Galectins as New Therapeutic Targets for Galactose-Containing Polysaccharides

Anatole A. Klyosov

ABSTRACT. The Galectin protein family includes 15 members that are characterized by galactose binding domains and are widely expressed in diverse cell types. Galectins are found in multiple intracellular compartments and are secreted into the extracellular space. There has been an explosion in information on these fascinating proteins in pathological states, particularly inflammation, fibrosis, and cancer. This Review summarizes attempts to cover the key areas of galectin-dependent disease and discusses the approaches to developing galectin blockers for treatment. The time is right for major efforts to advance galectin-based therapies into multiple human diseases. © 2014 Bull. Georg. Natl. Acad. Sci.

Key words: galectins, inflammation, carcinoma, angiogenesis, immunology, tumor, fibrosis, atherosclerosis, asthma, arthritis.

The term “galectins” was coined only 20 years ago [1], and for the preceding 15 years (Fig. 1) scientists had been reporting on what they called “galactose-binding proteins”. Over the last decade there has been a near exponential increase in the yearly publication rate of research papers on galectins (Fig. 1). By April 11, 2014, the number of publications on galectins reached 4493.

The number of publications and the important findings for biology and disease has led to a general recognition that galectins are an important class of molecules for multiple pathological processes and potential targets for therapy.

Galectins as a group are characterized by a galactose-specific carbohydrate binding domain which interacts with galactose moieties located on glycoproteins. Nature has created as many as 15 different galectins, known today, which have already been identified, isolated, and in some cases characterized – structurally and functionally [2]. In addition to cellular glycoproteins, all galectins show an affinity for galactose residues attached to other organic compounds, such as in lactose [(β-D-Galactosidol)-D-glucose], N-acetyl-lactosamine, poly-N-acetyllactosamine, galactomannans, fragments of pectins, as well as others. Galactose by itself does not bind to galectins, or binds so weakly that the binding can hardly be detected. Galectins also have domains which promote homodimerization. Thus, they are capable of acting as a “molecular glue” of
sorts between glycoproteins. Galectins are found in multiple cellular compartments, including the nucleus and cytoplasm, and are secreted into the extracellular space where they interact with cell surface and extracellular matrix glycoproteins [3]. The mechanism of molecular interactions depends on the localization. While galectins interact with glycoproteins in the extracellular space, in the intracellular space the interactions with other proteins occur via protein domains [4]. In the extracellular space the association of cell surface receptors may increase or decrease receptor signaling or the ability to interact with ligands. Additionally, galectins may promote cell-cell and cell-matrix interactions. Because of the critical importance of the interaction of glycoproteins and cells for tissue function, it is no wonder that galectins have been ascribed a plethora of functions in cellular and animal models.

The collective literature shows that galectins are instrumental to many crucial biological and pathobiological functions, such as inflammation, angiogenesis (blood supply, including that to cancer tumor cells), immune response (they were shown to turn off the “friend or foe” immune recognition system), cancer cell migration (leading to metastasis), and many others.

With respect to targeting galectins for therapy of disease, we believe that the understanding of biology and pathology associated with galectins is coming of age. In several disease areas there is sufficient evidence to suggest that targeting galectins may have an efficacious effect on disease processes. One of the primary reasons for this is that galectins are normally expressed in relatively low levels but are markedly increased in disease states such as cancer, inflammation and fibrosis.
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Therefore, a strategy to knock down expression or function may be effective while not interfering with normal basal function. If the past decade can be described as the decade of galectin function discovery, the coming decade may be the decade of the realization of galectin targeting therapeutics, and here is a number of reasons for that:

- Galectin targeting therapeutics is in the very early stages and there is as yet no convincing evidence of efficacy in a human disease. The pharmaceutical industry likes proven targets and once there is evidence of an effect in human disease, activity will increase.

- Galectins, as with many other lectins, present a challenge to researchers in terms of quantitative description of ligand-receptor interactions, which is density-dependent when glycan epitopes are located on the surface of cells. In other words, a quantitative description for galectin-cell interactions should include the density and number of glycan epitopes on the surface of cells, as well as the dissociation constant ($K_d$) that is not a single, well-defined (at least in theory) value as with respect to monovalent glycans in solution, but a relative $K_{d(ef)}$ value that includes density and number of epitopes on the cell surface [5].

- A number of the current galectin targeting approaches utilize complex carbohydrate drugs which are not common in the industry [6].

