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GALECTIN-3 IN SOLID ORGAN RECIPIENTS: ROLE IN GRAFT PATHOLOGY AND PROSPECTS FOR USE

D.A. Velikiy[1], M.A. Osoblivaya[1], O.P. Shevchenko[1, 2]

[1] Shumakov National Medical Research Center of Transplantology and Artificial Organs, Moscow, Russian Federation

[2] Sechenov University, Moscow, Russian Federation

Galectin-3 (Gal-3) is an important regulator of cell adhesion, migration, proliferation, differentiation and apoptosis under pathophysiological conditions. It plays a crucial role in diseases associated with chronic inflammation and fibrosis. In recent years, there have been reports indicating changes in serum Gal-3 levels in solid organ transplant recipients in the verification of kidney, liver, heart and lung transplant pathologies. Studies on Gal-3 levels and dynamics in solid organ recipients may serve to assess graft conditions using new minimally invasive methods and to identify therapeutic targets for personalized therapy. The first clinical trial data on Gal-3 pharmacological inhibition are emerging. This review summarizes the current understanding of the role of Gal-3 in transplant pathology and the prospects for its use as a diagnostic marker and therapeutic target in solid organ recipients.

Keywords: galectin-3, solid organ transplantation, graft pathology.

INTRODUCTION

In recent years, as survival rate and quality of life of solid organ transplant recipients got better, noninvasive screening and diagnosis of graft pathology have gained special relevance. Early diagnosis and treatment of complications allows for long-term graft functioning. Currently, to determine and verify the pathology of a transplanted organ, invasive diagnostic methods are used, such as biopsy (endomyocardial, transbronchial, puncture), coronary angiography, bronchoscopy and others. Performing these actions involve recipient management protocols or is dictated by the appearance of graft dysfunction signs. Multiple use of invasive methods is associated with certain limitations and risk of complications.

Changes in the concentration of individual molecules in the plasma or serum of solid organ transplant recipients may be associated with clinical symptoms, prognosis and structural changes detected by biopsy and subsequent morphological examination of the graft. Given the accuracy of concentration measurements and proven diagnostic significance, such molecules are classified as biomarkers [1]. In transplantology, a separate direction has been developed for the study of biomarkers for the diagnosis and prognosis of post-transplant complications in solid organ transplant recipients in order to reduce the frequency of invasive diagnostic interventions or partially replace them; biomarkers may have a separate value as targets of therapy [2].

Gal-3 is one of the actively studied biomarkers. Multiple organs (i. e., kidneys, lungs, stomach, colon, uterus, etc.) and diverse cells (i.e., inflammatory, endothelial, muscle or tumor cells, and fibroblasts) express Gal-3, leading to different roles in various pathophysiological conditions. Gal-3 is of particular importance in the development of diseases associated with chronic inflammation and fibrosis [3].

The purpose of this review is to analyze recent data on the role of Gal-3 in graft complications and the prospects for its use as a diagnostic marker and therapeutic target in solid organ transplant recipients.

FEATURES OF THE STRUCTURE AND FUNCTION OF GAL-3

Molecularly, galectins belong to the family of β-galactoside-binding proteins that may interact with several intracellular proteins. This interaction occurs via a specific carbohydrate-recognition domain (CRD) [4], thus making galectins take part in various biological processes (activation of proinflammatory factors, adhesion induction, phagocytosis of neutrophils and macrophages, pre-mRNA splicing etc.) [5].

At present, there have been 15 galectins discovered in mammals. They are divided into three groups according to the organization of polypeptide domains: galectins with a single CRD, tandem-repeat galectins with two distinct CRDs, and galectins with a single N-terminal CRD (chimeric type) [6, 7].

