Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Galectin-3 Inhibitors

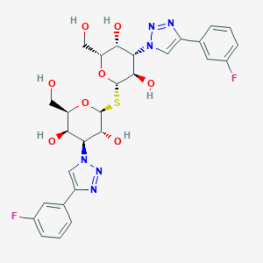
Evidence Summary

Have the potential to reduce organ fibrosis and protect against neuroinflammation. Clinically tested inhibitors show good safety but modest efficacy. More potent and specific inhibitors are in development.

Neuroprotective Benefit: Elevated galectin-3 is associated with cognitive decline. Galectin-3 inhibition may reduce pathological microglial neuroinflammation. Novel BBB penetrant inhibitors may need to be developed.

Aging and related health concerns: Elevated serum galectin-3 is a prognostic marker for reduced heart function, fibrotic disease, poor prognosis, and mortality. Inhibitors show potential benefits for fibrotic diseases in early clinical trials.

Safety: Good safety profile in clinical trials, but currently available inhibitors are relatively weak and non-specific. Many novel galectin-3 inhibitors are currently in preclinical development.

Availability: Modified Citrus Pectin is OTC GR-MD-02 and TD139 in clinical trials	**Dose:** Clinically effective dose not established. Varies by formulation and indication. PectaSol-C – oral GR-MD-02 – IV TD139 – inhaled powder	**Chemical formula and MW:** Low MW MCPs: 10-30 kDa GR-MD-02: ~50 kDa TD139: 648.6 g/mol $C_{28}H_{30}F_2N_6O_8S$  (Source: PubChem)
Half-life: GR-MD-02: 18-20 hours (IV) TD139: 7 hours (inhaled)	**BBB:** Clinically tested inhibitors not penetrant	
Clinical trials: Tested in clinical trials for cancer (n=9, 24), liver fibrosis (n=31, 161), pulmonary fibrosis (n=60), kidney disease (n=121).	**Observational studies:** Elevated serum levels associated with heart failure, fibrotic diseases, poor prognosis, and mortality.	

What is it?

Galectin-3 belongs to the family of water-soluble lectins, which are sugar binding proteins. Galectins preferentially bind to β-galactoside derivatives, and can cross link surface glycoproteins by binding galactose residues [1]. Galectin- 3 is the only known member of a family of chimera-type galectins which contains a C-terminal carbohydrate recognition domain (CRD) for sugar binding and an N-terminal non-CRD for self-association. Galectin-3 has ubiquitous subcellular distribution and functions in the nuclear, cytoplasmic, and extracellular compartments. It is synthesized in the cytoplasm and can be transported into the extracellular space via an unknown mechanism. Galectin-3 influences cell signaling and plays different roles depending on its localization in a given cell. Consequently, the effect of galectin-3 modulators depends on whether or not the drugs are cell permeable. All of the galectin-3 inhibitors that have been clinically tested have low cell permeability, and thus exert their effects through modulation of extracellular galectin-3. Galectin-3 is elevated in the context of inflammatory and fibrotic conditions, and has been used as a biomarker for poor outcome in the context of cardiovascular disease.

Galectin-3 inhibitors have been tested in clinical trials for cancer, kidney disease, liver disease (non-alcoholic steatohepatitis NASH), psoriasis, and pulmonary fibrosis.

The galectin-3 inhibitors tested thus far have been carbohydrate-based molecules that are not completely specific for galectin-3, and act extracellularly, as they have low cell permeability.

Modified citrus pectin is a form of pectin that has been chemically altered for improved absorption in the digestive tract. This carbohydrate mixture has a high molecular weight and is derived from the pulp and peels of citrus fruits. Modified citrus pectin contains a mixture of polysaccharides (sugars) and can act as a weak non-specific galectin-3 inhibitor. It is not clear whether it interacts with galectin-3 through its CRD, or if it affects galectin-3 via an indirect mechanism. Pectin likely interacts with several sugar binding proteins, thus would be expected to have pleiotropic effects. An intravenous (IV) formulation of modified citrus pectin called GCS-100 was tested in clinical trials by LaJolla Pharmaceutical, but the company has subsequently discontinued development of this compound. An oral formulation called PectaSol-C® is sold as an OTC supplement and is currently being tested in patients with prostate cancer.

