Clinical Trials and Applications of Galectin Antagonists

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(Received on March 16, 2018, accepted on March 30, 2018)

Key Words: glycomimetic, clinical trial, cancer, fibrosis, cardiovascular

Abstract
Galectins comprise a relatively large family of carbohydrate-binding proteins that recognize and bind to β-D-galactoside residues expressed on a variety of different molecules. Advances in the study of their biological activities demonstrate potential functions in cancer progression, inflammatory, immune, and fibrotic responses which have recently translated to target the galectins as novel therapeutic strategies to address unmet medical needs. This review will summarize the therapeutic applications of galectin antagonists to treat human diseases currently in clinical trials.

A. Introduction
The β-galactoside-binding lectins are widely expressed in many different species including primitive organisms such as the slime mold, Dictyostelium discoideum, described in 1975 as discoi- din (1). The search for the presence of similar β-galactoside-bind- ing proteins in vertebrates led to the discovery of “electrolectin” extracted from the electric eel (2) and galectins from mammalian tissues of calf heart (3) and chicken organs (4). Studies to charac- terize the binding epitopes of electrolectin led to the early discov- ery of thiodigalactoside (TDG) as a strong commercially available antagonist. TDG has since been used as a lead structure for the rational design of potent small molecule glycomimetic antagonists of the galectins now in clinical trials (5). Currently, 15 different ga- lectins have been described in mammals and 11 of them are found in humans. All of these galectins share a common sequence motif of about 130 amino acids known as the carbohydrate-recognition domain (CRD). While the binding motifs share similarities, slight differences of precise epitopes among the galectins have been identified and can be used to design antagonists with increased specificity for particular galectins in this family (6, 7).

The galectin family can be divided into 3 subgroups depending on their macromolecular structures as shown in Fig. 1. The first subgroup contains the prototypic galectins containing one CRD per monomer (galectin-1, 2, 5, 7, 10, 11, 13, 14 and 15) which can combine to form homodimers. The second subgroup is divalent with 2 CRD domains forming a tandem repeat with a covalent linker (galectin-4, 6, 8, 9 and 12). Galectin-3 comprises the last subgroup and is unique in that it is a multivalent macromolecule

![Galectin Family Diagram](image)

Fig. 1. Intramolecular interactions among the galectin family can promote multivalent lattice formation.
with CRD’s expressed in the C terminus that may be linked together by the N–terminal domain. Of these members, galectin-5, 6, 11 and 15 are not found in humans.

A common feature among these subgroups is the ability to form multivalent interactions with expressed galactoside ligands on cell surfaces. The biological activities of the galectins are consistent with the effects of multivalent interactions with target cells and may explain the molecular mechanisms of the galectins (Fig. 1). Some examples are the requirement of multivalent interactions to induce activation of pathways, such as the NFκB pathway in tumor cells inducing chemoresistance, the signaling interactions of galectin-9 and 3 with T-cell checkpoint inhibitors TIM-3 and LAG-3 to inhibit T-cell cytotoxicity for tumor cells (8, 9) and finally the multivalent lattice formation of galactosylated pro-collagen molecules to induce and promote fibrosis (10). Galectin antagonists such as highly potent univalent small molecule glycomimetics that can block the formation of galectin-mediated multivalent interactions would be expected to have an advantage on the biological impact on these disease-associated mechanisms.

B. Indications for Clinical Applications

B.1. Cancer

Aberrant glycosylation is one of the hallmarks of oncogenic transformation. The increased expression of galectins has also been reported in a wide variety of cancers such as colorectal (11), lung (12), breast (13), pancreatic (14), and liver (15) and hematological malignancies (16). The interactions of galectins with their carbohydrate ligands in cancer have been reported to promote these malignancies through mechanisms of inducing angiogenesis, metastasis, the apoptosis of immune cells, activation of chemoresistance pathways and immunosuppression of cytotoxic T-cells through checkpoint inhibition.