Gal-3 has a unique organization of polypeptide domains, its chimeric and specific structure includes a CRD, a polypeptide fold domain that binds carbohydrates. Gal-3's CRD interacts with various carbohyd-

Corresponding author: Maria Osoblivaya. Address: 1, Shchukinskaya str., Moscow, 123182, Russian Federation. Phone: (499) 193-87-62. E-mail: osoblivaya-91@yandex.ru

rate-containing proteins, activating different signaling pathways. A collagen-like sequence links CRD to N-link domain and is composed of nine collagen-like sequences (proline/glycine-rich domain) cleavable by matrix metalloproteinase. The N-link domain is essential to Gal-3 bioactivity. This domain has two sites where serins are phosphorylated.

Human Gal-3 has a molecular weight of 35 kDa. It is encoded by a single gene, LGALS3, located on chromosome 14, locus q21–q22. Gal-3 has the unique ability to bind proteins in two ways: carbohydrate-dependent and carbohydrate-independent. Using the C-terminal CRD domain, Gal-3 can bind to glycoconjugates containing N-acetyllactosamine, while the N-terminal domain enables the multimerization process. The N-terminal domain of Gal-3 is able to bind with proteins inside a cell and is sensitive to proteolysis by matrix metalloproteinases. These Gal-3 features determine its biological properties [8].

Gal-3 expression has been found in various tissues: in epithelial and endothelial cells, in many types of immune cells as well as in sensory neurons [9, 10]. At the early stages of embryogenesis, Gal-3 expression in tissues is more pronounced and is mainly localized in kidneys, liver, epithelium and chondrocytes [11, 12].

The ratio of intra- and extracellular levels of Gal-3 determines its ability both to induce cell growth and differentiation and to inhibit these processes [13]. Gal-3 may also play an important role in protecting the body against pathogens. It has chemotactic properties towards macrophages and monocytes and enhances proinflammatory signals. It also participates in phagocytic clearance of apoptotic neutrophils by macrophages, induces neutrophil adhesion and activation of leukocyte proinflammatory factors [14].

Gal-3 is predominantly located in the cytoplasm and in small amounts in the cell nucleus. In addition, it is secreted onto the cell surface and into biological fluids. Depending on the location, Gal-3 has revealed opposite effects: intracellularly it protects cells from their death, while extracellularly it can cause their apoptosis.

Nuclear Gal-3 participates in regulation of gene transcription and matrix RNA splicing. Cytoplasmic Gal-3 is essential for maintaining cell viability because it interacts with several critical proteins, including K-Ras gene activated by guanosine-5'-triphosphate (GTP) and anti-apoptotic protein (Bcl-2). The anti-apoptotic effect of Gal-3 inside cells is realized by binding to specific protein synexin (phospholipid-binding and Ca^{2+}-dependent protein). The resulting complex penetrates into mitochondria, where Gal-3 binds to Bcl-2, which leads to stabilization of mitochondrial membranes and inhibits cytochrome C release [12].

Extracellular Gal-3 plays an important role in adhesive interaction between epithelial cells and the extracellular matrix. On the other hand, there is evidence that extracellular Gal-3 induces T-cell apoptosis [16]. All this suggests the involvement of Gal-3 in various pathophysiological processes, including cell growth and differentiation, apoptosis, inflammation and fibrosis [9, 15].

It has been shown that in some inflammatory diseases (rheumatoid arthritis, recurrent chronic vasculitis), as well as in the development of atherosclerosis, patients have increased plasma Gal-3 levels. This may be due to the proinflammatory effects of Gal-3, which include stimulation of immune cell migration in tissues, increased adhesion of leukocytes to the vascular wall and adhesion to laminin [17].

GAL-3 AS A SPLICING FACTOR

Pre-mRNA splicing is an important step in gene expression. During this process, immature pre-mRNA is transformed into mature mRNA from which cell proteins are read (translated). Splicing is a co-transcriptional process during which non-coding sites (introns) are excised from pre-mRNA molecules and coding sites (exons) are spliced together [18].