GR-MD-02 (Belapectin) is a carbohydrate-based inhibitor derived from US Pharmacopeia apple pectin. It is a galactoarabino-rhamnogalacturonate polysaccharide polymer that can bind to galectin-3. These carbohydrates can bind both galectin-3 and galectin-1, but have a higher affinity for galectin-3. GR-MD-02 is being developed by Galectin Therapeutics and has been tested in clinical trials for cancer, psoriasis, and NASH.

TD139 is a thiodigalactoside analog which can bind and inhibit both galectin-1 and galectin-3. It is thought to bind to novel sites outside the CRD. It is being developed by Galecto Biotech for idiopathic pulmonary fibrosis.

There are currently efforts underway to develop more specific galectin-3 inhibitors with better pharmacokinetic and pharmacodynamic properties, however, these are still in the preclinical phase.

Neuroprotective Benefit: Elevated galectin-3 is associated with cognitive decline. Galectin-3 inhibition may reduce pathological microglial neuroinflammation. Novel BBB penetrant inhibitors may need to be developed.

Types of evidence:

- 8 observational association studies for serum galectin-3 levels

- Numerous laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?

Galectin-3 inhibitors have not yet been tested in patient populations with neurological conditions, however, **serum levels of galectin-3 have been found to be elevated in patient populations experiencing neurodegeneration and/or cognitive decline**. The rise in galectin-3 levels is generally indicative of increased inflammation, and associated with worse prognosis.

Alzheimer's disease (AD): Serum galectin-3 levels were found to be modestly elevated in AD patients (n=41) relative to healthy elderly controls (n=46) in China (mean ± SD: 6.42 ± 2.51 vs 5.27 ± 1.91 ng/mL; P = 0.017) [2]. The study also found a significant **correlation between cognitive impairment based on the Mini-Mental State Examination (MMSE) score and galectin-3 levels** (r = 0.341; P <0.001).

Parkinson's disease (PD): Serum galectin-3 levels were higher in PD patients (n=60) relative to age-matched healthy controls (n=30) in Turkey (2271.8, 95% CI 375.9 to 9673.4 vs 892.9, 95% CI 168.2 to 2416.3 pg/mL; P<0.01) [3]. Galectin-3 levels were also associated with Hoehn-Yahr stages (r: 0.691, P < 0.001), such that **PD patients at more advanced stages had higher galectin-3 levels.**

Amyotrophic lateral sclerosis (ALS): Plasma **galectin-3 levels were found to be correlated with disease duration** (r = 0.293, P = 0.037), such that plasma galectin-3 was significantly increased in ALS patients (n=51) in China relative to age-matched controls (n=60) (341.17, 95% CI 69.12 to 859.22 vs 201.64, 95% CI 22.3 to 401.63 ng/mL; P < 0.05), but only in ALS patients with disease duration greater than one year [4].

Stroke: Serum galectin-3 levels have been found to be elevated in stroke patients, and associated with worse prognosis in several cohorts. In acute ischemic stroke patients in the CATIS trial in China (n=3082), **galectin-3 had prognostic value for outcomes**, as those with the highest quartile for galectin-3 had increased risks for death or major disability (adjusted Odds Ratio OR: 1.55, 95% CI 1.15 to 2.09) [5]. In a separate cohort of acute ischemic stroke patients in China (n=233) galectin-3 levels were associated with severity (AUC = 0.884, 95% CI 0.827 to 0.941, P < 0.001), and were highest in those with poor outcomes [6]. In the REGARDS cohort of ischemic stroke patients in the Southern US (n=1001), **higher levels of galectin-3 based on quartile was associated with higher risk for cognitive impairment** (Odds Ratios: Q2: 1.00, 95% CI 0.68 to 1.46; Q3: 1.45, 95% CI 1.01 to 2.10; and Q4: 1.58, 95% CI 1.10 to 2.27 relative to Q1; P trend = 0.003) [7]. The association was only significant in non-diabetics, and was attenuated after adjustment for cardiovascular risk factors. Patients with aneurysmal