**Galectins in human diseases**

The majority of the 4493 papers on galectins are academic studies that investigate various aspects of galectin structure and function without a focus on a particular disease. Very few address pharmacological approaches to galectin targeting therapies. In order to analyze the published papers with respect to human diseases and pathologies, we have considered the most recent two thousand articles, from April 2014 back through August 2009, and broke them into categories according to diseases and pathologies. In more than one-third of those articles certain diseases and pathologies have been mentioned (Table 1).

(Diseases from number 79 through 137 have been found to be described in one paper each). The many diseases that have been linked to galectins underlie the pleotropic function of these proteins. There are a number of groupings that fall out of examining this list, with cancer, inflammation, fibrosis, and immune function being prominent.

A first in kind genome-wide association study of circulating galectin-3 has recently been performed [7] in 3776 subjects (of European descent), and among 2,269,099 autosomal SNPs two loci were identified: one locus harbors LGALS3 gene encoding galectin-3, which is quite understandable, and the other locus harbors the AB0 gene associated with inflammatory markers, and various blood measured traits and diseases, including cancer, inflammatory diseases, and cardiovascular diseases. This might explain why galectin-3 plays a role in inflammation, cancer, fibrosis, and proliferation, and why it is increasingly recognized as a potential biomarker of high clinical value.

**Galectins in Cancer**

It is clear from the literature that galectin proteins are increased in expression in the majority of cancers and they serve a variety of functions in cancer cell biology ([8-12] and references therein). When considering functions in cancer, a critical issue is whether the functional locations of the galectin proteins are intracellular or extracellular. This has important implications related to fundamental function, but also the ability to target galectin function with therapeutic agents. Intracellular functions in cancer related to apoptosis and signaling have been described ([13] and references therein). The Fig. 2 below shows the major areas in cancer biology, where galectins may function in the extracellular environment.

The importance of galectins for tumor cell invasion and metastasis has been reviewed extensively ([14-16] and references therein). Additionally, it has been well documented that galectin proteins, in particular galectin 1 and galectin 3, are markedly increased in expression in cancer cells and contribute
<table>
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<tr>
<td>Thyroid carcinoma</td>
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<td>Heart failure/myocardial dysfunction/injury</td>
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<td>Colorectal/gastric cancer/adenoma</td>
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<td>Rheumatoid arthritis/osteoarthritis</td>
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<td>Oral/laryngeal squamous cell carcinoma</td>
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<td>Prostate cancer/adenocarcinoma</td>
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<td>Cancer, carcinoma (non-specified)</td>
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<td>Diabetes</td>
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<td>Glioma-associated cancer/glioblastoma</td>
<td>13</td>
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<td>Preeclampsia</td>
<td>12</td>
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<td>Asthma/lung inflammation</td>
<td>12</td>
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<td>Renal carcinoma</td>
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<td>Ovarian cancer</td>
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<td>Hepatocellular carcinoma</td>
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<td>Follicular thyroid adenomas/carcinomas</td>
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<td>Pituitary tumors/adenocarcinoma/blastoma</td>
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<td>Spinal cord injury</td>
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<td>Lung cancer/non-small cell lung cancer</td>
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<td>Bladder cancer</td>
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<td>Liver fibrosis</td>
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<td>Ischemia (non-specified)</td>
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<td>HIV-1</td>
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<td>Human cervical (epithelial) adenocarcinoma</td>
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<td>Myelogenous leukemia</td>
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<td>Ophthalmology</td>
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<td>Lung diseases/pneumonia</td>
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<td>Nasopharyngeal carcinoma</td>
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<td>NASH</td>
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<td>Lymphoid malignancies/lymphomas</td>
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<td>Multiple sclerosis</td>
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<td>Renal fibrosis</td>
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<td>Malignant mesothelioma</td>
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<td>Lupus erythematosus</td>
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<td>Neuroblastoma</td>
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<td>Hepatitis</td>
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<td>Hodgkin lymphoma</td>
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<td>Myeloma, multiple myeloma</td>
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<tr>
<td>Brain cancer</td>
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<tr>
<td>Cholangiocarcinoma</td>
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<tr>
<td>Hypoxic-ischemic brain injury</td>
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<tr>
<td>Ulcer/ulcerative colitis</td>
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<tr>
<td>Amyotrophic lateral sclerosis</td>
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<td>Parathyroid carcinoma</td>
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<tr>
<td>Tongue carcinoma</td>
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<tr>
<td>Sercial squamous cell carcinoma</td>
<td>3</td>
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<td>Large cell lymphoma</td>
<td>3</td>
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<tr>
<td>Head and neck cancer</td>
<td>2</td>
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<tr>
<td>T-cell leukemia/lymphoma</td>
<td>2</td>
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<td>Venous thrombosis</td>
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<td>Cancer vaccines</td>
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<td>Malaria</td>
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Table 1. The number of publications according to PubMed in which a specific disease was identified and galectins were mentioned in association with the disease (in the order of that number). Some diseases might be combined under more general names.
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to the pathogenesis of tumor progression ([8-16] and references therein).