The production of new blood vessels in the tumor microenvironment, a process known as angiogenesis, is induced by the activation of the vascular endothelial growth factor receptor (VEGFR) by vascular endothelial growth factor (VEGF) and is known to promote tumor growth and metastasis (17). VEGF is a validated target for cancer therapy and the approved drug, Bevacizumab is an anti-VEGF antibody that blocks interactions with VEGFR. Interestingly, galectin-1 has been shown to bind carbohydrates expressed on VEGFR and can activate it and stimulate angiogenesis in the absence of VEGF (18).

Metastatic spread of cancer cells throughout the bloodstream to distal sites proceeds by binding to the vascular endothelium followed by extravasation and infiltration to target tissues. A common tumor-associated glycosylation alteration is the expression of a short galactose terminating carbohydrate known as the Thomsen-Friedenreich (TF) antigen. Galectin-3 binds the TF antigen and is found at the endothelial surface with highly metastatic TF expressing breast cancer cells, but not a TF negative variant breast cancer cell line (19). In addition, patients with metastatic disease express higher levels of circulating galectin-3 in comparison with patients with localized, primary tumors (20). Galectin-2, 4 and 8 are also elevated in colon and breast cancer patients and function to accumulate and bind cancer cells to the endothelium as a first step in the metastatic process (21).

Galectins also promote tumorigenesis by binding cancer cells and activating tumor survival pathways. Galectin-3 expression is greatly elevated in pancreatic tumor tissue and when bound to these cells will activate the AKT pathway thereby inducing a well-established chemoresistance in these cells (22). In KRAS-mutant cancers (lung and pancreatic), galectin-3 has been reported to bind integrin αvβ3 and promote KRAS-mediated activation of AKT and associated chemoresistance (23, 24).

Recent breakthroughs in cancer immunotherapy have relied on activation and promotion of the immune response to target and eradicate the patients’ tumor cells. One promising technique uses cytotoxic T-cells either acquired from the tumor (TILS), the bone marrow (MILS) or ex-vivo engineered CAR-T-cells. The success of these novel treatments is dependent on controlling the patient’s immunosuppressive responses to activated T-cells known as checkpoint inhibition. Several drugs have been successfully approved that target the immunosuppressive interaction between PD-1 and its ligand PDL-1. Galectin-3 and 9 however have also been shown to induce strong immunosuppression of activated T-cells. These checkpoints are the glycan-dependent binding interactions between galectin-9 and TIM-3 (23) and between galectin-3 and LAG-3 (24). Clearly there is an opportunity to design and develop galectin antagonists to block these checkpoint inhibitors and further promote the success of T-cell immunotherapy.

B.2. Cardiovascular Disease

Cardiovascular disease (CVD) is a silent killer and is a leading cause of death and disability worldwide. CVD progresses over time to cause cardiac remodeling associated with fibrosis and weakening of the cardiac tissues resulting in a condition known as heart failure (HF). After the diagnosis of HF, 60% of men and 45% of women will die within 5 years (25). Early diagnosis is critical for successful therapeutic intervention, but is currently lacking and is a recognized unmet goal. It is now well established that galectin-3 functions in promoting fibrosis and is elevated during cardiac remodeling. In a large clinical study of 3,353 participants over 8 years (26), the plasma level of galectin-3 was associated with the risk of incident HF with high statistical significance (p<0.0001). This observation is supported in several other studies. In the Aldo-
Galectin-3 was associated with worse outcome independent of treatment. Likewise, the results of the Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy (MADIT-CRT) clinical trial reported that elevated levels of galectin-3 were an independent predictor of adverse HF outcome (28). In another study (29) of 599 subjects presenting in the emergency room with acute dyspnea, the circulating levels of galectin-3 were significantly higher among those dying within 60 days ($p<0.001$). The Deventer-Alkmaar Heart Failure (DEAL-HF) clinical study reported galectin-3 levels in patients with chronic HF were an independent predictor of mortality (30). Using a multivariate model, the CARE-HF study showed the association of galectin-3 with elevated rates of death from HF. Even patients ($n=592$) with stable chronic heart failure, but with an ejection fraction of less than 35% (COACH study), galectin-3 was a prognostic marker of disease (31). Based on the consistent and reproducible association of Galectin-3 levels and the progression of CVD among many studies, the use of galectin-3 as a biomarker in the Emergency Department to guide clinical decisions for the treatment of incoming patients has been proposed (32). An automated commercial assay for galectin-3 to be used in a hospital setting has been developed by Abbott laboratories on their ARCHITECT system and has been approved for the diagnosis of chronic heart failure (33). Finally, as a biomarker, galectin-3 has been given a class II recommendation for the management of heart failure as stated in the ACCF/AHA guidelines (34).