subarachnoid hemorrhage in Japan (n=83) had higher plasma galectin-3 levels relative to controls (n=10) (3.42 ± 1.60 vs 2.21 ± 1.16 ng/mL, p = 0.023) [8]. **High galectin-3 was a predictor of poor outcome** in this cohort (OR: 3.08, 95% CI 1.58 to 6.00; P = 0.001).

Delirium: Elevated serum galectin-3 levels was found to be a predictor for delirium in postpartum

women (n=824) based on a cutoff value of 20 ng/mL (OR: 1.170, 95% CI 1.116 to 1.226; P = 0.001) [9]. In these women, **galectin-3 levels were indicative of elevated inflammation** and were associated with high c-reactive protein (CRP) levels and APCHCE II score, which is an assessment of disease severity and mortality risk.

Genetic variation in the galectin-3 gene (lgals3) was found to be associated with reduced cognitive function in the PROSPER cohort (n=5675) of elderly individuals (age 70-82) at risk for cardiovascular disease [10]. Carriers of the single nucleotide polymorphisms (SNPs) rs4644, rs4652, and rs1009977 had higher baseline CRP levels (inflammation marker) and worse performance on attention and immediate recall cognitive tests. It is hypothesized that these SNPs increase galectin-3 levels, though that has not been confirmed.

Human research to suggest benefits to patients with dementia: None

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

Alzheimer's disease: Galectin-3 was found to be **increased 10-fold in the cortex of patients with AD** and associated with plaque-associated microglia, based on postmortem tissue analysis [11]. A similar upregulation and localization of galectin-3 was seen in the 5XFAD and APP/PS1 AD mouse models [11; 12]. In a galectin-3 knockout background, there was a decrease in Aβ oligomerization, plaque formation, and reactive glia in the context of these AD models. The loss of galectin-3 was also associated with increased performance on cognitive tests in these animals. Galectin-3 has been implicated in the inhibition of memory formation by inhibiting integrin-α3 signaling. The overexpression of galectin-3 was found to impair fear memory formation in rats, which was mediated through the inhibition of integrin signaling [13]. While these studies suggest that galectin-3 promotes pathology in AD, its association with TREM2 suggests that it may have mixed roles. Galectin-3 was found to co-localize with TREM2 in the processes of plaque-associated microglia, and the microglial activation of galectin-3 is mediated by TREM2 [11; 12]. Similar to TREM2, galectin-3 is primarily associated with an alternatively active phenotype. Loss of TREM2 also leads to a decrease in plaques and plaque-associated microglia, however, this ultimately leads to an exacerbation of neuronal damage as the animals age [14]. Therefore, the effects of a galectin-3 inhibitor in AD patients may be mixed.

Parkinson's disease: Galectin-3 was shown to play a role in driving inflammation in microglia in response to alpha-synuclein aggregates [15]. Knocking down galectin-3 could reduce the alpha-synuclein induced microglial expression of pro-inflammatory mediators (iNOS, IL-1β, IL-12).

Stroke: There are contradictions in the results from studies examining the role of galectin-3 in animal models of stroke, which are likely related to the diverse roles of galectin-3 in mediating responses to neurological injury. The studies suggest that the **modulation of the inflammatory response by galectin-3 is complex** and varies in acute and chronic phases based on environmental context. In the MCAO ischemic stroke model, galectin-3 knockout mice were found to lack the TLR2 mediated neuroinflammatory brain injury response, leading to a decrease in microglial proliferation and increase in lesion size [16], while recombinant intracerebroventricular galectin-3 was neuroprotective and decreased lesion size [17]. However, galectin-3 knockout mice were also found to be protected against the TLR4 mediated loss of enteric neurons in the gastrointestinal system following MCAO [18]. These effects stem from the **ability of galectin-3 to modulate the secretory profile, morphology, and migration of microglia** [19]. Galectin-3 is generally associated with promoting an alternatively activated-like phenotype that does not appear to be clearly pro- or anti-inflammatory, and could potentially be beneficial or deleterious depending on the context.