A recent book [17] contains a number of chapters, which review and extend our knowledge on how galectins function in cancer. Several chapters review the role of galectins in melanoma, glioma, breast cancer, leukemia, and myeloma, and approaches for using galectin targeting for prevention of cancer metastases. Analysis of these cancers highlight the variety of functions of galectins in cancers.

Tumor angiogenesis

Tumor growth depends on a continuous blood supply to deliver oxygen, nutrients, and other biologically important factors to the tumor. The growth of new capillaries from preexisting blood vessels which is called neovascularization or angiogenesis, is a complex process involving endothelial cell activation, disruption of vascular basement membranes, proliferation of endothelial cells and their migration. This multistep cellular process, the molecular machinery, leading to growth of new vessels into the tumor, hence, tumor angiogenesis is dependent on a number of galectins, among them galectin-1, -2, -3, -4, -8, which presumably play important roles in mediating cell-cell and cell-matrix interactions. The role of galectins in tumor angiogenesis and the potential of targeting galectins for therapy was recently reviewed [18].

Fig. 2. The major areas in cancer biology, where galectins may function in the extracellular environment.
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Tumor Immunology

A growing literature shows that the recognition and killing of tumor cells by the cellular immune system is modulated by galectins. In a seminal paper for the field, Pierre Van der Bruggen and his colleagues have shown that galectin-3 has a critical effect on tumor specific CD8+ cells [19]. They showed that in the presence of galectin-3, cytotoxic T cells lose the colocalization of the T-cell receptor and CD8, which results in relative anergy of the T cells when confronted with tumor antigen. The function of CD8+ cells and the TCR-CD8 colocalization was restored, when galectin ligands were added. This has led to the hypothesis that tumor secreted galectin-3 binds to cytotoxic T cells and renders them anergic, unable to kill tumor cells. A summary of this “galectin effect” as described by the van der Bruggen group is illustrated in the Fig. 3 below and reviewed in [20].

Galectin-1 has also been shown to be important in modulating cellular immunity to tumor cells. In an elegant set of experiments using knockout mice and syngeneic tumors with variable galectin-1 expression, it was shown that tumor associated expression of galectin-1 was involved in mediating tumor progression through intratumoral immunomodulation [21]. It is possible that other galectins are involved in modulating the cellular immune response to tumors and it appears that inhibition of galectins may be an approach to enhance tumor killing by cytotoxic T cells.

Galectins in inflammation, immune cell function, and fibrosis

The process of inflammation and repair involves multiple cell types including cells of the immune system and many inflammatory mediators in a complex and interconnected cascade of events. Acute inflammation can be terminated or progress to a chronic phase which may lead to fibrosis. The enormous complexity of this process cannot be summarized in this review, but we evaluate some of the data related to the components of inflammation, immune cell function, and fibrosis. It should be stated up front that separating these three only facilitates discussion because the processes in tissues are all intertwined.

Inflammation

Acute inflammation is a critical defense mechanism against invading pathogens and tissue damage.
When inflammation becomes chronic, systemically or locally, multiple pathologies ensue with negative consequences. Most of the information on galectins involvement in inflammation results from studies of chronic inflammatory models. However, as discussed in [22], galectins also play a role in acute inflammation, particularly galectin-1, 3, and 9.

Multiple studies show that galectins are important in regulating chronic inflammatory responses; however, the current data do not provide a clear picture. Some galectins appear to suppress responses of inflammatory cells, while some galectins stimulate and promote them. It seems that the specific effect of a galectin depends on the targeted cell, its microenvironment (such as a pattern of the specific glycosylation of target cells), and the inflammatory stimulus. It has been suggested that differing results may be related to the fact that studies are performed in vitro which employ recombinant galectins, typically lacking certain portions of the protein [23]. Where more relevant studies were conducted, for instance, with galectin-3-null mice, it was found that galectin-3 promotes inflammatory responses [24]. Much of the confusion in the field is likely related to the relevancy of in vitro models and non-physiological proteins and concentrations. A recent review [25] considers relevant data in intact animal models of multiple inflammatory diseases. This analysis begins to unwind the stories of galectin involvement in chronic inflammatory disorders.