The criteria for splicing activity reduction and restoration were analyzed in a cell-free system to assess the role of Gal-3 in pre-mRNA processing. The results of the study suggested that Gal-3 is one of the proteins involved in nuclear pre-mRNA splicing. At the same time, disruption of the pre-mRNA splicing process can cause or modify various human diseases [19].

Another study to determine the intracellular localization of Gal-3 also showed that this marker is a splicing factor. Immunofluorescence microscopy revealed inclusions in nuclear structures containing both Gal-3 and known splicing factors (snRNPs and SC35). It was suggested that the domain structure of Gal-3, or more precisely the homologous CRD domain, is required for splicing activity. Experimental data confirmed that isolated Gal-3 CRD restored splicing activity in the galectin-depleted system, although the whole structure of Gal-3 was 10 times more effective at restoring splicing than either of the CRDs alone [20].

It was found that the addition of the proline- and glycine-rich N-terminal domain of Gal-3 to the splicing complex resulted in a dose-dependent inhibition of splicing activity and a concomitant blocking of active spliceosome formation. Whereas intact Gal-3 or its C-terminal domain had no effect on splicing activity or spliceosome formation. This determines the effect of the N-terminal domain on pre-mRNA splicing and suggests that Gal-3 forms oligomers or interacts with other splicing components [21].

BINDING OF GAL-3 AND MIRNAS

MiRNAs are a class of small (20–23 nucleotides long) endogenously encoded noncoding RNAs. They can regulate translation or directly degrade their target genes by binding to base binding regions. Because of their ability to regulate target genes, miRNAs play an important role in cellular processes such as cell differentiation, proliferation, and apoptosis. There is an increasing body of information on the role of miRNAs in cardiac function regulation and heart failure progression [22].

MiRNAs have been identified as an important regulator of ischemia-reperfusion-induced cardiac injury. Song Z et al. investigated the effects of miR-27-3p, Gal-3 and HIF1A (hypoxia-inducible factor 1-alpha) on cell viability and apoptosis in ischemic myocardial injury. The expression level of miR-27-3p was shown to be reduced in the myocardium during hypoxia. Overexpression of miR-27-3p, like HIF1A, reduced ischemia-reperfusion-induced myocardial injury. At the same time, overexpression of Gal-3 reduced the protective effect of miR-27-3p on cardiomyocyte injury, while downregulation of miR-27-3p promoted myocardial cell injury and was a stimulus for Gal-3 activation [23].

A study by Meiqi Zhang et al. in an *in vivo* and *in vitro* model of cardiac hypertrophy showed that expression of miR-27b was down-regulated in mice with cardiac hypertrophy. At the same time, the cardiac function of the mice with cardiac hypertrophy could be restored with the overexpression of miR-27b. Depletion of Gal-3 significantly attenuated cardiac hypertrophy in both *in vitro* and *in vivo* tests. It has been suggested that Gal-3 is a target gene of miR-27b; as a consequence, miR-27b can be used to exert a protective role against cardiac dysfunction and hypertrophy by decreasing the expression level of Gal-3 [24].

A study by Ali A Shati et al. investigated the effect of resveratrol (RES), an anti-apoptotic lectin that is highly overexpressed in ovarian cancer cells, on Gal-3 levels. In SKOV3 and OVCAR-3 OC cell lines, RES induced cell death and inhibited cell migration and invasion. RES enhances levels of miR-424-3p which is able to degrade Gal-3. The results of this study show that RES-induced apoptosis in cancerous cells is associated with increased levels of miR-424-3p and reduced levels of Gal-3 [25].

ROLE OF GAL-3 IN THE DEVELOPMENT OF FIBROTIC CHANGES AND INFLAMMATORY REACTIONS

The long-term post-transplant period can be characterized by graft fibrosis. Fibrotic changes in the transplanted organ result in graft dysfunction due to structural and functional remodeling. The main causes of fibrosis progression include acute or chronic graft rejection, as well as concomitant conditions such as diabetes mellitus, lipid metabolism disorders and others [3, 49].