Traumatic brain injury (TBI): In a mouse model of TBI (controlled cortical impact), treatment with a galectin-3 neutralizing antibody led to a decrease in the level of pro-inflammatory cytokines (IL-1β, IL-6, TNFα), whereas the addition of recombinant galectin-3 led to a decrease in neuronal survival [20]. Galectin-3 that is released from microglia can bind TLR4 and initiate pro-inflammatory signaling cascades. **Galectin-3 is hypothesized to act as an alarmin after trauma to promote neuroinflammation.**

APOE4 interactions: Not known

Aging and related health concerns: Elevated serum galectin-3 is a prognostic marker for reduced heart function, fibrotic disease, poor prognosis, and mortality. Inhibitors show potential benefits for fibrotic diseases in early clinical trials.

Types of evidence:

- 6 clinical trials (GR-MD-02 in Cancer Ph1 n=9, NASH Ph1 n=31, Ph2 n=161; GCS-100 in Cancer Ph2 n=24, Kidney disease Ph2a n=121; TD139 in Pulmonary fibrosis Ph1 n=60)
- 11 observational association studies of serum galectin-3 levels

- Numerous laboratory studies

Longevity: Low galectin-3 associated with successful aging

Centenarians (n=81, ages 100-104) were found to have lower serum levels of galectin-3 relative to elderly controls (n=41, ages 70-80) (2.4±1.7 vs 4.8±2.8 ng/mL), and low galectin-3 was a predictor of healthy aging (AUC=0.75, 95% CI 0.66 to 0.84, sensitivity 46%, specificity 96%, optimal cutoff <5.3 ng/mL) [21].

Heart failure: High galectin 3 associated with heart dysfunction and worse outcomes

The ability of serum or plasma levels of galectin-3 to serve as a prognostic biomarker for heart failure in high risk populations has been studied extensively in numerous clinical cohort studies. Galectin-3 levels have generally been found to be elevated in patients with worse prognosis, and to correlate with other markers associated with cardiovascular disease. While elevated galectin-3 alone was found to have prognostic value, it is more informative when used in combination with a panel of other heart function-associated markers.

In a clinical study analyzing twelve biomarkers associated with heart failure in four longitudinal community-based cohorts (n=22756), galectin-3 had a modest association with overall heart failure (Hazard Ratio HR: 1.07, 95% CI 1.02 to 1.12) [22]. In the large longitudinal PREVEND Caucasian cohort study (n=7968), serum galectin-3 levels correlated with a range of cardiovascular disease risk factors including blood pressure, serum lipids, body mass index, renal function, and N-terminal pro-hormone BNP (NT-proBNP), though the associations were stronger in women [23]. **Galectin-3 levels are also elevated as a function of age, and remained a predictor of all-cause mortality** independent of cardiovascular risk factors (Hazard ratio per standard deviation galectin-3: 1.09, 95% CI 1.01 to 1.19; P=0.036). A similar association with all-cause mortality (HR: 1.26, 95% CI 1.01 to 1.59) was found in the TRIUMPH cohort of acute heart failure patients in the Netherlands (n=496) [24]. Patients with a history of heart disease had higher levels than newly diagnosed patients. In patients with pulmonary hypertension, those with higher levels of galectin-3 had a higher risk of mortality (HR: 2.19 per tertile, 95% CI 1.06 to 4.54) [25]. Serum galectin-3 levels had a borderline association with mortality (AUC 0.607) in an Asian cohort of patients with chronic systolic heart failure in Taiwan (n=105) [26], and was not significantly associated with heart failure in the Cardiovascular Healthy Study (n=5277) which included African Americans (14.7%) [22]. This suggests that its prognostic value may vary with ethnicity, and be most informative for Caucasians. In a prospective cohort study of patients undergoing routine echocardiography in Germany, serum galectin-3 levels correlated with progressive diastolic dysfunction

such that patients with galectin-3 levels over 17 ng/mL were 6 times more likely to have grade III diastolic dysfunction [27].