While galectin-3 is acknowledged as a biomarker for cardiac fibrosis, pre-clinical studies have been advanced to determine whether it plays a functional role and can be considered a target for therapeutic intervention. Early studies using a homozygous transgenic rat model of hypertensive mediated heart failure (TGRm-Ren2-27 rats), identified galectin-3 as the most overexpressed gene associated with HF. Galectin-3 co-localized with activated myocardial macrophages, induced cardiac fibroblast proliferation, collagen production and injection of galectin-3 into the pericardial sac of wild type rats induced left ventricular dysfunction of the heart (35). In another pre-clinical study, cardiac remodeling was induced by treating mice for 28 days with either angiotensin II or transverse aortic constriction. Wild type mice developed fibrosis and left ventricle (LV) hypertrophy and dysfunction. Treatment of galectin-3 knock-out mice resulted in significantly less fibrosis and LV hypertrophy. Furthermore, treatment of mice undergoing transverse aortic constriction with the galectin-3 carbohydrate inhibitor, N-acetyllactosamine, attenuated cardiac remodeling suggesting a therapeutic benefit of targeting galectin-3 with small molecule antagonists (36).

### B-3. Fibrotic Diseases

Fibrosis is a debilitating process of tissue scarring and injury to organs that leads to irreversible functional decline and eventual failure. The biological features of this process are consistent with the functions of galectin-3 which include abnormal proliferation of fibroblasts and stellate cells, the excessive production of extracellular matrix proteins including collagen, and the stimulation of angiogenesis. The roles of galectin-3 in the progression of fibrotic disease in different organs have been studied in pre-clinical models as well as clinical specimens. Both galectin-1 and 3 stimulate the proliferation of hepatic stellate cells and are upregulated in their transformation to myofibroblasts. The small molecule glycomimetic antagonist of galectins-1 and 3, TDG, blocks these effects (37). Galectin-3 expression was upregulated and co-localized with fibrosis in human liver sections from patients with a variety of causes of liver fibrosis including, hepatitis B or C infection, primary biliary cirrhosis, alcohol induced, or copper or iron overload. In a rat model of injury-induced liver fibrosis (CCL4-treated) galectin-3 is strongly upregulated in fibrotic liver. Galectin-3 knockout mice ($Gal-3^{-/-}$) in this model show significantly lower levels of collagen, procollagen, smooth muscle actin and attenuated liver fibrosis. TGF-$\beta$ levels were similar in $Gal-3^{-/-}$ mice suggesting that galectin-3 is required for the effects of TGF-$\beta$ on activation of myofibroblasts and extracellular matrix production (38).

