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

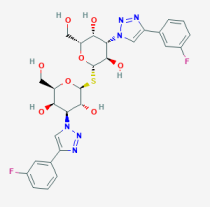
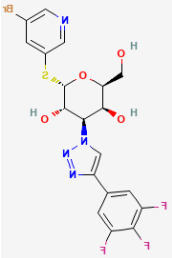
Evidence Summary

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: Galectin-3 is elevated in neurodegenerative disease in conjunction with severity. Galectin-3 can have mixed effects but appears to promote pathology in the environment of the AD brain. Novel BBB penetrant inhibitors may be needed.

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: Clinically tested inhibitors show good safety, but most are relatively weak or non-specific. Profile depends on route of administration; oral formulations show gastrointestinal effects. Many novel galectin-3 inhibitors are currently in preclinical development.

<table>
<tr>
<td>Availability:
Modified citrus pectin is OTC.
GR-MD-02, GB0139, GB1211, and TB006 are being tested in clinical trials.</td>
<td>Dose: Clinically effective dose not established. Varies by formulation and indication.
PectaSol-C®: oral
GR-MD-02: IV
GB0139: dry inhaled powder
GB1211: oral
TB006 (antibody): IV</td>
<td rowspan="2">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
GB1211: 533.3 g/mol
$C_{19}H_{16}BrF_3N_4O_4S$
 
Source: PubChem</td>
</tr>
<tr>
<td>Half-life:
GR-MD-02: 18-20 hours (IV)
GB0139: 7 hours (inhaled)
GB1211: 16 (healthy)-28 (hepatic impairment) hours</td>
<td>BBB: Varies. Clinically tested inhibitors for peripheral indications are not penetrant.</td>
</tr>
<tr>
<td>Clinical trials: GR-MD-02 has been tested in cancer (n=9; n=20), and NASH (n=31; n=162). MCP has been tested in cancer (n=24; n=59), kidney disease (n=121), and osteoarthritis (n= 50). GB0139 has been tested in idiopathic pulmonary fibrosis (n=60) and Covid-19 (n=41). GB1211 has been tested in cirrhosis (n=30). TB006 has been tested in Alzheimer's disease (n=157).</td>
<td>Observational studies: Elevated serum levels are associated with heart failure, fibrotic diseases, poor prognosis, and mortality.</td>
</tr>
</table>

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. 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 is involved in the programming of repair and wound healing mechanisms and the activation of immune cells toward a state of alternative activation. When left unchecked these mechanisms drive fibrosis, thus galectin-3 inhibitors have primarily been designed and tested to halt the progression of fibrosis in diseases characterized by fibrotic pathology. Additionally, galectin-3 is dysregulated in a variety of cancers, and galectin-3 inhibitors are being developed to augment the efficacy of cancer immunotherapy.
Galectin-3 inhibitors have been tested in clinical trials for cancer, kidney disease, liver disease, psoriasis, pulmonary fibrosis, Covid-19, and Alzheimer's disease.

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 on this compound. An oral formulation called PectaSol-C® is sold as an OTC supplement by ecoNugenics and was tested in patients with prostate cancer.
GR-MD-02, also called 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 has 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 non-alcoholic steatohepatitis (NASH). It is currently in a Phase 2/3 clinical trial for NASH.
GB0139, formerly called 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, and is being tested in a Phase 2b RCT for this indication. It has also been tested for Covid-19.
GB1211 is a galectin-3 inhibitor that showed 68% oral bioavailability in mice and >100-fold selectivity for galectin-3 over other galectins (except galectin-4C) in *in vitro* assays and is currently in clinical development by Galecto Biotech for liver cirrhosis and cancer [2].
TB006 is a humanized monoclonal antibody against galectin-3 in clinical development by True Binding for Alzheimer's disease and acute ischemic stroke.

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: Galectin-3 is elevated in neurodegenerative disease in conjunction with severity. Galectin-3 can have mixed effects but appears to promote pathology in the environment of the AD brain. Novel BBB penetrant inhibitors may be needed.

Types of evidence:

- 1 systematic review/ meta-analysis of galectin-3 expression studies in neurodegenerative disease
- 1 clinical trial for TB006 in Alzheimer's disease
- 13 observational association studies for biofluid galectin-3 levels
- Numerous laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?
Serum levels of galectin-3 have been found to be elevated in patient populations experiencing neurodegeneration and/or cognitive decline. A systematic review and meta-analysis of 17 studies including 905 participants examining galectin expression in postmortem brain tissue, plasma/serum, or cerebrospinal fluid (CSF), found that galectin-3 expression was higher in patients with neurodegenerative disease relative to healthy controls (Standardized mean difference [SMD]: 0.85, 95% Confidence Interval [CI] 0.53 to 1.18, $P < 0.00001$) [3]. Different galectins were preferentially dysregulated in different types of neurodegenerative disease, such that the rise of galectin-3, was most prominent in the content of Alzheimer's disease (AD) (SMD: 0.64, 95% CI 0.45 to 0.83, based on six studies) and Parkinson's disease (PD) (SMD: 0.58, 95% CI 0.28 to 0.88, based on two studies). The rise in galectin-3 levels is generally indicative of increased inflammation, and associated with worse prognosis.

