [58,59]. L-selectin also binds similarly to both sites in PSGL-1, however, binding to HEV during normal lymphocyte trafficking has

been reported to require sulfation directly on the sixth position of GlcNAc in 6-sulfo-sialyl Le<sup>x</sup> [60,61].

### Applications for inflammatory disease and cancer metastasis

Selectins are responsible for the initial recognition and adhesion of leukocytes to the vascular endothelium in the earliest events of the inflammatory cascade. P-selectin rapidly translocates to the surface of endothelial cells from stored Weibel–Palade bodies upon activation by a variety of factors, and E-selectin is expressed by de novo protein synthesis 2–3 h after endothelial cell activation. During the inflammatory response, the cellular events of recognition, rolling, adhesion, and extravasation of leukocytes occur in a strictly sequential order. Selectins are required for the earliest recognition and rolling event and therefore represent an excellent therapeutic target to treat inflammatory diseases.

Numerous animal studies have successfully demonstrated and validated the use of selectin inhibitors for the treatment of inflammation in applications such as asthma [62,63], arthritis [64], psoriasis [65], ischemia/reperfusion [66–74], transplantation [75,76], and vascular remodeling [77].

Sialyl Le<sup>a</sup> was originally discovered as a tumor marker on gastrointestinal and pancreatic cancers [6]. Although sialyl Le<sup>x</sup> is present on leukocytes such as neutrophils and monocytes, this carbohydrate is also highly expressed on a variety of adenocarcinomas [22,39–44].

It is now clearly established that these carbohydrates are markers of metastatic disease, since they function in the extravasation of cancer cells from the bloodstream and promote metastatic spread to other tissue sites [78]. Human colon cancer cell lines display metastatic potential directly related to expression of sialyl Le<sup>x</sup> and binding to E-selectin [79]. Colorectal cancer, *in situ*, has an invasive front stained by anti-sialyl Le<sup>x</sup> antibody when the tumor becomes metastatic to the liver [80]. Likewise, expression of sialyl Le<sup>x</sup> on bladder carcinomas correlated with invasion and metastasis [81]. In mouse models, L- and P-selectin interactions with tumor cells also facilitate extravasation and metastasis [82]. Many clinical studies show a clear association of expression of sialyl Le<sup>a</sup> and sialyl Le<sup>x</sup> on tumors with enhanced progression and metastasis. Cancers arising from specific tissue locations preferentially express type 1 or type 2 core structures. Sialyl Le<sup>a</sup> is a prognostic indicator of metastatic disease in pancreatic cancer [83,84], melanoma [85], urothelial cancer [86], and colorectal cancer [87,88], whereas sialyl Le<sup>x</sup> is a better prognostic indicator for gastric cancer patients [89].

<sup>1</sup> Abbreviations used: HEV, high endothelial venules; HSEA, hard-sphere exoanomer.

A particularly impressive long-term study was published by Matsumoto et al. [90]. The survival of colorectal cancer patients was directly related to expression of sialyl Le<sup>a</sup> and sialyl Le<sup>x</sup> on their tumors. Over a 10-year period, 80% of colorectal cancer patients whose tumor expressed high levels of sialyl Le<sup>a</sup> died, whereas 90% of these patients survived if their tumors lacked expression of sialyl Le<sup>a</sup>. It is presumed that these tumor surface carbohydrate markers enhance extravasation and metastasis by interaction with E-selectin expressed on endothelium. Cimetidine, which was shown to inhibit E-selectin expression, had a dramatic effect on survival. Patients expressing high amounts of sialyl Le<sup>a</sup> on their tumors went from 20.1% survival to over 90% survival over a 10-year period if expression of E-selectin was inhibited by treatment with cimetidine. These recent results support our original hypothesis that the expression of Lewis blood type affects the incidence of gastrointestinal cancer [48] and points to a specific new form of therapy for metastasis and tumor progression by directly inhibiting the interactions of sialyl Le<sup>a</sup> and sialyl Le<sup>x</sup> with the selectins.