Idiopathic pulmonary fibrosis (IPF) results from damage to the epithelial lining within lung alveoli which stimulates the differentiation of these cells and fibroblasts into activated myoblasts secreting extracellular matrix proteins and promoting irreversible scarring. There is currently no effective treatment for IPF and the prognosis is usually poor. Patients with stable IPF express high levels of galectin-3 in their bronchoalveolar lavage fluid which rises during exacerbation and is not found in healthy lungs or in other lung diseases such a nonspecific pneumonitis (39). A classic IPF mouse model uses bleomycin to induce lung injury resulting in long term pulmonary fibrosis. When compared to control wild type mice, Gal-3$^{-/-}$ mice in this model have significantly reduced fibrosis as determined by reduced myofibroblast activation and collagen production. Treatment of wild type mice with the small molecule glycomimetic antagonist of galectin-3 known as TD-139, blocked $\beta$-catenin activation, collagen production and attenuated late-stage progression of lung fibrosis (39). Chronic Obstructive Pulmonary Disease (COPD) is a prevalent lung disorder that usually results from injury caused by cigarette smoking and effects an estimated 80 million people worldwide. There are no effective therapies and patients gradually lose lung function eventually leading to death. Serum levels of galectin-3 in COPD patients are significantly higher during periods of acute exacerbation and are correlated with...
the inflammation markers, hsCRP and pro-BNP (40). Using immunohistology of lung bronchial epithelium, increased galectin-3 expression and neutrophil accumulation were observed in the small airways of lungs from COPD patients compared to normal lungs (41).

As determined by studies using both pre-clinical models and clinical samples, the expression of galectin-3 is consistent with the presence of fibrotic disease in a wide variety of tissues and organs.

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<th>Proposed target</th>
<th>Origin</th>
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*Specificity and in vivo targeting currently undefined.
Through multivalent binding interactions with β-1,2-galactoside ligands, galectin-3 activates the process of fibrosis and therefore is a functional biomarker and presents a novel and promising target for a new class of therapeutic treatments to address unmet medical needs.

C. Galectin Antagonists

Many different strategies have been reported to target the galectins as antagonists in pre-clinical animal models. They include traditional small molecule drugs, antibodies and natural products. This report will focus on the antagonists currently being tested in human clinical trials.

C-1. Small Molecule Drugs

These drugs typically range in size from molecular weight 500 to 1,000 and are selected to bind and inhibit the galectin target. They are tradition drug-like compounds that are chemically synthesized and are highly characterized for purity, pharmacokinetics and toxicity. Strategies to discover these drugs range from large scale screening of galectin activity inhibition to rational design of a specific structure based on structure–activity relationships between the drug and its receptor on the galectin target. Glycomimetics are small molecule drugs that are rationally designed to bind the carbohydrate recognition domain (CRD) on the galectin target based on the bioactive conformation of the native carbohydrate ligand (42). TD139 is an example of a glycomimetic designed as a potent antagonist to galectin-3 (43) tested in a clinical trial for idiopathic pulmonary fibrosis (Table 1). One of the advantages of small molecule drugs is the potential to design a smaller structure with the proper characteristics (polar surface area, log D, H bond donors and acceptors) to be orally bioavailable. Small molecule drugs also benefit from controlled, reproducible, large scale synthesis resulting in highly characterized products and well-established properties of acceptable toxicity and pharmacokinetics. OTX008 is a small molecule drug that differs in being an allosteric inhibitor of galectin-1 (44). That is, it binds to different domain outside of the CRD on galectin-1 but is able to inhibit the CRD from binding this “other site” (allosteric). Allosteric inhibition, by nature, increases the risk of off-site activity from the target molecule.

C-2. Antibodies

Antibody drugs can be highly specific and maintain a long serum half-life, but are usually costly for commercial scale production. While mouse monoclonal antibodies to the galectins have been tested in pre-clinical animal models (i.e., anti-galectin-1-antibody, F8.67), no human or humanized anti-galectin antibodies are currently in clinical trials. Antibodies to TIM-3 which is a binding partner for galectin-9 (45) and a checkpoint inhibitor for T-cell mediated cancer immunotherapy are in clinical trials for the treatment of solid tumors (Table 1).