Alzheimer's disease: 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 ng/mL vs 5.27 ± 1.91 ng/mL; P = 0.017) [4]. The study also found a significant correlation between cognitive impairment based on Mini-Mental State Examination (MMSE) score and galectin-3 levels (r = 0.341; P <0.001). A separate study in Turkey comparing serum galectin-3 levels also found an elevation in AD patients (n=57) relative to controls (n=61) (mean 238.524 ± 160.17 pg/mL vs. 178.001 ± 8.329 pg/mL; P = 0.003) [5]. The level of galectin-3 increased in a stepwise manner with increasing disease severity (Stage 1: 193.623 ± 100.423 pg/mL vs. Stage 3: 391.83 ± 35.977 pg/mL). Within the CSF, galectin-3 levels were increased in AD patients (n=119), relative to controls (n=36) (1168.8 pg/mL vs 960.5 pg/mL). In this study, the association between galectin-3 and MMSE did not persist following adjustment for age, sex, and education [6]. The elevation in galectin-3 was associated with other neuroinflammatory mediators in the CSF, including sTREM2, GFAP, and YKL-40. Additionally, the increase in galectin-3 showed a stronger association with tau and synaptic markers than with amyloid, suggesting that the rise in galectin-3 may be indicative of neuronal damage.

Parkinson's disease: 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 pg/mL vs 892.9, 95% CI 168.2 to 2416.3 pg/mL; P<0.01) [7]. 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. Similar trends have been shown in subsequent studies. Another study in Turkey found that serum levels of galectin-3 were higher in patients with idiopathic PD (n=48) relative to controls (n=63) (413.38 ± 313.93 pg/mL vs 198.63 ± 139.07 pg/mL; P < 0.001), and that the levels increased along with disease progression (Stage 1: 125.1 ± 14.3 pg/mL vs. Stage 3: 778.8 ± 328.6 pg/mL) [8]. A study in Taiwan also found that plasma galectin-3 levels were higher in patients with PD (n=56) relative to controls (n=46) (9.93 ± 3.94 ng/mL vs 8.39 ± 1.95 ng/mL), and that levels were positively associated with Hoehn and Yahr stages (R^2 = 0.218, P < 0.001) [9].

Amyotrophic lateral sclerosis: 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 [10]. In a separate study, galectin-3 levels in the serum and CSF were also found to be elevated in ALS patients (10.45 ± 3.48 ng/mL and 7.92 ± 2.56 ng/mL, respectively) (n=19) relative to controls (8.76 ± 3.03 ng/mL and 5.19 ± 2.23 ng/mL, respectively) (n=50) [11].

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=3,082), 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) [12]. 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 [13]. In the REGARDS cohort of ischemic stroke patients in the Southern US (n=1,001), 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 the Q1; P trend = 0.003) [14]. 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) [15]. 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). Blood galectin-3 levels ≧ 9 ng/mL were also found to be associated with the development of atrial fibrillation after stroke (OR: 3.10, 95% CI 1.03 to 9.254) [16].

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) [17]. 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=5,675) of elderly individuals (age 70-82) at risk for cardiovascular disease [18]. 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:

The humanized monoclonal galectin-3 antibody TB006 developed by the biotech True Binding, has been tested in a Phase 1b/2 (NCT05074498) proof-of-concept clinical trial in patients with mild to severe AD (n=157). Inclusion criteria used clinically diagnosed AD based on a baseline MMSE of less than 24 (range

2-24), but did not require evidence of amyloid positivity. Topline results were presented at the Clinical Trials in Alzheimer's Disease 2022 annual conference (Company release) (Company presentation). The Phase 1b (n=25) included doses of 140 mg, 420 mg, or 1,000 mg for one month, while the Phase 2 (n=132) portion used a dose of 1,000 mg for one month. Patients were treated with five weekly IV infusions of TB006 or placebo over the course of one month and were followed for an additional 2.5 months. The primary outcome was the Clinical Dementia Rating-Sum of Boxes (CDR-SB). There was a trend (P=0.08) toward improvement with TB006 relative to placebo on the CDR-SB (change of -0.44 points) at the end of the follow-up period (day 104). A reduction in plasma Aβ42 levels was also observed with TB006. An open-label extension of the Phase 2 study (n=180) is currently ongoing (NCT05476783). In this study, TB006 is administered at a dose of 4,000 mg as an IV infusion over the course of one hour every 28 days. Based on available data, it is unclear whether appreciable levels of TB006 reach the brain, or whether its action is primarily peripheral. As an antibody, TB006 is expected to target extracellular galectin-3, though it is unclear whether it has preferential action on particular cell types and/or shows preferential disruption of particular galectin-3 interactions.