Wound healing is the critical end process of the inflammatory cascade. The role of galectins in wound healing was recently reviewed [26].

**Immune cells**

While immune cells are critically involved in the inflammatory process, it is useful to look directly at the effects of galectins on individual effector and regulatory cells of the immune system. The function of galectins with respect to immune cells is complex and, at times appears contradictory. It appears that the function varies depending on the source and stage of immune activation. Some galectins can disable T cells by inducing apoptosis. For example, galectin-1 induces apoptosis in activated human T cells, apparently through the binding to T cell surface glycoproteins, such as CD7, CD43, and CD45. This mechanism may be concentration dependent and has not been observed by all investigators.

Publications [27,28] present intriguing approaches to modulating T cells. The first describes the role of a cross-linking GM1 ganglioside in the suppression of autoimmune disorders, the second one describes the use of fluorinated glucosamine analogs to enhance the activity of anti-tumor T cells.

**Fibrosis**

Chronic inflammation in organs often leads to an accumulation of fibrotic tissue. In fact, the end result of inflammation from multiple underlying etiologies is fibrosis and resultant organ dysfunction. This is evident in lung, heart, kidney, pancreas, and liver. Multiple lines of evidence point to galectin proteins, and galectin-3 in particular, as critical in the pathogenesis of organ fibrosis. The best evidence in this regard comes from experiments in knockout mice. Galectin-3 null mice are resistant to fibrosis of the liver in response to hepatotoxins, lung fibrosis in response to intrathecal bleomycin, kidney and heart fibrosis, and chronic pancreatitis [29]. This important area of pathology is reviewed in [30]. In addition, a novel mechanism for the activation of stellate cells in the liver, the primary fibrogenic cell in the liver, is discussed in [31].

An important liver disease that results in fibrosis is non-alcoholic steatohepatitis (NASH). Fatty liver and NASH with liver fibrosis, which was invariably detected in galectin-3 (+/+ ) mice on a high fat diet, was much less pronounced and was found in only 38% of these galectin-3 null mice [32]. Taken together, these data suggest that galectin-3 is an attractive therapeutic target for liver fibrosis that occurs as a result of multiple liver diseases as well as fibrotic conditions in multiple organs. A first experi-
mental demonstration of regression of liver fibrosis and reversal of cirrhosis following treatment with galectin inhibitors was reported [33].

A US Patents were granted in 2012 and 2014 [34,35] regarding inhibition or slowing down the progression of liver fibrosis or cirrhosis or reduction of established liver fibrosis or cirrhosis based on evidence comprising reduction of the level of biochemical markers of liver fibrosis as a result of administering of a galacto-rhamnogalacturan compound from an apple pectin.

Cardiovascular disease

Atherosclerosis is an inflammatory lipid accumulation in arterial vessels which is the cause of a huge burden of morbidity and mortality world wide [36]. Reviews [37-39] consider the roles of galectins in atherosclerosis, representing a potentially new approach to this disease.

Heart failure is generally defined as a failure of the heart to supply sufficient blood volume to meet the requirements of the body. Heart failure is the result of myocardial injury or hemodynamic overload, which goes beyond mechanical dysfunction; heart failure is associated with a number of pathophysiologic mechanisms, including inflammation, tissue remodeling, endocrine signaling, and interactions with the renal and nervous systems; it is the result of interplay of a number of biochemical factors, collectively referred to as biomarkers [40,41].

A series of studies [36, 42-54] have convincingly shown an importance of galectin-3 in heart failure and mortality. Study [38] reviews data that shows galectin-3 is important in heart fibrosis and failure and may be an important target for therapy.

Asthma

Asthma is a chronic disease characterized by airway inflammation, airway hyperresponsiveness, reversible airway obstruction, predominance of Th2 cells and eosinophilic inflammation. A number of studies point at an important role of galectins in these outcomes and mechanisms leading to them. Review [30] describes some data in galectin-3 knockout mice on the role of this galectin in allergic disease and airway inflammation.