C-3. Natural Products

Natural products that have been reported to bind galectins are carbohydrate structures from various sources. More common oligosaccharides such as N-acetylactosamine usually lack potency and drug-like properties to advance into drug development. A glycoprotein (TFD100) purified from cod fish is reported to have unusually high affinity for galectin-3 (46). Most of the natural products now in clinical trials are pectins derived from several different plant sources. Pectins are large heterogeneous glycans ranging in molecular weights from 60,000 to 130,000. The natural products now being tested in the clinic are GCS-100 derived from citrus, GR-MD-02 from apples, DAVANT from guar gum and MCP which is a modified citrus pectin. These large glycans from plant pectins lack specificity for a particular galectin and their precise binding interactions are not well-characterized and activities are controversial (47).

D. Clinical Trials

Nine (9) programs targeting the galectins or their associated ligands have been registered on www.clinicaltrials.gov (see Table 1). While these trials span a variety of indications, the majority of clinical trials are focused on fibrotic diseases and cancer indications.

**GCS-100**

GCS-100 is a complex polysaccharide that was prepared from modified citrus pectin by La Jolla Pharmaceuticals. Following Phase I dose-escalation safety studies in patients with refractory solid tumors and chronic kidney disease, the company completed separate Phase II studies in patients with chronic kidney disease and chronic lymphocytic leukemia (CLL).

The results of the Phase II study in CLL were presented at the American Society of Clinical Oncology (ASCO). In this study, 25 patients with recurrent CLL were treated at a dose of 160 mg/m² of GCS-100 in a 5-day regimen, given every 21 days. In this exploratory trial, GCS-100 was well-tolerated with no cases of drug-related grade 3 or 4 hematological toxicity or other serious adverse events reported. Two patients discontinued treatment due to rash (Grade 3 erythematous, maculopapular rash was the dose-limiting toxicity (DLT) in Phase I), which resolved with cessation of treatment. As for efficacy, twelve (50%) patients had stable disease and six (25%) patients experienced a partial response, including 4 patients with >50% shrinkage of lymph node lesions.

The results of the Phase II study in chronic kidney disease were presented at the American Society of Nephrology’s Kidney Week Annual Meeting. In this trial, blinded subjects were ran-
domized 1:1:1 to receive placebo, 1.5 or 30 mg/m² GCS-100 IV weekly for 8 weeks, followed by a 5-week observational period. The 1.5 mg/m² dose was chosen based on prior clinical activity and the 30 mg/m² dose was chosen because it was the maximum tolerated dose (MTD) observed in Phase I. The primary endpoint in the trial was change in estimated glomerular filtration rate (eGFR) from baseline to week 8, comparing placebo to each dose group separately. A total of 121 patients were enrolled and 171 completed the study.

From a safety perspective, GCS-100 was well tolerated with no serious adverse events considered to be related to study drug. GCS-100, at a dose of 1.5 mg/m², resulted in a statistically significant ($p=0.045$) improvement in eGFR versus placebo after 8 weeks of dosing (see table below). Interestingly, GCS-100’s effect on eGFR was more pronounced ($p=0.029$) in the prospectively defined subset of patients with diabetic etiology. Unfortunately, the statistically significant result at the 1.5 mg/m² dose was confounded by a lack of consistent response in the 30 mg/m² group. The investigator attributed this lack of effect to potential off-target drug effects, as this dose is 1,400-fold in excess, on a molar basis, vs. known circulating galectin-3 levels.

Despite plans to continue testing GCS-100 in patients with chronic kidney disease and expand the evaluation in other cancer settings, La Jolla Pharmaceuticals announced that they were discontinuing development of GCS-100 in 2015 following discussion with the Food and Drug Administration (FDA) after the Agency pointed out that the company would need to demonstrate the relative contribution of each component of the complex compound before advancing into late-stage development. In light of the time, expense and uncertainty of being able to adequately characterize the complex compound to the FDA’s satisfaction, La Jolla decided to terminate the GCS-100 program. Whether the same FDA “combination product” requirement will be imposed on other modified citrus pectin-based compounds in development has yet to be determined.