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

Alzheimer's disease: POTENTIAL BENEFIT FOR GAL3 INHIBITION
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 [19]. Galectin-3 positive microglia have also been associated with neurons containing tau inclusions in human postmortem brain tissue [6]. Galectin-3 has been identified as a marker of disease associated microglia (DAM), and microglial neurodegenerative phenotype (MGnD) in AD models [20]. However, these terms are likely too broad, in that they contain multiple subpopulations of microglia, which could be protective or deleterious depending on the stage of disease, and neural microenvironment. This would explain why studies have found that depending on the marker used, the removal of these populations has been demonstrated to be beneficial or harmful in different models [21]. Broadly, galectin-3 is involved in the activation of microglia and astrocytes with an alternative activated phenotype, that has enhanced phagocytic capacity [20]. As such, galectin-3 positive glia are found in white matter in response to myelin damage to facilitate the removal of myelin debris. This may also explain the association of galectin-3 positive cells with plaques. Additionally, galectin-3 has been found to promote lysosomal repair mechanisms and an unconventional secretory autophagy pathway [22]. Galectin-3 acts as an endogenous ligand for toll-like receptors (TLRs) including TLR2 and TLR4, which are involved in mediating the inflammatory response to endotoxins, such as LPS, and thus plays a role in the immune response to pathogens [23]. Under

physiological conditions, these activities are expected to be neuroprotective. However, under pathological conditions, these activities may instead exacerbate neuronal damage by facilitating the removal of stressed but viable neurons, promote the secretion and cell transfer of pathogenic misfolded proteins, and drive chronic pro-inflammatory signaling. With respect to galectin-3, context is vitally important [24]. The vast majority of studies in AD models suggest that the environment of the AD brain produces conditions where galectin-3 activity is primarily deleterious. Due to the pleiotropic nature of galectin-3 activity, depending on its localization and binding partner, it will be important to gain a clear understanding of which pathways are most negatively impacted by galectin-3 in AD, in order to develop targeted inhibitors that disrupt these interactions while preserving interactions that may be beneficial. Galectin-3 may be detrimentally elevated in AD, in part, due to a documented alteration in the sialyation pattern of glycoproteins and glycolipids in the brain [25]. Since galectin-3 binds to sugar molecules, changes into the sugar molecules found on its prospective interacting partners can profoundly influence the activity of galectin-3. Sialic acid is a monosaccharide that is enriched in the CNS. When present, sialic acid can cover up the binding sites for galectin-3. The removal of sialic acid (de-sialylation) can trigger the binding of galectin-3, resulting in immune system activation and increased phagocytosis. It is important to maintain the proper balance between these processes. In the AD brain, protein sialyation has been found to be decreased, resulting in increased galectin-3 activity. This occurs in conjunction with the dysregulation of de-sialyating enzymes (neuraminidases). The dysregulation of the lysosomal neuraminidase, Neu1, may promote the accumulation of pathological Aβ in lysosomes [26], resulting in lysosomal membrane damage, which may then trigger the induction of galectin-3 mediated secretory autophagy [22; 27]. This could then result in the release of Aβ, as well as Neu1 [28]. This extracellular Neu1 could then improperly change the sialyation pattern of neighboring cells. Meanwhile, changes in the sialyation of TLRs could result in their chronic activation and inflammation [25]. Additionally, post-translational modifications to galectin-3 can alter its binding activity [29], such that galectin-3 may itself be differentially modified in AD. The cell type and activation status of the cell may influence the modification profile of galectin-3, such that the galectin-3 secreted from pathogenically activated glia in AD may induce further pathology [30], whereas galectin-3 secreted from other cell types, such as mesenchymal stem cells [31], may be modified in a manner that is neuroprotective.

Similar to human postmortem brain tissue, galectin-3 has also been found to be upregulated and localized to plaque-associated microglia in the 5XFAD and APP/PS1 AD mouse models [19; 30]. 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-β3 signaling. The overexpression of galectin-3 was found to impair fear memory formation in rats, which was mediated through the inhibition of integrin signaling [32]. Galectin-3 was shown to disrupt the cellular dynamics of hippocampal neurons, resulting in impaired gamma oscillation power and rhythmicity, similar to what is seen in the presence of Aβ [33]. 5XFAD mice lacking galectin-3 exhibited normal gamma oscillations, and in hippocampal slices, treatment with the galectin-3 inhibitor TD139 prevented the Aβ-induced impairment of these gamma oscillations. In the APP/PS1 model, galectin-3 levels increased in conjunction with the degree of Aβ oligomerization, and microglia-secreted galectin-3 directly interacted with Aβ [34]. In contrast, secreted galectin-3 was identified as the mediator of neuroprotection following ventricular administration of human umbilical cord blood-derived mesenchymal stem cells (hUCB-MSCs) into six-month-old 5XFAD mice [31]. Treatment with the hUCB-MSCs reduced tau aggregation and tau phosphorylation at the thr181, and ser404 residues. The effect was driven by the galectin-3 associated reduction in GSK3β activity.

TREM2 is another DAM signature protein, but it has been associated with neuroprotection. The loss of TREM2 leads to a decrease in plaques and plaque-associated microglia, but this ultimately leads to an exacerbation of neuronal damage as the animals age [35]. Galectin-3 has been shown to act as an endogenous ligand for TREM2, and inducer of TREM2-Dap12 signaling [19; 30], but it is unclear how this interaction impacts AD progression. This highlights the potential mixed roles for galectin-3, such that the effects of a galectin-3 inhibitor may depend on which interactions it preferentially alters.