A normal reference range for serum galectin-3 was established in a clinical observational study with healthy volunteers (n=1092), which found that the 90th, 95th, 97.5th percentiles of the normal reference interval were 17.6, 20.3, and 22.1 ng/ml, respectively [28]. In this study, 22.1 ng/mL was used as the cutoff for acute heart failure patients.

Galectin-3 may contribute to the decline in heart function by promoting cardiac fibrosis through increased collagen production, as well as driving inflammation and ventricular remodeling [29]. However, the timing of a galectin-3 inhibitor based therapeutic approach may be critical for its efficacy. Galectin-3 plays an important role in the initial phases of normal wound healing and thus helps maintain the integrity of cardiac tissues, but its sustained expression and secretion can drive fibrotic adverse remodeling. Therefore, galectin-3 inhibitors may be most beneficial in slowing fibrosis after the onset of damage.

Atherosclerosis: Galectin-3 inhibition may benefit (preclinical)

Galectin-3 is implicated in atherosclerotic processes based on its ability to **promote adverse vascular remodeling and to recruit monocytes and macrophages** which drive vascular inflammation [29]. However, preclinical rodent studies have been conflicting regarding the role of galectin-3 in atherosclerotic plaque development and stability [30]. It is hypothesized that the discrepancies may be due to strain related differences and/or be dependent on baseline levels of circulating cholesterol. Galectin-3 may play a role in the switch in the inflammatory profile toward the M2-like pro-fibrotic state which drives plaque progression. In late stage atherosclerotic mice (ApoE -/- fed a high fat diet), treatment with a non-specific galectin-3 inhibitor (Modified citrus pectin) for 4 weeks reduced plaque volume by 30% [30]. Since serum galectin-3 is elevated in the context of cardiovascular disease and atherosclerotic stroke, galectin-3 inhibition may be beneficial for reducing atherosclerotic plaque accumulation.

Obesity: Galectin-3 inhibition protective (preclinical)

Obese rodents were found to have increased levels of galectin-3 in adipose tissue, which may have played a role in **promoting adipocyte differentiation** through the activation of the transcription factor PPARγ [31; 32]. Male galectin-3 knockout mice were found to have less white adipose tissue following consumption of a high-fat diet [32]. The non-specific galectin-3 inhibitor, Modified citrus pectin, did not prevent the high-fat diet induced increase in adipose tissue in rats, but did prevent the induction of

fibrotic processes, such as pericellular collagen deposition [31]. This suggests that galectin-3 plays a role in adipose tissue remodeling in the context of obesity.

Cancer: Potential mixed benefit depending on cancer type

Modified citrus pectin from LaJolla Pharmaceutical, GCS-100, was tested in a Phase 2 open label trial in patients with relapsed chronic lymphocytic leukemia (n=24) in an IV formulation at 150 mg/m^2 for 5 days every 21 days for 5-9 months [33]. Six patients had a partial response, but the development of GCS-100 has been discontinued. GR-MD-02, which is a polysaccharide polymer from Galectin Therapeutics, is currently being tested in combination with anti-PD-1 therapy in patients with metastatic melanoma (NCT02575404) in an open label trial (ASCO 2017 Poster). Preliminary analysis from the first cohort of patients (n=9) found that the objective response rate of 56% was better than the historical average for anti-PD-1 alone (33%). Further testing is needed to determine if the addition of the galectin-3 inhibitor provides a sustained clinically meaningful benefit.