DAVANAT (GM-CT-01)

DAVANAT is a polysaccharide, carbohydrate polymer, composed of mannose and galactose (galactomannan) extracted from Guar seeds that was developed by Galectin Therapeutics (previously known as Pro-Pharmaceuticals). A Phase I open-label trial was completed in cancer patients with advanced solid tumors (minimum of 12 weeks to live) that were not amenable to surgery, radiation, or chemotherapy. While the objectives of this study were to determine the safety and pharmacokinetics of DAVANAT (280 mg/m²) as a single agent, and when administered in combination with 5-fluorouracil (5-FU), efficacy was also assessed as per RECIST criteria. A total of 20 subjects were enrolled in the trial, all of whom had at least two previous chemotherapy treatments. DAVANAT in combination with 5-FU, (500 mg/m²), given four times monthly until disease progression or unacceptable toxicity. While combination treatment was well-tolerated, median progression free survival was 8.4 weeks and only one objective response was reported.

While a series of Phase II trials were planned in patients with cancer in the US and Europe, these trials were never initiated with status reported as “withdrawn/terminated” on www.clinicaltrials.gov.

GR-MD-02

GR-MD-02 is a polysaccharide derived through chemical processing and modification from pharmaceutical grade apple pectin. The investigational new drug (IND) application was filed in 2013 and following completion of Phase I studies, the company has focused its attention on the use of GR-MD-02 for the treatment of liver fibrosis, plaque psoriasis, and in cancer therapy in combination with immune-system modifying agents. Specifically, two Phase II trials were conducted in liver fibrosis associated with fatty liver disease (NASH)—the NASH CX trial in patients with cirrhosis and the NASH FX trial in patient with advanced fibrosis, but not cirrhosis.

The NASH FX trial was the first of the liver fibrosis studies to report top-line results. Specifically, this was an exploratory trial that enrolled 30 patients with advanced fibrosis (Brunt Stage 3 fibrosis within 12 months of randomization) and treated them for four months duration. Patients were randomized to either GR-MD-02 (8 mg/kg) or placebo given IV every other week for 16 weeks (total of 9 doses). While the investigational therapy was found to be safe and well-tolerated with no serious adverse events reported, the trial failed to show a statistically significant difference on the primary endpoint of fibrosis using LiverMultiScan (Perspectum Diagnostics) or show any difference on secondary endpoints of liver stiffness (MRE) or fibrosis (FibroScan).

The second Phase II study of GR-MD-02 in NASH (NASH CX Trial) enrolled a total of 161 patients who were randomized 1:1:1 to either 8 mg/kg or 2 mg/kg of GR-MD-02 or placebo every other week for 52 weeks, for a total of 26 doses. The primary endpoint for this well-powered study was change in hepatic venous pressure gradient (HVPG) and secondary endpoints included changes in FibroScan and $^{13}$C-methacetin breath test, an indicator of liver metabolism. Like the exploratory NASH FX trial, GR-MD-02 was found to be well tolerated with only two serious adverse events deemed to be possibly related to study drug (transient ischemic attack and worsening of hyponatremia) by the Principal Investigator. With regards to efficacy, the NASH CX trial failed.
to demonstrate a statistically significant difference on the primary endpoint at either dose level. As part of the data analysis, a statistically significant effect of GR-MD-02 on HPVG was observed in the subgroup of NASH cirrhosis patients without esophageal varices (81 patients or 50% of total study group). Unfortunately, this difference in HPVG was limited to the low dose of 2 mg/kg (no effect was observed with the 8 mg/kg dose on several of the same post-hoc analyses). Despite this ambiguous outcome and prior failed study in a similar population (NASH FX trial), the company has announced that it intends to pursue a Phase III trial in this subpopulation of NASH patients without esophageal varices and has recently filed an application with the FDA for Breakthrough Therapy Designation for this indication.