Parkinson's disease: POTENTIAL BENEFIT FOR GAL3 INHIBITION (Preclinical)

Galectin-3 was shown to play a role in driving inflammation in microglia in response to alpha-synuclein aggregates [36]. Knocking down galectin-3 could reduce the alpha-synuclein induced microglial expression of pro-inflammatory mediators (iNOS, IL-1β, IL-12). In cell culture, galectin-3 was found to be involved in coordinating the cellular autophagic response following lysosomal damage [22]. Galectin-3 plays a role in the recruitment of autophagic proteins to damaged lysosomal membranes which facilitates an autophagic secretory pathway. In induced pluripotent stem cell (iPSC) derived midbrain dopamine neurons, the induction of this pathway could promote the secretion of alpha-synuclein fibrils, and contribute to the intercellular propagation of alpha-synuclein pathology.

ALS: POTENTIAL HARM FOR GAL3 INHIBITION (Preclinical)

In contrast to models of other neurodegenerative diseases, such as AD and PD, galectin-3 inhibition is association with worse outcomes in mouse models of ALS. Galectin-3 expression was found to be increased (~12 fold) in the spinal cords of patients with sporadic ALS [37]. In the SOD^{G93A} model, mice

lacking galectin-3 (Gal3-/-) showed increased oxidative damage and faster rates of disease progression [37]. This suggests that galectin-3 may be playing a neuroprotective role in motor neurons. In the SOD^{G37R} and SOD^{G93A} mouse models, the calcium activity of perisynaptic Schwann cell at the neuromuscular junction was found to be dysregulated [38]. Relative to wildtype mice, the Schwann cells from ALS mice failed to upregulate galectin-3 in response to a denervating injury. The upregulation of galectin-3 is important for the Schwann cells to adopt a phagocytic phenotype and participate in debris clearance and facilitate repair. This suggests that galectin-3 may play divergent roles in ALS, depending on the cell type.

Stroke: MIXED EFFECTS FOR GAL3 INHIBITION (Preclinical)
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 highlight 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 middle cerebral artery occlusion (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 [39], while recombinant intracerebroventricular galectin-3 was neuroprotective and decreased lesion size [40]. 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 [41]. These effects stem from the ability of galectin-3 to modulate the secretory profile, morphology, and migration of microglia [42]. 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. Additionally, the neuroprotective effects may be related to the activation of growth and repair mechanisms that are part of galectin-3's role in healing and remodeling, such as angiogenesis and neurogenesis [43].

Traumatic brain injury: POTENTIAL BENEFIT (Preclinical)
In the controlled cortical impact mouse model of traumatic brain injury (TBI), 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 [44]. 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.

Glaucoma: POTENTIAL BENEFIT FOR GAL3 INHIBITION (Preclinical)
In contrast to AD, the ApoE4 allele is associated with decreased risk for glaucoma. ApoE and galectin-3 were found to be upregulated in the retinas of glaucoma patients as well as in mouse models of glaucoma (DBA/2J and microbead) [45]. In the mouse models, loss of ApoE or the presence of the ApoE4 allele prevented the upregulation of galectin-3 in retinal microglia, and ApoE4 glaucoma patients showed lower retinal levels of galectin-3, relative to those with ApoE3. Intravitreal injection with the galectin-3 inhibitor TD139 protected against retinal ganglion cell loss in mouse models. These studies suggest that retinal targeted galectin-3 inhibitors may be protective against glaucoma, particularly in non-ApoE4 carriers.

APOE4 interactions: Not established.

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:

- 11 clinical trials (GR-MD-02 in cancer Ph1 n=9, n=20, NASH Ph1 n=31, Ph2 n=162; GCS-100 in Cancer Ph2 n=24, kidney disease Ph2a n=121; GB0139 in pulmonary fibrosis Ph1 n=60, Covid-19 Ph1/2 n=41, GB1211 in cirrhosis Ph1/2 n=30, MCP in cancer n=59, osteoarthritis n=50)
- 18 observational association studies of serum galectin-3 levels
- Numerous laboratory studies

Longevity: LOW GAL3 IS ASSOCIATED WITH HEALTHY 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 ng/mL 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) [46].

Heart failure: ELEVATED GAL3 IS ASSOCIATED WITH WORSE PROGNOSIS
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 12 biomarkers associated with heart failure in four longitudinal community-based cohorts (n=22,756), galectin-3 had a modest association with overall heart failure (Hazard Ratio [HR]: 1.07, 95% CI 1.02 to 1.12) [47]. In the large longitudinal PREVEND Caucasian cohort study (n=7,968), serum galectin-3 levels correlated with 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 [48]. **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) [49]. 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) [50]. 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) [51], and was not significantly associated with heart failure in the Cardiovascular Healthy Study (n=5,277) which included African Americans (14.7%) [47]. 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 [52]. Elevated galectin-3 was found to be associated with thrombus formation. Plasma galectin-3 levels were positively correlated with collagen-induced platelet aggregation in platelet rich plasma from patients with coronary artery disease (n=182) [53]. This thrombotic effect could be inhibited by treatment with the galectin-3 inhibitor TD139. Periodontitis, gum disease, has been associated with increased risk for heart disease. A biomarker study (NCT04564950) including 155 participants found that serum galectin-3 levels were elevated in patients with periodontitis (7.2, 95% CI 6.8 to 7.6 ng/ml), coronary heart disease (6.4, 95% CI 5.9 to 6.5 ng/ml), or both (7.4, 6.9 to 7.9 ng/ml), relative to controls (5.6, 95% CI 5.3 to 5.9 ng/ml) [54]. The increase in galectin-3 with periodontitis may be indicative of a systemic inflammatory response.