#### Development of glycomimetic drugs based on the bioactive conformation of sialyl Le<sup>a</sup> and sialyl Le<sup>x</sup>

Sialyl Le<sup>a</sup> and sialyl Le<sup>x</sup> function in early recognition and binding events of cell extravasation from the bloodstream. Compelling results with inhibitors in animal models validate these structures as targets for drug development in the pharmaceutical industry. Unfortunately, native carbohydrates lack many desired properties of small molecule drugs. They are prone to enzymatic degradation and display short half-lives in the bloodstream. In general, affinity is low and the physiological interaction favors the avidity of native multivalent targets. Their hydrophilic, polar nature also works against desired oral availability. However, by determining the bioactive conformation of the native carbohydrate in its binding site, the structure–activity relationships may be used to develop glycomimetic drugs that possess the correct properties for drug development.

The original discovery that both sialyl Le<sup>a</sup> and sialyl Le<sup>x</sup> bind to E- [54] and L-selectins [56] led to a comparison of the three-dimensional structure and determined by hard-sphere exoanomeric (HSEA) calculations [54]. In this early study, three monosaccharide residues, sialic acid, galactose, and fucose in sialyl Le<sup>a</sup> and sialyl Le<sup>x</sup>, were shown to be located in a similar three-dimensional arrangement. The *N*-acetylglucosamine twists out of alignment and did not appear to be required for binding. Using transfer NOE/NMR techniques, Thomas Peters and co-workers [91,92] demonstrated the exact three-dimensional conformation of sialyl Le<sup>x</sup> in the

binding site of E-selectin. A prominent feature of this conformation is the stacking of the galactose and fucose residues and the position of the carboxyl groups in the sialic acid (Fig. 3). This bioactive conformation was docked into the crystal structure of E-selectin to determine possible molecular interactions. Supporting earlier work, both fucose and galactose closely interact with the lectin binding domain and the position of the carboxyl group on sialic acid was required for binding E-selectin. The *N*-acetylglucosamine extends out of the binding site and does not directly interact with E-selectin (Fig. 4).

Several different glycomimetics were quickly developed that replaced *N*-acetylglucosamine with more hydrophobic aromatic groups and the sialic acid was replaced with cyclohexyl and acidic side chains that maintain the carboxyl group in the correct orientation (Fig. 5). Further modification of aromatic groups that replaced *N*-acetylglucosamine revealed that a bulky group on C-5 of the ring mimic (glucal) forced a preformed stacking of the galactose and fucose as determined by NOE/NMR [93]. Using a series of such mimics, Thoma et al. [94] demonstrated that