Initial results from an open-label, Phase II pilot study with GR-MD-02 (8 mg/kg given every other week for 13 infusions) in 5 patients with moderate to severe plaque psoriasis (biopsy proven psoriasis and active moderate to severe plaque psoriasis with a psoriasis area and severity index (PASI) of ≥12 and at least 10% of involved body surface area) reported an improvement in PASI of 51.9%. While an improvement in PASI ≥75% from baseline is the typical benchmark for continued development, the results are considered encouraging, albeit in a small, uncontrolled, open-label trial.

Investigator-initiated studies combining GR-MD-02 with Keytruda (Pembrolizumab; a programmed death receptor-1 [PD-1]-blocking antibody) and Yervoy (Ipilimumab; a human cytotoxic T-lymphocyte antigen 4 [CTLA-4]-blocking antibody) in patients with melanoma are being sponsored by the Providence Portland Medical Center. While enrollment in this open-label combination study with Keytruda is ongoing, encouraging early clinical data has been reported in the first two cohorts with 5 of 8 patients with advanced melanoma achieving an objective response (2 complete responses and 3 partial responses). Given the lack of control, it is too early to decipher whether these responses are due to incremental anti-tumor activity of GR-MD-02 over what would be expected with Keytruda-alone.

**TD139**

In contrast to plant-based complex compounds, Galecto Bio has taken a rational drug design approach and synthesized a highly potent, selective small-molecule antagonist of galectin-3 (TD139). Formulated as a dry-powder for inhalation, TD139 recently completed a phase I/II randomized, double blind, placebo controlled, clinical trial with results presented at the 2017 American Thoracic Society Annual Meeting. The initial part of this trial was a randomized, double-blind, placebo-controlled, single-ascending dose trial that evaluated the safety, tolerability, pharmacokinetics and pharmacodynamics of TD139 in 36 healthy men. Once a dose was selected, the second part of the study consisted of a randomized, double-blind, placebo-controlled, multiple dose expansion trial that evaluated the safety, tolerability, pharmacokinetics and pharmacodynamics of TD139 in 24 patients with idiopathic pulmonary fibrosis (IPF). For eligibility, patients had to have a forced vital capacity ≥45% predicted and a forced expiratory flow/forced vital capacity ratio ≥0.7. After consent, patients were randomly assigned in a blinded fashion to receive a single dose of TD139 or placebo once daily for 14 days in a 2 : 1 (TD139 to placebo) ratio.

Dosing of TD139 in both healthy volunteers and patients (dosing: 0.3 mg, 3 mg, and 10 mg once daily for 14 days) was well tolerated without causing serious side effects. By performing bronchoscopies before and after the treatment period, the investigators were not only able to confirm TD139 delivery to the target tissues, but they were also able to detect biomarker reductions in galectin-3 expression on bronchoalveolar lavage macrophages. As elevated galectin-3 concentrations are associated with interstitial lung abnormalities coupled with a restrictive pattern, including decreased lung volumes and altered gas exchange, these early results are considered quite promising. Based on these encouraging results, a phase Ib study is planned in patients with IPF to further investigate the effects of TD139 in this patient population.

**OTX008**

OTX008 is a calixarene-based compound and galectin-1 inhibitor given by subcutaneous administration. While a Phase I trial in patients with advanced solid tumors is currently listed as actively recruiting (last update provided in 2012), the overall status of the program remains unknown following the acquisition of OncoEthix by Merck in 2014.