A normal reference range for serum galectin-3 was established in a clinical observational study with healthy volunteers (n=1,092), 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 [55]. 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 [56]. 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: POTENTIAL BENEFIT FOR GAL3 INHIBITORS (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 [56]. However, preclinical rodent studies have been conflicting regarding the role of galectin-3 in atherosclerotic plaque development and stability [57]. 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% [57]. 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. In ApoE-/- mice eating high fat diet, a model of atherosclerosis, an increase in plasma galectin-3 levels was found to be associated with increased platelet activation/aggregation [53]. Treatment with the galectin-3 inhibitor TD139 protected these mice against thrombus formation and occlusion following induction of vascular injury with $FeCl_3$.

Obesity: POTENTIAL BENEFIT FOR GAL3 INHIBITORS (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 PPAR [58; 59]. Male galectin-3 knockout mice were found to have less white adipose tissue following consumption of a high-fat diet [59]. 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 [58]. This suggests that galectin-3 plays a role in adipose tissue remodeling in the context of obesity.

Cancer: POTENTIAL BENEFIT FOR GAL3 INHIBITORS IN CANCER-TYPE DEPENDENT MANNER
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 [60]. Six patients had a partial response, but development of GCS-100 has been discontinued.
Modified citrus pectin, supplied as Petasol-C® from ecoNugenics (4.8 grams 3X/day), was tested in a Phase 2 open label trial in 59 patients with non-metastatic biochemically relapsed prostate cancer (NCT01681823) for six months plus a 12 month extension for patients without disease progression [61]. At six months, 78% showed a response to therapy based on decreased or stable prostate specific antigen (PSA) (58%), or improvement of PSA doubling time (PSADT) (75%), and negative radiological scans. There was a favorable change in PSADT risk grouping in 27% of patients, and only 5% of patients showed meaningful disease progression on PSA and radiological measures over the course of the study. Since there was no comparator group in this study, the treatment effect is unclear.

GR-MD-02, which is a polysaccharide polymer from Galectin Therapeutics, was tested in combination with anti-PD-1 therapy (pembrolizumab (200 mg IV every three weeks for five cycles) in patients with metastatic melanoma (n=14) or head and neck squamous cell carcinoma (HNSCC) (n=6) (NCT02575404) in an open label trial [62]. Objective responses at day 85 were observed in 50% (7/14) of patients with metastatic melanoma and 33% (2/6) of patients with HNSCC (2/6). High baseline galectin-3 expression in the tumor coupled with high PD-1 expression on CD8 T cells was associated with treatment response. Responders showed a significant expansion of effector memory CD8+ T cells, increased proliferation of effector memory T-cells, and a reduction in monocytic myeloid-derived suppressor cells. Further testing is needed to determine if the addition of the galectin-3 inhibitor provides a sustained clinically meaningful benefit.

GB1211 is an orally bioavailable galectin-3 inhibitor being developed by Galecto Biotech [2]. It is currently being tested in an open label study followed by a randomized, double-blind, placebo-controlled, parallel group and an extension study in combination with atezolizumab in patients with non-small cell lung cancer (NSCLC) (NCT05240131). GB1211 is being tested at doses of 200 mg and 400 mg BID. The study is designed to test the safety and efficacy of this combination.

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 [63]. 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 [64]. Galectin-3 may drive the expansion of M2-like tumor associated macrophages which inhibits tumor immunosurvelliance [65].

However, its effects 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, elevated nuclear galectin-3 is associated with worse prognosis in renal cell carcinoma [64]. 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): POTENTIAL BENEFIT FOR GAL3 INHIBITORS
GR-MD-02, a polysaccharide-based galectin-3 inhibitor from Galectin Therapeutics, has been tested in Phase 1 (NCT01899859) (n=31) [66] and Phase 2b (NCT02462967) (n=162) RCTs in NASH cirrhosis patients. In the Phase 2b NASH-CX trial, patients with NASH with cirrhosis and portal hypertension, defined as hepatic venous pressure gradient (HVPG) ≥ 6 mm Hg were treated via IV infusion every other week for 52 weeks at doses of 2 mg/kg or 8 mg/kg [67]. At the end of the study, there were no significant differences in the least-squares mean change in HVPG across the study arms. However, there was a significant reduction in the 2 mg/kg dose in a preplanned subgroup analysis of patients without esophageal varices (–1.61 mm Hg) relative to placebo (0.40 mm Hg), though the reduction was not significant at the 8 mg/kg dose (–0.28 mm Hg). This subgroup also showed a reduced risk of developing new varices relative to the placebo (0% vs 18%). There was no significant effect of treatment in patients with varices. Histologically, there were no significant improvements on change from baseline in collagen proportion area, NAFLD activity score, lobar inflammation, or steatosis, though there was a reduction in hepatocyte ballooning at the 2 mg/kg dose (OR: 2.42, 95% CI 1.09 to 5.37; P = 0.030). There were no significant differences in the median time to complications of cirrhosis across the groups. Based on the

results of this study, GR-MD-02 is currently being tested in a Phase 2b/3 RCT in (estimated 1,010) patients with NASH cirrhosis and clinical signs of portal hypertension but without esophageal varices at baseline at IV doses of 2 mg/kg and 4 mg/kg every other week for 78 weeks (NCT04365868).