Galectin-3 plays mixed and diverse roles in cancer in a cancer-cell type dependent manner. In a meta-analysis, high galectin-3 was found to be oncogenic in colorectal, ovarian, and non-small cell lung cancers [34]. Meanwhile, high galectin-3 is associated with better outcome for other cancer subtypes. Galectin-3 can modulate the surface expression of a wide range of glycoproteins and regulate the function of receptor kinases, which play important roles in driving tumor growth. Galectin-3 can modulate the tumor microenvironment in ways that affect cancer cell survival, metastasis, angiogenesis, drug resistance, and immune suppression [35]. Galectin-3 may drive the expansion of M2-like tumor associated macrophages which inhibits tumor immunosurveillance [36].

However, the effects of galectin-3 are influenced by protein glycosylation patterns, such that it may preferentially bind to and modulate different proteins under different conditions, thus leading to different downstream effects. Similarly, the subcellular localization of galectin-3 (nuclear, cytoplasmic, extracellular) also influences its functional effects. In some cancers, galectin-3's association with outcomes are dependent on subcellular location in a cancer-cell type dependent manner. For example, high galectin-3 is a good prognostic factor for neuroblastoma and melanoma, but only if it is in the nuclear compartment, meanwhile, high nuclear galectin-3 is associated with worse prognosis in renal cell carcinoma [35]. This suggests that galectin-3 inhibitors may be beneficial in patients with high galectin-3 levels that have cancers where high galectin-3 is associated with worse prognosis.

Non-alcoholic steatohepatitis (NASH): Galectin-3 inhibition has potential benefit

GR-MD-02, a polysaccharide-based galectin-3 inhibitor from Galectin Therapeutics, has been tested in Phase 1 (NCT01899859) (n=31) [37] and Phase 2b (NCT02462967) (n=161) RCTs in NASH cirrhosis patients. In the Phase 2b NASH-CX trial, treatment every other week for 52 weeks at the 2 mg/kg IV dose led to significant improvement in the reduction of the hepatic venous pressure gradient (HVPG), but only in patients without esophageal varices (Change from baseline -9% vs +12%, P=0.01) (Galectin Therapeutics Corporate Presentation). Patients also had a reduction in portal hypertension, less collagen production and a reduction in the development of new varices. There was higher variance and less clear benefit in the patients with pre-existing esophageal varices. This suggests that galectin-3 inhibition may slow liver fibrosis. Galectin Therapeutics is planning a Phase 3 trial for NASH.

Kidney disease: Galectin-3 inhibition has potential benefit

The positive association between plasma galectin-3 levels and the risk for incident chronic kidney disease was identified as part of the ARIC study (n=9148), indicating a near linear relationship between kidney disease risk and galectin-3 at levels above 10-15 ng/mL (HR: 2.22, 95% CI 1.89 to 2.60) [38]. The effect was strongest in those with hypertension at baseline. Galectin-3 overexpression is a feature of pro-fibrotic M2-like macrophages, and macrophage secretion of galectin-3 has been found to be a key driver of kidney fibrosis in animal models [29; 39].

GCS-100, which is a formulation of Modified citrus pectin from LaJollla Pharmaceutical, was tested in a Phase 2a RCT (NCT01717248) in patients (n=121) with chronic kidney disease (LaJolla Corporate Presentation). It was tested in an IV formulation at 1.5 or 30 mg/m^2 once weekly for 8 weeks, and the 1.5 mg dose led to an improved change in the enhanced glomerular filtration rate (eGFR), with the greatest benefit seen in diabetic patients. However, in 2015, LaJolla decided to discontinue its development of galectin-3 inhibitors, including GCS-100, to focus on other priorities. Other companies are continuing to work on galectin-3 inhibitors for fibrotic disease indications.