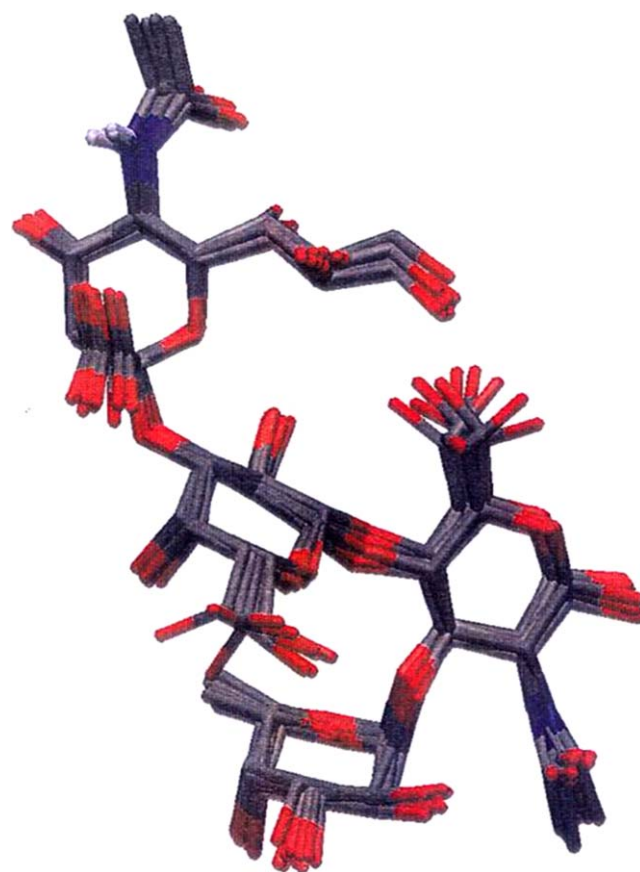


Fig. 3. Bioactive conformation of sialyl Le<sup>x</sup> in the binding site of E-selectin was determined by transfer NOE/NMR [91,92]. Stacking of the fucose below the galactose is crucial for activity. The position of the carboxyl group of the sialic acid perpendicular to the plane of the image is also required for tight binding.

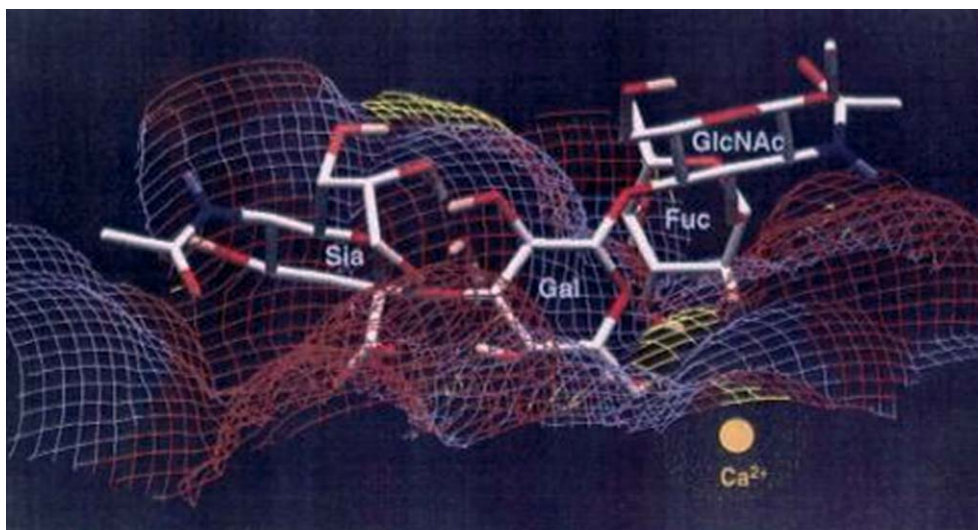


Fig. 4. The bioactive conformation of sialyl Le<sup>x</sup> is docked into the lectin domain on the surface of E-selectin. Clearly, the stacked fucose and galactose residues strongly interact with the E-selectin surface as does the carboxyl group of the sialic acid. The GlcNAc and reducing end project out of the binding site and show little interaction.