The orally bioavailable galectin-3 inhibitor from Galecto Biotech, GB1211, is currently being tested in the three part Phase 1b/2a GULLIVER-2 (NCT05009680) clinical trial which will evaluate the safety and pharmacokinetics of GB1211 in patients with decompensated cirrhosis and moderate to severe hepatic impairment (Child-Pugh Classes B and C) and matched healthy participants. The study will also include a placebo controlled RCT assessing the impact of GB1211 100 mg orally twice daily for 12 weeks on safety and liver outcomes in 30 patients with cirrhosis. Topline results were presented at the American Association for the Study of Liver Diseases 2022 annual meeting [68]. GB12111 showed evidence of target engagement, via a reduction in galectin-3 levels. Markers of liver damage, including the liver enzymes alanine aminotransferase (ALT) (mean -58.44%, 95% CI -79.00 to -37.88), aspartate aminotransferase (AST) (mean-32.40, 95% CI -51.63 to -13.17), and gamma-glutamyl transferase (GGT) (mean -37.77, 95% CI -69.47 to -6.06) decreased with GB1211 treatment relative to placebo, with progressive improvement. Improvements in liver stiffness (mean change from baseline −9.66 ± 22.52 kPa vs. −7.62 ±11.34 kPa) and the controlled attenuation parameter (−20.23 ±42.81 dB/m vs 4.13 ±63.35 dB/m) were also seen with GB1211 treatment at week 12 relative to placebo. The model for end-stage liver disease score was also reduced with GB1211.

Kidney disease: ELEVATED GAL3 IS ASSOCIATED WITH RISK FOR RENAL FIBROSIS
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=9,148), 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) [69]. 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 [56; 70].
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: POTENTIAL BENEFIT FOR INHALED GAL3 INHIBITORS
TD139, the thiodigalactoside analog that acts as a glycomimetic to inhibit galectin-3 and galectin-1, is being developed by Galecto Biotech for idiopathic pulmonary fibrosis (IPF), and has been tested in a Phase 1b/2a RCT (NCT02257177) including 36 healthy men and 24 IPF patients [71]. TD139 is formulated as an inhaled powder and administered via a dry powder inhaler to facilitate lung delivery, and was shown to effectively reduce galecin-3 expression on bronchoalveolar macrophages relative to placebo at the 3 mg (−38.66%. 95% CI −69.59 to −7.73%) and 10 mg (−44.63%, 95% CI −80.44 to −8.81%) doses. The change in galectin-3 lung macrophage expression was correlated with changes in plasma biomarkers of inflammation and fibrosis, including PDGF-BB, plasminogen activator inhibitor, galectin-3, CCL18 and YKL-40, in the 10 mg dose group. Further studies are needed to determine, whether this offers clinical benefits. Inhaled TD139, now called GB0139, is currently being tested at a dose of 3 mg/day for 52 weeks in a Phase 2b RCT (n=426) in patients with IPF (NCT03832946).

Arthritis: ELEVATED GAL3 IN RHEUMATIC DISEASES, BUT NO CLEAR BENEFIT FOR TESTED GAL3 INHIBITORS
Serum galectin-3 levels were assessed in a cohort of patients with different rheumatic diseases (n=179) [72]. Relative to controls (9.45 ng/mL), levels of serum galectin-3 were significantly elevated in patients with rheumatoid arthritis (18.75 ng/mL), systemic sclerosis (19.4 ng/mL), and systemic lupus erythematosus (19.2 ng/mL). Based on receiver operating characteristic (ROC) analysis, serum galectin-3 levels exhibited good utility as a diagnostic biomarker for rheumatoid arthritis (AUC= 0.911).
A pilot placebo-controlled clinical trial (NCT02800629) tested oral modified citrus pectin (4g twice per day) for 12 weeks in patients with osteoarthritis (n=50) [73]. By the end of study, there were no significant changes in osteoarthritis severity, based on WOMAC-Knee and RAPID-3 scores, pain, or galectin-3 levels following treatment. The lack of response may have been related to the low baseline levels of serum galectin-3 in this cohort, which were 6.31 ng/mL and 6.51 ng/mL in the modified citrus pectin-treated and placebo-treated groups, respectively. However, it remains to be established whether modified citrus pectin, or treatment with a different galectin-3 inhibitor would have a beneficial effect on arthritis symptoms in patients with high baseline levels of galectin-3.