Ge et al. [55] investigated a murine model of chronic allergic airway inflammation aiming at the role played by galectin-3 in airway remodeling, a characteristic feature of asthma that leads to airway dysfunction and poor clinical outcome in humans. They found that the higher degree of airway remodeling in wild-type mice was associated with higher Gal-3 expression. Furthermore, using galectin-3-null mice they found diminished remodeling of the airways with significantly reduced mucus secretion, subepithelial fibrosis, smooth muscle thickness, and peribronchial angiogenesis. The authors concluded that Gal-3 promotes airway remodeling via airway recruitment of inflammatory cells, specifically eosinophils, and the development of a Th2 phenotype, as well as increased expression of eosinophil-specific chemokines and profibrogenic and angiogenic mediators [55].

Arthritis

Arthritis is an inflammatory disease of one or more joints in the body. Rheumatoid arthritis (RA), a common autoimmune form of arthritis, is a chronic, systemic inflammatory disorder that may affect many tissues and organs, and destroys cartilages or bones at the joints. RA is initiated by self-attack using own immune system, but the detail of pathological mechanism is unclear. Galectins appear to be involved in the pathogenesis of RA and autoimmune disorders [56], particularly galectin-3 and galectin-9.

Other diseases

Because of the ubiquitous nature of inflammatory processes in disease, it is not surprising that galectins have been implicated as potentially important in a diverse number of disorders. Here we provide information on a number of other diseases that have been evaluated.

Galectin-3 has been evaluated in Behçet’s disease (BD), a rare immune-mediated systemic vasculitis, often manifested by mucous membrane ulceration.
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In a 2-year study [57], 131 subjects, 39 of which were BD active, 31 inactive, 22 disease controls with leucocytoclastic vasculitis confirmed with a skin biopsy, and 39 healthy control subjects were evaluated. It was found that serum galectin-3 levels were significantly higher in active BD patients compared to inactive BD patients and healthy control subjects. Serum galectin-3 levels were positively correlated with clinical activity scores of active BD patients. In addition, galectin-3 levels were significantly higher during the active disease period when compared with the inactive period during follow-ups. It was also reported that patients with vascular involvement had significantly higher galectin-3 levels than other active BD patients [57].

Galectins have been evaluated in multiple sclerosis lesions [58]. Among 11 different galectins tested, those which were present at detectable levels in control white matter were galectins-1, -3, -8 and -9, and their expression was significantly enhanced in active multiple sclerosis lesions. Galectin-9 showed a distinctly different intracellular localization in microglia/macrophages when comparing active and inactive MS lesions. In active lesions, it was mainly found in nuclei, while in inactive lesions, it was primarily located in the cytoplasm. The authors concluded that some galectins are associated with multiple sclerosis pathology.

In a series of papers [59-62], St-Pierre, Sato et al. have suggested a role for galectin-1 as a host factor that influences HIV-1 pathogenesis by increasing its drug resistance. In brief, galectin-1 increases HIV-1 infectivity by accelerating its binding to susceptible cells. By comparison, it seems that galectin-1 directly binds to HIV-1 through recognition of clusters of N-linked glycans on the viral envelope gp120, by binding to CD4, the host receptor for gp120. In turn, it results in promoting of virus attachment and infection events, since viral adhesion is a rate-limiting step for HIV-1 entry. The authors have tested some glycosides, such as mercaptododecyl glycosides with a terminal β-galactosyl group, and for some derivatives found “high binding responses” with galectin-3, -4, and 8. This opens possibilities in developing new drugs to prevent and treat HIV-1 infection.

Galectin-3 was suggested as a biomarker for amyotrophic lateral sclerosis (ALS), a neurodegenerative disease [63], after studying the appropriate mouse model and then validating the finding in human tissues. 14 of 1299 proteins evaluated were found to be dramatically altered in the ALS mice compared with the two control groups. Galectin-3 emerged as a lead biomarker candidate on the basis of its differential expression. Spinal cord tissue from ALS patients also exhibited 2-fold increased levels of galectin-3 when compared to controls.

**Galectin targeting agents and approaches**

Clearly, one of the obvious approaches to galectin therapy would be to design galectin blockers that specifically inhibit galectins, and examine those inhibitors against certain pathologies, first, of course, in experimental animal models. This, however, is not so easy. First of all, “classical” ligands of galectins are rather weak binders, and are not really applicable as drugs. For example, lactose (4-O-β-D-Galactopyranosyl-D-glucose) binds to galectin-3 with $K_d$ between 0.2 and 1 mM, to galectin-4 with $K_d$ of 0.9-2.0 mM, and quite poorly binds to galectin-7, -10, -13 ([23] and references therein). N-acetyllactosamine binds better, however, still not good enough to become a drug: 50 µM with galectin-1, 30-200 µM with galectin-3, 1-2 mM with galectin-4 (ibid).