Idiopathic pulmonary fibrosis: Galectin-3 inhibition has potential benefit

TD139, the thiodigalactoside analog that acts as a glycomimetic to inhibit galectin-3 and galectin-1, is being developed by Galecto Biotech for IPF, and has been tested in a Phase 1b/2a RCT (NCT02257177) including 36 healthy men and 24 IPF patients [40]. TD139 is formulated as an inhaled powder to facilitate lung delivery, and was shown to effectively reduce galecin-3 expression on bronchoalveolar macrophages relative to placebo at the 3 and 10 mg doses. Further studies are needed to determine, whether this offers clinical benefits.

Safety: Good safety profile in clinical trials, but currently available inhibitors are relatively weak and non-specific. Many novel galectin-3 inhibitors are currently in preclinical development.

Types of evidence:

- 7 clinical trials (GR-MD-02 in Cancer Ph1 n=9, Psoriasis Ph2 n=5, NASH Ph1 n=31, Ph2 n=161; GCS-100 in Cancer Ph2 n=24, Kidney disease Ph2a n=121; TD139 in Pulmonary fibrosis Ph1 n=60)
- Numerous laboratory studies

Several non-specific galectin-3 inhibitors have been tested in small clinical trials, and have been shown to exhibit a very good safety profile. The tested inhibitors have all been carbohydrate-based molecules, which may account for their safety and tolerability. These large molecules have extremely low cell permeability and primarily exert their effects by binding to extracellular galectin-3. Due to their low oral bioavailability, these molecules have been clinically tested in IV formulations.

GCS-100, which is an IV formulation of Modified citrus pectin, was well tolerated and did not induce grade 3 or 4 hematological toxicity or serious adverse events when used at a dose of 150 mg/m^2 for 5 days every 21 days for 5-9 months in patients with chronic lymphocytic leukemia (ages 40-86) [33]. However, two patients discontinued due to a rash that resolved upon cessation of the treatment. There were also no grade 3 or 4 adverse events at the efficacious dose of 1.5 mg/m^2 (IV once weekly for 8 weeks) in patients with chronic kidney disease (NCT01717248), although there were grade 3/4 events in the 30 mg/m^2 group, which were described as not drug related (Corporate Presentation). GR-MD-02 at 8 mg/kg lean body mass IV every other week for 24 weeks did not lead to any serious adverse events in patients with moderate to severe plaque psoriasis (NCT02407041) [41]. In a Phase 1 RCT for NASH (NCT01899859) (up to 8 mg/kg), the rate of adverse events was similar to placebo, with no differences in vital signs, ECG parameters, blood laboratory tests, renal function, lipid parameters, glucose, or urinalysis parameters [37]. Mild headache was the only adverse event that was possibly drug related. In the follow-up Phase 2 RCT for NASH (NCT02462967) (2 or 8 mg/kg every other week for 52 weeks), the drug was well-tolerated with no major safety concerns and similar numbers of adverse events across the groups (Corporate Presentation). An inhaled powder formulation of TD139 (up to 10 mg/day for 14 days) was found to be well-tolerated and did not induce any serious adverse events in a Phase 1b/2a trial (NCT02257177) in healthy men or patients with idiopathic pulmonary fibrosis (ATS Abstract).

There are no known drug-interactions with the tested galectin-3 inhibitors, and GR-MD-02 was safely used in combination with PD-1 inhibitors in metastatic melanoma patients. Since modified citrus pectin

is derived from citrus, and GR-MD-02 is derived from apple pectin, they could potentially cause allergic reactions in people allergic to these fruits.

Sources and dosing:

Modified citrus pectin is sold as a nutritional supplement by a variety of suppliers. The PectaSol-C® formulation has been the most extensively tested, and is available through numerous suppliers. A therapeutic dose has not been established, and will likely vary depending on the indication. A formulation of PectaSol-C® by ecoNugenics is currently being tested in a clinical trial for prostate cancer at a dose of 4.8 grams in 6 capsules 3X per day without food (NCT01681823). Since pectins are poorly absorbed in the gastrointestinal system and clinical trials showing potential benefits used IV formulations, it is unclear whether oral formulations would offer similar benefits. Due to their large size, pectins are not blood brain barrier penetrant. GR-MD-02 and TD139 are currently in clinical development by Galectin therapeutics and Galecto Biotech, respectively.