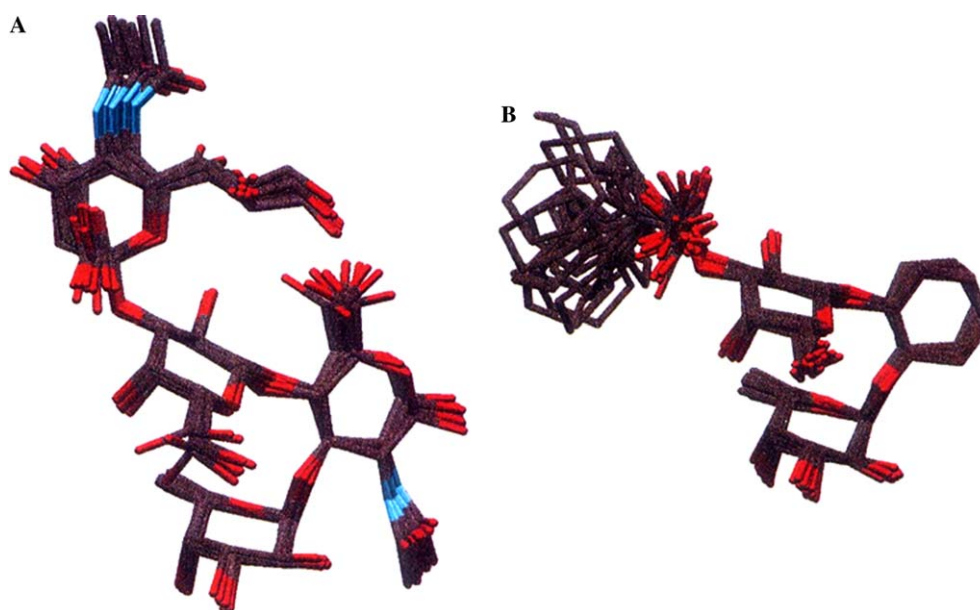


Fig. 5. The bioactive conformation for a glycomimetic (B) that binds E-selectin is compared with the bioactive conformation of sialyl Le<sup>x</sup> (A). The glycomimetic retains the stacking of fucose under the galactose residue and retains the position of the carboxyl group that mimics the sialic acid [93].

preformation of this stacking, which is the bioactive conformation, greatly enhanced binding to E-selectin. Variations on this structure lead to the synthesis of mimics containing other hydrophobic groups on this carbohydrate scaffold. Interestingly, substitution of the C-2 position of galactose with a benzyl group resulted in the most potent glycomimetic inhibitor to E-selectin currently described [95,96]. Smaller in size and far more hydrophobic, this glycomimetic inhibits E-selectin about 1000-fold more potently than sialyl Le<sup>x</sup> in an E-selectin-mediated cell adhesion assay (Fig. 6).

The binding specificity for E-selectin differs from those of P- and L-selectins. Several groups have reported a second binding site adjacent to the lectin domain on P- and L-selectins that react with sulfate groups on the peptide backbone of the native receptor, PSGL-1 [58,59,97]. In contrast, E-selectin lacks this sulfate binding domain. As a result, many highly charged molecules have been reported to strongly inhibit P- and L-selectins but show no or weak activity for E-selectin. Examples of such highly charged structurally diverse inhibitors for P- and L-selectins are: sulfatides,

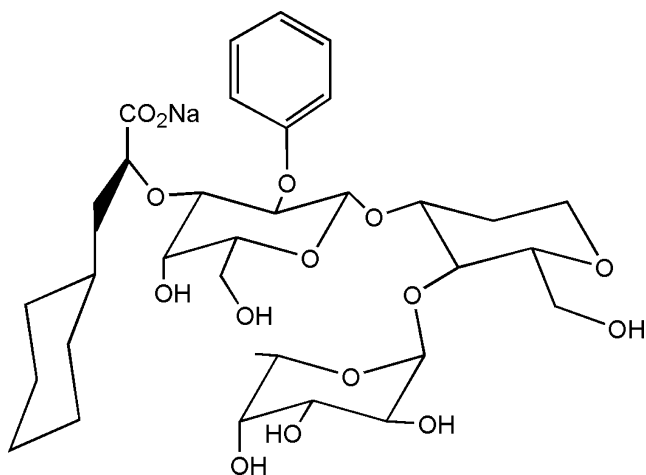


Fig. 6. A glycomimetic that exhibits one of the most potent inhibitory activities for E-selectin contains a hydroxyl on the glucal that preforms the stacking of fucose under the galactose [93]. The benzyl group on the galactose interacts with a hydrophobic domain on E-selectin, greatly improving binding activity to about 1000-fold higher than sialyl Le<sup>x</sup> [95].

fuciodan, heparin, dextran sulfate, heparin sulfates, and polyvinylsulfate. In fact, Kretschmar [98] reported that trace contaminants in compounds obtained by chromatography on acidic ion exchangers drastically affect their potency of inhibition in P- and L-selectin assays. Obviously, these highly charged ionic interactions are not specific for P- and L-selectins but are the basis of binding a wide range of proteins for chromatographic separation. In fact, one of the pitfalls of relying solely on *in vitro* assays for P- and L-selectins is the lack of specificity of inhibition by negatively charged molecules.