A number of approaches have been taken to developing molecules that target galectin proteins for therapeutic purposes. These include small organic molecules that target primarily the carbohydrate binding domain [64,65], peptidomimetics that target other areas on the protein, and natural plant derived complex carbohydrates that have exposed galactose residues. There are two primary groups of plant-derived compounds that have been explored, pectin-based compounds exemplified by modified citrus
pectin, and 1,4-β-D-galactomannan-based compounds exemplified by GM-CT-01 (DAVANAT®) [6]. While there are other potential approaches, these are the primary ones that have been reported and are in various stages of development.

**Small galectin ligands molecules as potential galectin blockers**

A group of researchers at Lund University, Sweden, has synthesized small organic compounds, derivatives of galactose, and tested them with respect to binding to the carbohydrate binding domain of different galectins ([65-67] and references therein). Inhibitors of galectin-3 were the most potent, with $K_d$ values as low as 29 nM (3,3’-ditriazolyl thiodigalactoside), 50 nM (3,3’-diamido thiodigalactoside), 320 nM (3’-amido lacNAC derivative), and 660 nM (3’-triazolyl lacNac derivative). Their strategy so far has been less successful for inhibiting galectin-1, since apparent $K_d$ values indicated rather weak binding, varying from 40 µM (digalactosyl sulfone) and 313 µM (C-galactoside derivative) to 1.25 mM (3-O-triazolylmethyl galactose derivative). Inhibitors of galectin-4, -7, and -9 were also relatively weak, with $K_d$ values as high as 160 µM (2,3-dibenzoyl taloside, galectin-4), and 23 µM; 140 µM (3’-thiourea lacNac and phenyl thio-galactoside derivatives, respectively, galectin-7), and 540 µM (3’-triazolyl mannoside, galectin-9).

The galectin-3 inhibitors are promising therapeutic agents, but little is known about critical drug characteristics such as in vivo potency, absorption, metabolism, pharmacokinetics, and toxicology. While they have been shown to be active in certain disease models, more work is needed on the mechanism of action and to determine if they are active in a therapeutically acceptable delivery and dosing model. For example, the thiodigalactoside diester galectin-3 inhibitor ($K_d = 660$ nM; named Td131_1), when tested against papillary thyroid cancer (PTC) cell lines and human ex vivo PTC, actually increased the percentage of apoptotic cells in a dose-dependent manner (with 100-600 µM of the inhibitor, that is in the 150-1000 higher concentrations compared with the $K_d$ value). However, this treatment was found to be largely ineffective in terms of the chemosensitivity of PTC cell lines to doxorubicin, which is normally enhanced upon suppression of galectin-3. Administration of as much as 0.6 mM of the thiodigalactoside compound actually decreased the IC$_{50}$ of doxorubicin by 43-46%, or showed no detectable change in caspase-3 or PAEP cleavage [66].

**Summary comments on galectin inhibitors**

In general, more characterization of galectins employing various approaches would be helpful in sorting out the mechanisms of action. One should be cautioned to assume that all compounds that bind to galectins will act similarly in biological systems and in disease. For example, the small organic molecules are designed to target a single galectin molecule at the carbohydrate binding domain. In contrast, GM-CT-01 binds up to three galectin molecules per drug molecule and occupies a larger portion of the galectin molecule that includes the dimerization domain. These differences in binding characteristics could have important implications for function.

Another important, and largely unexplored issue, is what happens following binding of these agents to galectins. Is the effect simply a result of competitive inhibition, or are there changes in degradation, trafficking, or synthesis as a result of binding? Additionally, the downstream effects after binding of galectins are largely unknown for these agents.

**Conclusions and perspectives**

This overview and the cited papers reveal that there are multiple galectin dependent diseases that may be amenable to therapies targeted at galectins. It is now time for efforts to shift from academic descriptions and experiments into pharmaceutical development. As part of this effort, as stated above, the current set of therapeutic agents need to be characterized in rela-
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The diseases to target need to be carefully chosen based on the relevance to human disease. While there is some data in human cancer, careful thought needs to be given to the right cancers and approach to therapy, including combinations with existing therapy. We believe that the next decade will be an exciting and formative one that will see successes of galectin-targeted therapy in human disease. It may be the start of a new class of agents for a target that could have widespread use.

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