It has been shown that during fibroblast division, Gal-3 moves from the cytoplasm to the cell nucleus, which, along with increased expression, may indicate the involvement of Gal-3 in proliferative processes. Activation and proliferation of resting fibroblasts occurs under the influence of Gal-3, which is secreted in the area of tissue damage [26]. Fibroblast activation stimulates the synthesis of cytoskeleton proteins COL1A1 (collagen, type I, alpha 1 chain) and aSMA (smooth muscle alpha-actin), which leads to fibrotic changes. There is evidence that Gal-3 can induce degradation of extracellular matrix components indirectly through its interaction with matrix metalloproteinases [27].

Gal-3 is a chemoattractant for monocytes and macrophages, which stimulates the processes of phagocytosis and secretion of cytokines, including interleukin-1. It has been established that Gal-3 can interact with tissue basophils inducing thereby the release of inflammatory mediators and development of hypersensitivity reactions. It has also been shown that Gal-3 participates in angiogenesis and development of atherosclerotic lesions in vessels [27].

Gal-3 expression is most expressed in lungs, spleen, stomach, adrenal glands, uterus and immune system cells, especially in cancer [28]. It is also expressed to a lesser extent in the heart, liver, kidneys, brain and pancreas [29]. At the same time, a change in plasma Gal-3 levels in patients with cardiovascular diseases [30], respiratory dysfunction [31] and liver dysfunction[32] has been shown, suggesting its possible diagnostic significance.

GAL-3 IN KIDNEY DISEASE AND TRANSPLANTATION

In the kidney, Gal-3 is expressed mainly in the collecting ducts of renal tubules, inside or on the apical membrane of α-intercalated cells. This suggests a role for Gal-3 in renal tubular development, possibly through intercellular adhesion or interaction with the extracellular matrix to promote tubulogenesis. In the adult kidney, Gal-3 expression is detected in basal and intercalated cells, in the proximal tubules and the major ascending branch [33].

Gal-3 binds to β-galactoside sugars in its carbohydrate recognition domain, exhibiting a variety of properties, including cell adhesion and proliferation via several glycosylated matrix proteins (laminin, fibronectin and integrins). Gal-3 also promotes pathological processes such as inflammation, angiogenesis and organ fibrogenesis in the presence of tissue damage. Gal-3 depletion has been found to reduce collagen matrix accumulation and severity of renal fibrosis [34, 35]. Other studies have shown that higher plasma or serum Gal-3 levels have

been associated with increased risk of chronic kidney disease (CKD) and rapid decline in renal function [33]. Tsai MT et al. found that higher plasma Gal-3 levels were associated with more severe renal fibrosis as verified by biopsy [36].

O'Seaghdha et al. presented evidence that level of Gal-3 circulating in the blood is inversely associated with renal function and development of CKD [37]. The findings are consistent with a study of the relationship between Gal-3 concentration and progression of congenital CKD [38]. Renal fibrogenesis, including after transplantation, has been found to depend on Gal-3 expression and secretion [33]. At the same time, experimental studies have shown that kidney damage and fibrosis can be prevented by pharmacological inhibition of Gal-3 [39, 40, 41].

Plasma Gal-3 has been found to be associated with organ fibrosis, but whether urinary Gal-3 is a potential biomarker of kidney disease progression has not been well explored. S.M. Ou et al. examined 280 patients that were divided into three groups based on their urinary Gal-3 levels (<354.6, 354.6−510.7, and ≥510.8 pg/mL). Criteria for evaluation of renal disease progression were defined as ≥40% decline in the estimated glomerular filtration rate (eGFR) or end-stage renal disease. Urinary Gal-3 levels were shown to correlate inversely with eGFR and positively with plasma Gal-3 levels, creatinine levels, and urine total protein to creatinine ratio (UPCR). Moreover, there was a gradual increase in urinary Gal-3 levels as CKD progressed, with the increase being greatest among patients with stage 5 CKD. Combined determination of urinary and plasma Gal-3 levels may provide greater diagnostic efficacy in monitoring renal disease [42].