Rather than developing glycomimetics based on the rational design of the bioactive conformation of the native ligand, several other groups have produced libraries of compounds by combinatorial chemistry techniques. Wong and co-workers [99] have developed solid phase techniques to produce a library of fucopeptides for *in vitro* screening. Kaila et al. [100,101] produced focused libraries based on  $\beta$ -C mannose structure shown in Fig. 7. Modifications at the C-1 and

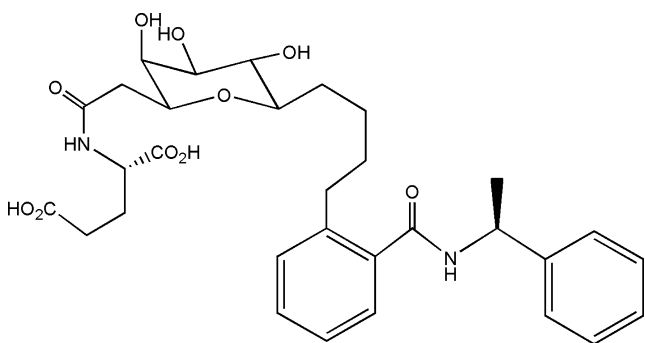


Fig. 7. Example of a glycomimetic for P-selectin obtained from  $\beta$ -C-mannoside library screening.

C-6 positions on the mannose ring led to a series of inhibitors with modest activity for P-selectin ( $IC_{50}$  = 2.5 mM) and negligible activity for E-selectin ( $IC_{50}$  = 5 mM). Some of the most extensive studies were conducted by a group led by Kondo. They published a series of papers [102,103] using dipeptides as scaffolds and developed a mimic containing a mannoside on a heterocycle backbone (Fig. 8). While this molecule displayed potent activity for P- and L-selectins (2.57 and 2.34  $\mu$ M, respectively), it was inactive for E-selectin [104]. Kondo's group also screened databases of compounds based on the 3D pharmacore model of 3' sulfated Le<sup>x</sup> bound to E-selectin. A series of glycomimetics devoid of carbohydrates were developed with good activities for E- and P-selectins.

Using high throughput screening of an ELISA-based P-selectin assay, Slee et al. [105] discovered an imidazole-based lead compound devoid of carbohydrate (Fig. 9).

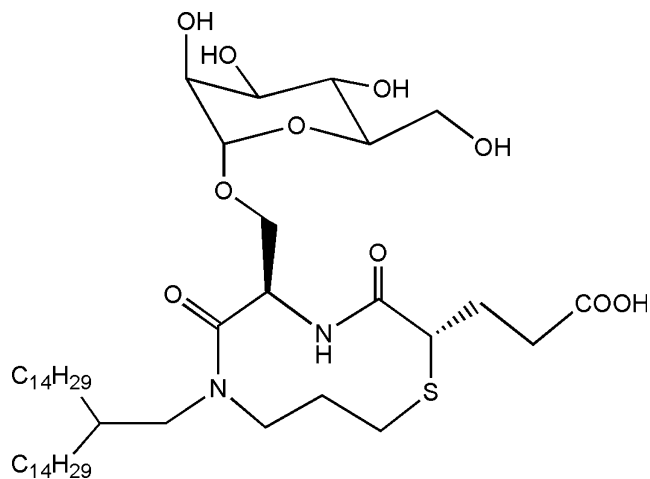


Fig. 8. Example of a P-selectin inhibitor obtained by screening dipeptide libraries.