Covid-19: ELEVATED GAL3 IS ASSOCIATED WITH WORSE PROGNOSIS
Circulating galectin-3 levels have been evaluated as a potential prognostic biomarker for Covid-19 severity. One retrospective observational study including 156 participants found that patients with plasma galectin-3 levels greater than 35.3 ng/mL was associated with a higher risk for 30-day mortality (HR: 1.027, 95% CI 1.003 to 1.051) [74]. These patients also tended to have elevated levels of the

inflammatory markers CRP and IL-6. A study including 78 patients with severe Covid-19 and 40 controls found that serum galectin-3 levels were associated with Covid-19 mortality (OR: 2.135, 95% CI 1.076 to 4.236) [75]. While elevated in Covid-19 patients in general, levels were highest in non-survivors (3.9 ± 1.3 ng/mL), relative to survivors (2.9 ± 0.9 ng/mL), or controls (1.7 ± 0.3 ng/mL). A study of 280 patients with Covid-19 found that serum and peripheral blood mononuclear cell (PBMC) galectin-3 levels progressively increased with the stage of disease severity and that elevated galectin-3 was associated with higher levels of proinflammatory cytokines [76]. Galectin-3 serum levels over 38.76 ng/mL were also associated with increased risk for Covid-19-related pneumonia (OR: 1.087) [77]. Similar associations between galectin-3 and severe outcomes for Covid-19 have been reported in a variety of other observational studies [78; 79]. Although, these observational biomarker studies do not indicate whether galectin-3 plays a causal role in disease severity, they suggest that elevated galectin-3 is indicative of an inflammatory environment which drives poor outcomes.

The inhaled thiodigalactoside galectin-3 inhibitor GB0139, formerly known as TD139, was tested in a Phase 1b/2a RCT (NCT04473053) as an add-on therapy for patients hospitalized with Covid-19 pneumonitis (n=41) [80]. GB0139 was administered at a dose of 10 mg via a dry powder inhaler (Plastiape; Berry Bramlage) twice daily during the first 48 hours of hospitalization and then once daily for up to 14 days in combination with standard of care treatment. Circulating levels of GB0139 were within range of what was seen following use of GB0139 in IPF patients, and treatment was associated with a reduction in circulating galectin-3 levels. GB0139 treated patients showed a greater rate of decline of the inflammatory biomarkers CRP and YKL-40, as well as an increase in platelet count. However, this trial was not powered to determine efficacy, and there were no significant differences in patient outcomes or mortality between the groups.

Safety: Clinically tested inhibitors show good safety, but most are relatively weak or non-specific. Profile depends on route of administration; oral formulations show gastrointestinal effects. Many novel galectin-3 inhibitors are currently in preclinical development.

Types of evidence:

- 11 clinical trials (GR-MD-02 in cancer Ph1 n=9, n=20, psoriasis Ph2 n=5, NASH Ph1 n=31, Ph2 n=162; GCS-100 in cancer Ph2 n=24, kidney disease Ph2a n=121; GB0139 in pulmonary fibrosis Ph1 n=60, Covid-19 Ph1/2 n=41, GB1211 in cirrhosis Ph1/2 n=30, MCP in cancer n=59)
- 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, most of these molecules have been clinically tested in IV formulations, however, newer compounds with better oral bioavailability are starting to be tested in the clinic, such as GB1211 [2].

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) [60]. However, 2 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).

PectaSol-C®, an oral supplement formulation of modified citrus pectin, was tested in an open label trial in patients with prostate cancer at a dose of 4.8 grams 3x/day (NCT01681823) [61]. Twenty percent (12/56) of patients experienced grade 1 transient bloating that resolved without discontinuation. This is consistent with reports of abdominal cramps and diarrhea with the use of modified citrus pectin supplements (CancerResearchUK).

GR-MD-02 was found to be well-tolerated at a dose of 2 mg/kg lean body mass IV every other week for 52 weeks in a Phase 2 RCT for NASH (NCT02462967) [67]. The majority of treatment-emergent adverse events (TEAE) were grade 1 or 2, and included infections and infestations, gastrointestinal disorders, and musculoskeletal and connective tissue disorders. TEAEs requiring study discontinuation occurred in three participants, all at the 8 mg/kg dose, and included spasmodic cough, which was possibly drug-related, and esophageal variceal bleeding, which was not considered drug-related. Additionally, at the 2 mg/kg dose, there were no apparent treatment-related effects in the clinical laboratory, vital sign, physical examination, or 12-lead ECG results. 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) [81]. 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 [66].

GB0139 (formerly TD139) is an inhaled powder formulation which was found to be well-tolerated in single doses up to 50 mg in healthy men and multiple doses of 10 mg/day for 14 days in patients with IPF in a Phase 1b/2a trial (NCT02257177) [71]. Two TEAEs were considered possibly related to the drug, including diarrhea and dysgeusia/oropharyngeal pain. In a Phase 1b/2a clinical trial (NCT04473053) in patients with Covid-19, GB0139 at 10 mg/day for up to 14 days was not associated with any treatment-related serious adverse events [80]. There were five adverse events considered possibly related to the drug, including an isolated instance of prolonged corrected QT interval on ECG with no arrhythmia that resolved spontaneously, nausea, sore throat, oral thrush, and hair loss, which were all of mild severity.

GB1211 is an oral drug currently being tested in a three-part Phase 1b/2a trial for patients with cirrhosis of the liver (NCT05009680). Topline results based on 30 patients indicates that there were equal numbers of TEAEs between the GB01211 100 mg BID and placebo arms (Corporate presentation). Adverse events with GB1211 included infection, blood loss anemia, increased blood urea, increased blood creatinine, and pruritus. There were no adverse changes in standard safety laboratory parameters, including bilirubin, albumin, or the international normalized ratio. The half-life of the drug was found to be extended 35% with repeated dosing in patients with hepatic impairment relative to healthy subjects, leading to a three-fold steady-state accumulation for Child-Pugh B patients relative to a two-fold accumulation in healthy subjects. GB1211 was tested in an oral capsule formulation in a Phase 1 single ascending dose (5 to 400 mg) and multiple ascending dose (50 and 100 mg BID) study in healthy subjects (n=78) (NCT03809052). There were no serious adverse events. TEAEs considered possibly related to GB1211 included constipation, diarrhea, dry mouth, dyspepsia, abdominal pain, headache, rash, irregular menstruation, pollakiuria, and dysuria.