In recent years, Gal-3 has been shown to modulate inflammation and immune cell infiltration in various pathophysiological conditions. Graft dysfunction is associated with activation of immune cells. In a study by Dang et al. on two groups of animals, Gal-3-null mice had less tubular damage, moderate fibrosis, and lower immune cell infiltration compared to the normal animal group that showed characteristic changes in the graft. in the form of renal tubular atrophy, as well as upregulation in Gal-3 expression in tissues and blood plasma [43]. This study suggests a potential role for Gal-3 in immune cell recruitment upon rejection, as evidenced by the improved outcome of kidney injury with pharmacological inhibition of Gal-3.

Thus, Gal-3 may play an important role in renal inflammation and fibrosis, which are involved in the development of kidney graft dysfunction. Further clinical studies are needed to investigate the potential association of Gal-3 with adverse outcomes in patients with CKD and in kidney transplant recipients.

GAL-3 IN PATIENTS WITH HEART FAILURE AND IN HEART TRANSPLANT RECIPIENTS

Several studies have shown the diagnostic potential of Gal-3 as a biomarker of development and progression of heart failure (HF). Changes in Gal-3 concentrations have been observed during the development of myocardial fibrotic disorders, as well as under the influence of drug therapy. The estimation of plasma Gal-3 levels in HF patients may allow to identify those patients who are at increased risk of rehospitalization [44, 45].

Yu.V. Shchukin et al. showed the pathogenetic role of Gal-3 in the development of HF. Blood Gal-3 level in patients was associated with the severity of chronic HF and correlated with markers of oxidative stress and inflammation [46].

In another study, it was also found that in patients with coronary heart disease, blood Gal-3 levels progressively increased according to HF severity. Moreover, Gal-3 levels in patients correlated with the level of inflammation markers: C-reactive protein and interleukin-6. It has been shown that Gal-3 is able to interact with the transmembrane glycoprotein CD98, thereby activating phosphatidylinositol-3-kinase thus triggering the alternative macrophage activation process. As a consequence, myocardial infiltration by activated macrophages increases [47].

It is known that the risk of subclinical chronic HF increases over time in heart recipients due to a combination of various pathological factors, which leads to the formation of graft myocardial fibrosis [48, 49]. The role of Gal-3 in heart recipients has been less studied, but it has been shown that patients with transplanted heart myocardial fibrosis have higher plasma Gal-3 concentrations than recipients without fibrotic changes [50].

In our previous study, it was established that over 75% of heart recipients at different periods after transplantation had fibrotic changes in graft myocardium verified by endomyocardial biopsy. In addition, it was shown that the proportion of patients with myocardial fibrosis in the late post-transplant period almost doubled among the cardiac recipients who had acute transplant rejection. At the same time, Gal-3 was diagnostically significant in transplant myocardial fibrosis: in heart recipients with plasma Gal-3 levels above a certain threshold value, the frequency of detecting fibrotic changes in the myocardium increased more than 1.5-fold [51].

The results of this work confirm the assumption that acute rejection crises influence the development of myocardial fibrosis in the transplanted heart. This occurs against the background of interstitial edema and infiltration by lymphocytes and macrophages, increased production of proinflammatory and profibrogenic mediators, typical for acute graft rejection. [52, 53].

GAL-3 IN LIVER DISEASE AND TRANSPLANTATION

Gal-3, involved in the development of fibrosis and inflammation, is actively expressed in patients with advanced liver disease. Gal-3 expression levels correlate with concentrations of markers of liver inflammation and hepatic decompensation and may be useful in identifying high-risk patients. Gal-3 has been shown to mediate hepatic stellate cell activation and plays an important role in the development of hepatic fibrotic changes. Gal-3 levels are higher in patients with cirrhosis than in the healthy cohort. Intrahepatic Gal-3 has also been detected in hepatocellular carcinoma and in liver biopsies of cirrhotic patients [32].