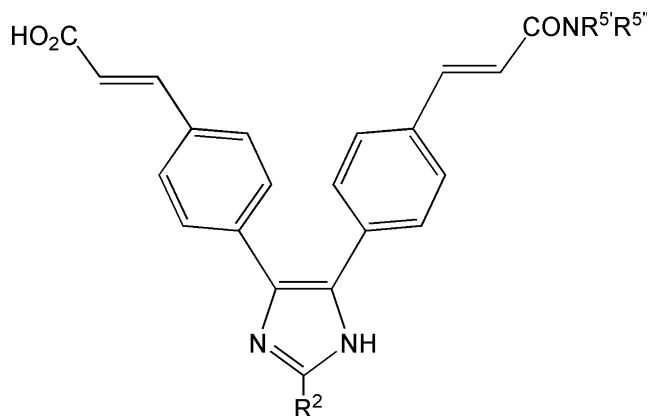


Fig. 9. Non-carbohydrate imidazole-based selectin inhibitors obtained by high throughput screening an ELISA-based P-selectin assay. Certain variants on this backbone also bind E-selectin.

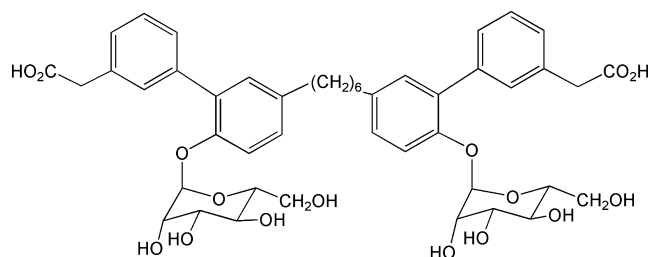


Fig. 10. A dimeric mimic that inhibits E-, P-, and L-selectins (TBC 1269). This glycomimetic is built on a rigid biphenyl core, is being tested in phase II clinical trials for asthma, and is recently entering clinical trials for psoriasis.

Molecular modeling of the human P-selectin domain based on the available crystal structure of human E-selectin allowed for the generation of complexes with inhibitors based on a Monte Carlo docking protocol. These complexes were energy minimized using the Discover program and a molecular model of these binding interactions was proposed. Variations on the lead compound for P-selectin generated several inhibitors that also bound E-selectin and were active in selectin-mediated cell adhesion assays.

Another backbone devoid of carbohydrate is the biphenyl group explored by Kogan et al. [106]. To mimic the fucose of sialyl Le<sup>x</sup>, the biphenyl group was coupled to mannose, while a carboxyl group replaced the sialic acid. This simple molecule weakly bound to E- and P-selectins, however, activity was increased by dimerizing the molecule [107]. The current inhibitor, TBC 1269 (Fig. 10) was successful in animal models of asthma, and acute ischemic renal failure [108,109] but failed to reduce myocardial injury post-cardiopulmonary bypass surgery, or to reduce edema or microvascular permeability in a second bypass study [110,111]. It also failed to attenuate early or late asthmatic responses in asthmatic patients when given in a single dose prior to challenge [112]. TBC 1269 has been advanced to human clinical trials and is currently in phase II studies for the therapy of asthma [113].

As stated earlier, although sialyl Le<sup>a</sup> and sialyl Le<sup>x</sup> bind all three selectins, there are slight differences required for potent inhibition. P- and L-selectins also bind to sulfated tyrosine residues adjacent to the lectin domain on the native glycoprotein ligand, PSGL-1, whereas E-selectin does not. A glycosulfopeptide containing these elements from PSGL-1 has been reported to strongly inhibit P- and L-selectins [60,114]. Likewise, a larger more potent native ligand for E-selectin has been described by Hakomori et al. [115] as a fucosylated, sialylpolylactosamine structure called myeloglobulin. Thus, secondary binding interactions adjacent to the precise lectin domain add specificity and activity to these molecular interactions. The next generation of glycomimetics may incorporate these features for in-

creased potency and specificity required for therapeutic effects.

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