TB006 is a monoclonal antibody, and treatment up to 1,000 mg weekly administered via IV infusion for one month was found to be safe and well-tolerated in patients with AD in a Phase 1b/2 trial (NCT05074498) (Corporate Presentation). The rates of treatment-related adverse events were 6.3% for TB600 vs. 0% for placebo. These include four grade 1 adverse events, dizziness, phlebitis, and two infusion reactions. There were no treatment-related serious adverse events. In a Phase 1 single ascending dose trial in healthy volunteers, IV doses up to 5,000 mg were found to be safe and well-tolerated. Adverse events including headache, were generally mild, and not dose dependent. There were no significant findings related to vital signs, laboratory tests, or ECG parameters. A six-month GLP toxicology study found that doses up to 150 mg/kg were safe in cynomolgus monkeys.

Drug interactions: 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. Pectin is known to interfere with the absorption of beta-carotene, as well as the medications, digoxin, statins, and tetracycline antibiotics (WebMD). Since modified citrus pectin is derived from citrus, and GR-MD-02 is derived from apple pectin, people with allergies to these fruits should first consult a medical professional.

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 was 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, which has an IV formulation, is currently in clinical development by Galectin Therapeutics for NASH at doses of 2 mg/kg and 4 mg/kg every other week. GB0139 has an inhaled formulation and is in clinical development for idiopathic pulmonary fibrosis by Galecto Biotech, at doses of 3 mg/day and 10 mg/day. GB1211 has an oral formulation and is in clinical development for liver cirrhosis at doses of 100 mg BID and non-small cell lung cancer at doses of 200 mg and 400 mg BID by Galecto Biotech. TB006 is a monoclonal antibody administered via IV infusion at doses of 1,000 mg/week or 4,000 mg/month being developed for Alzheimer's disease by True Binding.

Research underway:

There are several companies working on developing galectin-3 inhibitors for clinical indications, as well as novel galectin-3 inhibitors with improved pharmacokinetic properties. A recent patent review noted that major pharma companies are shifting toward monosaccharide-based inhibitors, as opposed to polysaccharide-based inhibitors, such as TD139, which are difficult to synthesize [82]. Small molecule heterocyclic compounds would be preferred; however, their development is still in early phases.

Clinical Programs:

Galectin Therapeutics has an ongoing Phase 2b/3 clinical trial for its lead clinical candidate GR-MD-02 in NASH. They are also working to develop new oral carbohydrate-based and small molecule galectin-3 inhibitors.

Galecto Biotech is currently testing GB0139 in a Phase 2b trial for idiopathic pulmonary fibrosis (NCT03832946). They also have Phase 1/2 clinical trials underway for their oral galectin-3 inhibitor GB1211 in liver cirrhosis (NCT05009680) and in non-small lung call cancer in combination with atezolizumab (NCT05240131). GB1211 will also be tested in metastatic melanoma and HNSCC in combination with pembrolizumab, likely starting in 2023. The company is also developing an oral LOXL-2 inhibitor, GB-2064, which is being clinically tested in patients with myelofibrosis (NCT04679870).

True Binding is testing their galectin-3 monoclonal antibody, TB006 in a Phase 2b open-label extension trial in patients with Alzheimer's disease (NCT05476783). They are also testing TB006 in Phase 2 RCT in patients with acute ischemic stroke (NCT05156827).

Preclinical Programs:

Glycomimetics is developing small molecule glycomimetic antagonists of galectin-3 for fibrotic diseases and cancer, but are still in early preclinical phases. In March 2022, they announced the selection of a lead candidate galectin-3 inhibitor, GM-2093, which was reported to have high affinity and selectivity for galectin-3 along with 30% oral bioavailability (Company filing). The company is testing their E-selectin inhibitor, uproleselan (GM-1271) in several clinical trials for acute myeloid leukemia (Clinicaltrials.gov). A separate E-selectin antagonist, GM-1687 is being developed for sickle cell disease.

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 biologics are being developed for cancer and fibrosis, compounds for metastatic prostate cancer and liver fibrosis/NASH are entering IND enabling phases, while compounds for breast cancer and lung fibrosis are in earlier stages of development. The GM300 series of small molecules being developed for metastatic colorectal cancer are in preclinical development.

G3 Pharmaceuticals is developing galectin-3 inhibitors for renal and heart failure to target the carbohydrate recognition domain and according to their website they are currently in the lead optimization stage.

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.

MandelMed is a private biotech company based in California that is developing a dominant-negative protein inhibitor of galectin-3, MM-003, for cardiac fibrosis and liver fibrosis. It is currently in preclinical development.

Search terms:

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

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

Websites visited for Galectin-3 Inhibtiors:

- 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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