Gal-3 plays an important immunological role and has been found to contribute to the regulation of innate and adaptive immune responses. Gal-3 has been shown to decrease the number of monocytes by influencing differentiation from dendritic cells as well as T-cell antigen presentation. It also inhibits T cell activation by reducing T cell receptor levels and has been shown to induce IL-2 production and induce apoptosis of activated T cells and suppress their proliferation [54].

A study by H.W. Zimmermann et al. also showed that patients with advanced liver cirrhosis had significantly elevated serum Gal-3 levels. Moreover, Gal-3 levels correlated with such indicators as interleukin-6, granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-8 and monocyte chemoattractant protein-1 (MCP-1) [55]. The established relationship between Gal-3 and activation of inflammatory and damaging factors in liver cirrhosis requires further study.

In liver transplantation, the level of circulating Gal-3 can be considered as a biomarker for identifying recipients with a higher risk of developing infectious complications, which are one of the important factors influencing recipient survival after transplantation. It has been shown that the serum Gal-3 levels in liver recipients with a higher incidence of infectious complications was significantly higher than that in other recipients [54].

GAL-3 IN LUNG TRANSPLANTATION

Lung transplantation (LT) is the only possible treatment for patients with end-stage lung diseases, such as emphysema, cystic fibrosis, pulmonary fibrosis and pulmonary arterial hypertension, which cannot be treated with medication [56, 57, 58]. Long-term recipient survival after LT is still lower than in other solid organ transplants, due to the development of chronic graft dysfunction [59]. Currently, there are several forms of chronic lung graft dysfunction – these are obliterative bronchiolitis syndrome and restrictive allograft syndrome.

Bronchiolitis obliterans syndrome (BOS) is characterized by bronchiolar thickening and obstruction due to damage and inflammation of epithelial cells and small subepithelial structures of the airways. Then a fibroproliferative stage develops with proliferation of fibroblasts and accumulation of collagen under bronchiolar epithelium, which leads to obliteration of airway lumen [60].

A study by Miriana d'Alessandro et al. assessed serum Gal-3 levels in recipients after LT with and without BOS, as well as in healthy control subjects to evaluate the potential diagnostic role of this biomarker [61]. It was found that in patients with verified BOS, Gal-3 levels were higher than in healthy subjects, but it did not differ significantly in comparison with lung recipients without signs of chronic graft dysfunction.

Respiratory complications associated with airway obstruction lead to postoperative graft dysfunction in lung recipients. Gal-3 is known to be actively expressed in inflammatory processes and fibrotic changes in various organs. Other potential biomarkers of respiratory diseases and post-transplant complications are small miRNA regulatory molecules.

In our previous work, miR-339 expression levels and Gal-3 concentrations were assessed in the plasma of lung recipients. Lung recipients with airway obstruction had significantly higher miR-339 expression levels and Gal-3 concentrations compared with recipients without any complications. Exceeding the calculated threshold values of miR-339 and Gal-3 in plasma in lung recipients was associated with a high risk of post-LT airway obstruction. Determination of miR-339 expression level in combination with Gal-3 may be promising for identification of lung recipients with high risk of respiratory complications and graft dysfunction [31].

GAL-3 INHIBITORS

Pharmacological inhibition of Gal-3 has been investigated to evaluate its involvement in target organ damage. This lectin binds to multiple cellular sites and has extracellular fixation and permeability abilities. This property is crucial for Gal-3 inhibitors, which are classified according to their carbohydrates' binding characteristics. The currently used Gal-3 inhibitors are listed in the Table [38].

The results of these multicenter studies will allow us to assess the prospects for the therapeutic use of Gal-3 inhibitors in fibrotic changes in various organs and in oncological diseases.