**Anti-TIM-3 Monoclonal Antibodies**

Given its role in limiting the anti-tumor response of T-cells, there has been increasing attention focused on TIM-3, the ligand for galectin-9, as an emerging immunotherapy target. Currently, there are three (3) anti-TIM-3 monoclonal antibodies in early-stage development—TSR-022 (Tesarco Inc.); LY3321367 (Eli Lilly and Co.); and MBG453 (Novartis). Each of these programs are evaluating the safety and efficacy, either as monotherapy or in combination with anti-PD-1 antibodies, in patients with advanced solid tumors or hematologic malignancies. As there has not been any public disclosure of clinical data from these corporate-sponsored trials, the early results from these Phase I programs are greatly anticipated for clinical proof-of-concept and to further support the theory that blocking negative regulators of immune function will overcome resistance and enhance response rates.
E. Conclusions

Galectins are a family of carbohydrate-binding proteins that have evolved from primitive organisms to play a variety of biological roles in humans that in certain conditions can impact or promote disease. As shown in Fig. 1, all human galectins have the ability to form multivalent molecules which can interact with glycans on cell surfaces to activate pathways or to bind glycosylated molecules to form biologically active lattices. Examples include the activation of the NFκB pathway in tumor cells to promote survival and chemoresistance or the immunosuppression of T-cells by galectin-9 and 3 at checkpoints with TIM3 and LAG3 respectively. Galectin-1 can bind cell surface VEGFR and stimulate angiogenesis in the absence of VEGF or in the presence of VEGF inhibitors. Likewise, galectin-3 can bind and activate myofibroblasts to produce glycosylated procollagen and establish multivalent lattices thereby promoting fibrosis. In fact, galectin-3 is now recognized as a functional biomarker in the ACCF/AHA guidelines for the treatment of heart failure. These biological functions translate into opportunities to target the galectins for therapeutic intervention for a variety of cancers and fibrotic diseases. Strategies range from the design of potent synthetic small molecule antagonists (i.e., glycomimetics) to natural products. Recent heightened interest from pharmaceutical and biotechnology companies have resulted in the initiation of many new clinical trials (Table 1) to test these novel therapies. Some of these strategies will be more successful than others and as the galectins become validated pharmaceutical targets, opportunities for translational research for other carbohydrate binding proteins in the field of Glycobiology (i.e., siglecs, selectins, etc.) will advance and be recognized as a relatively untapped source of novel therapeutics for unmet medical needs.

References

Armand Girard holds an M.B.A. from St. Joseph’s University Haub School of Business, and a B.A. from Lehigh University. In his current role as GlycoMimetics’ Vice President, Corporate Development, he is responsible for corporate strategy and partnering activities to create, capture and maximize the value of the company’s proprietary programs. Prior to joining GlycoMimetics in 2014, he held the position of Vice President, Technical Assessment at Shire Pharmaceuticals, where he was involved in the acquisition of Transkaryotic Therapies and Ferrokin Biosciences as well as strategic partnerships with Sangamo Biosciences, Santaris Pharmaceuticals and Noven Pharmaceuticals. Armand has more than 20 years of pharma experience at companies such as Shire Pharmaceuticals, Straken Life Sciences, Pro-Virus, Inc. and Otsuka Pharmaceuticals.

John L. Magnani received his Ph.D. from Princeton University and then joined the Laboratory of Biological Pharmacology headed by Dr. Victor Ginsburg at the National Institutes of Health. He remained at the NIH for ten years, finally serving in a tenured position as a Research Chemist. Dr. Magnani left the NIH in 1988 and helped co-found the U.S. subsidiary of BioCarb and became its Vice President of Research. In 1992, he founded and managed GlycoTech Corp. as its President and CEO. In 2003, he co-founded GlycoMimetics, Inc based on technology acquired from GlycoTech and currently serves as the company’s Chief Scientific Officer, Senior Vice President and Board Member. Dr. Magnani was the discoverer of Sialyl Lewis α and its functions such as the FDA-approved pancreatic cancer diagnostic CA19-9. He was the first to identify the binding domain to the selectins common to both Sialyl Lewis α and Sialyl Lewis x and used this information to develop potent selectin inhibitors. During his career, he also developed fundamental technology for the identification of carbohydrate epitopes, and used this technology to identify and characterize many carbohydrate markers and functional carbohydrates. He has used his knowledge of functional carbohydrates and medicinal chemistry to pioneer a new source of novel therapeutics known as glycomimetics.