Research underway:

There are several companies working on developing galectin-3 inhibitors for clinical indications.

Clinical Programs:

PectaSol-C® Modified citrus pectin is being tested in a Phase 2 open label clinical trial for its effects on Prostate Specific Antigen (PSA) kinetics in men with relapsed prostate cancer (NCT01681823). The sponsor for this trial is the supplement company ecoNugenics, and it has an estimated completion date of September 2019. Preliminary results based on 46 patients found that 76% of patients achieved the primary endpoint of a lack of disease progression for 6 months [42].

Galectin Therapeutics is currently in the planning phase for a Phase 3 clinical trial for its lead clinical candidate GR-MD-02 in NASH. The trial using GR-MD-02 in combination with anti-PD-1 immunotherapy (pembrolizumab, Keytruda®) is still ongoing with an expected completion of October 2021 (NCT02575404). They are also working to develop new oral carbohydrate-based and small molecule galectin-3 inhibitors. In the Spring of 2019, they raised $47 million through rights offering and warrant exercise to use for their Phase 3 NASH trial (Press release).

Galecto Biotech is currently recruiting for a Phase 2b trial for TD139 for idiopathic pulmonary fibrosis (NCT03832946). This Swedish company raised 79 million Euros in Series C financing to use for their Phase 2/3 trial for TD139 pulmonary fibrosis, and initiate clinical studies for their other programs. Their

other galectin-3 inhibitor programs are still in preclinical development. GAL-400 is being developed for NASH, GAL-300 for cancer, and GAL-200 is for age related macular degeneration and ocular fibrosis. A preclinical study found that a topical eye formulation, GAL-200-10 could reduce corneal angiogenesis, opacity, and fibrosis in mice (ARVO Abstract).

Preclinical Programs:

Glycomimetics is developing small molecule glycomimetic antagonists of galectin-3 for fibrotic diseases and cancer, but are still in early preclinical phases. They are currently developing their clinical selectin inhibitor program.

Glycomatra is developing recombinant glycoprotein galectin-3 inhibitors designed to outcompete with the endogenous extracellular ligands for galectin-3 (picomolar affinity vs nanomolar affinity). GM100 series compounds are being developed for cancer, and one has entered the preclinical toxicology stage for prostate cancer. GM200 series compounds are being developed for liver and lung fibrosis, but are still in early discovery phases. In 2018, they received SBIR grants for the development of their galectin-3 inhibitors for metastatic prostate cancer and NASH related liver fibrosis (SBIR.gov).

G3 Pharmaceuticals is developing galectin-3 inhibitors to target the carbohydrate recognition domain and are currently in the lead optimization stage. In the Fall of 2018, they announced an exclusive license and option agreement with the Henry Ford Health System in Detroit for the development and commercialization of the galectin-3 inhibitors for diastolic heart failure (Press release).

MediaPharma is an Italian company developing monoclonal antibody-based therapeutics for cancer. Their pipeline includes MP-1959 (SP-2)-ADC, which is a non-internalizing antibody-drug conjugate consisting of a humanized version of the SP-2 monoclonal antibody against galectin-3 conjugated to cytotoxic maytansinoids. They also have MP-E-8-3/1959, which is a bi-specific humanized antibody against endosialin and galectin-3.

Search terms:

Pubmed, Google: Galectin-3, GR-MD-02, TD139, Modified citrus pectin

- Alzheimer's disease, Parkinson's disease, Stroke, Neurodegeneration, Aging, Cardiovascular, fibrosis, atherosclerosis, cancer, safety, clinical trials

Websites visited for Galectin-3 Inhibitors:

- Clinicaltrials.gov GR-MD-02, TD139, Modified Citrus Pectin
- WebMD.com Pectin
- PubChem TD139
- DrugBank.ca TD139, GR-MD-02
- Cafepharma TD139

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