In a phase IIa, blinded, multicentre, randomized clinical trial, patients with stage 3b and 4 CKD received the Gal-3 inhibitor GCS100 [62]. In CKD patients who received the Gal-3 pharmacological inhibitor, the glomerular filtration rate significantly improved, the level of uric acid and urea nitrogen in the blood decreased compared with patients receiving placebo. The authors

of the study did not report any serious side effects when using GCS100 at a dosage of 1.5 mg/m^2 [63].

Lau et al. studied the use of modified citrus pectin (MCP) in hypertension-induced cardiovascular disorders in a randomized controlled trial. It was found that Gal-3 inhibition did not affect the expression of cardiac biomarkers of fibrosis but was associated with lower plasma creatinine levels and higher eGFR in patients treated with MCP [64].

In a study by Hirani et al., Gal-3 was evaluated as a therapeutic agent for the treatment of fibrosis in lung diseases. Inhaled Gal-3 inhibitor was found to be well tolerated in healthy individuals and reduces plasma biomarkers associated with pulmonary fibrosis in patients [65].

Additional preclinical studies are needed to confirm the feasibility of Gal-3 inhibition as a potential therapeutic target.

CONCLUSION

The biological effects of Gal-3 include involvement in the regulation of various pathophysiological processes, including cell growth and differentiation, apoptosis, inflammation, and fibrosis.

In solid organ recipients, a change in Gal-3 levels has been shown in graft pathology verification. In kidney transplantation, less severe tubular damage, a moderate degree of fibrosis and lower infiltration by immune cells in the graft were associated with lower Gal-3 levels. In liver transplantation, Gal-3 concentrations were significantly higher in recipients with advanced graft fibrosis and infectious complications. In heart and lung recipients, the diagnostic significance of Gal-3 with regard to the development of post-transplant complications has been shown both as an independent test and in combination with molecular genetic markers (miRNA). All this suggests that Gal-3 is a promising biomarker for detecting post-transplant organ damage.

Recent data from clinical studies on pharmacological inhibition of Gal-3 suggest the possibility of using this protein as a therapeutic target to slow down and prevent the development of graft pathology in solid organ recipients.

The authors declare no conflict of interest.

Table

Galectin-3 inhibitors [38]

Name	Structure	Pharmacokinetic	Clinical evidence
Modified citrus pectin (MCP)	Polypeptide formed with anhydro-galacturonic acid and galactose with shorter carbohydrate chains modified by pH and temperature	Gal-3 antagonist, soluble protein binding with Gal-3 carbohydrate recognition domain (CRD)	*Cancer:* Phase II, single-center, open label, trial evaluating the safety and efficacy of MCP on prostate-specific antigen kinetics in prostate cancer (NCT01681823) *Cardiac fibrosis:* Phase III, randomized study, single-center trial evaluating the efficacy of MCP treatment to reduce cardiac fibrosis in patients with hypertension. (NCT01960946)
GBC590 / GCS100 A combination of purified MCP (polymerized)	A combination of purified MCP (polymerized)	Gal-3 antagonist, soluble protein binding with CRD	*Renal disease:* – Phase I, open label study, evaluated the security of weekly doses of GCS-100 in patients with chronic kidney disease. (NCT01717248) – Phase IIa, placebo-controlled, randomized, single-blind study evaluated of weekly doses of GCS-100 in patients with chronic kidney disease and eGFR change. (NCT01843790) *Cancer:* – Phase II trials evaluated the reduction of metastasis and stabilized colorectal carcinomas during outcompeting Gal-3 in binding to its receptors. (NCT00110721)
Davanat and Belapectin	Galactomannan polysaccharide	Multivalent binding with Gal-3 CRD	*Liver fibrosis:* Phases I, II, and III study in a multi-center, study, to evaluate the safety and pharmacokinetic of modified Davanat in subjects with non-alcoholic steatohepatitis (NASH) with advanced hepatic fibrosis to improve portal hypertension and oesophagial varice (NCT02462967, NCT04365868)

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