**Eliezer Zomer Ph.D.**
Vice President
Drug Discovery and
Manufacturing
**Galectin**
**Therapeutics**

# Galectin Therapeutics, Inc.

# Galectin Sciences, LLC

**Therapeutics for Chronic Fibrotic Diseases**

- The next generation of Galectin-3 inhibitors: from R&D through to phase III clinical trials
- Discovery of functional allosteric inhibitors

# FORWARD LOOKING STATEMENTS

This presentation contains, in addition to historical information, forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. These statements relate to future events or future financial performance and use words such as “may,” “estimate,” “could,” “expect” and others. They are based on our current expectations and are subject to factors and uncertainties that could cause actual results to differ materially from those described in the statements.

These statements include those regarding potential therapeutic benefits of our drugs, expectations, plans and timelines related to our clinical trials, supporting activities, potential partnering opportunities and estimated spending for 2019 and beyond. Factors that could cause our actual performance to differ materially from those discussed in the forward-looking statements include, among others, our trials and supporting CMC information may not lead to positive outcomes or regulatory approval.

We may experience delays in our trials, which could include enrollment delays. Future phases or future clinical studies may not begin or produce positive results in a timely fashion, if at all, and could prove time consuming and costly. Plans regarding development, approval and marketing of any of our drugs are subject to change at any time based on the changing needs of our company as determined by management and regulatory agencies. Strategies and spending projections may change. We may be unsuccessful in developing partnerships with other companies or obtaining capital that would allow us to complete our clinical trials or further develop and/or fund any future studies or trials.

To date, we have incurred operating losses since our inception, and our future success may be impacted by our ability to manage costs and finance our continuing operations. For a discussion of additional factors impacting our business, see our Annual Report on Form 10-K for the year ended December 31, 2018, and our subsequent filings with the SEC. You should not place undue reliance on forward-looking statements. Although subsequent events may cause our views to change, we disclaim any obligation to update forward-looking statements.

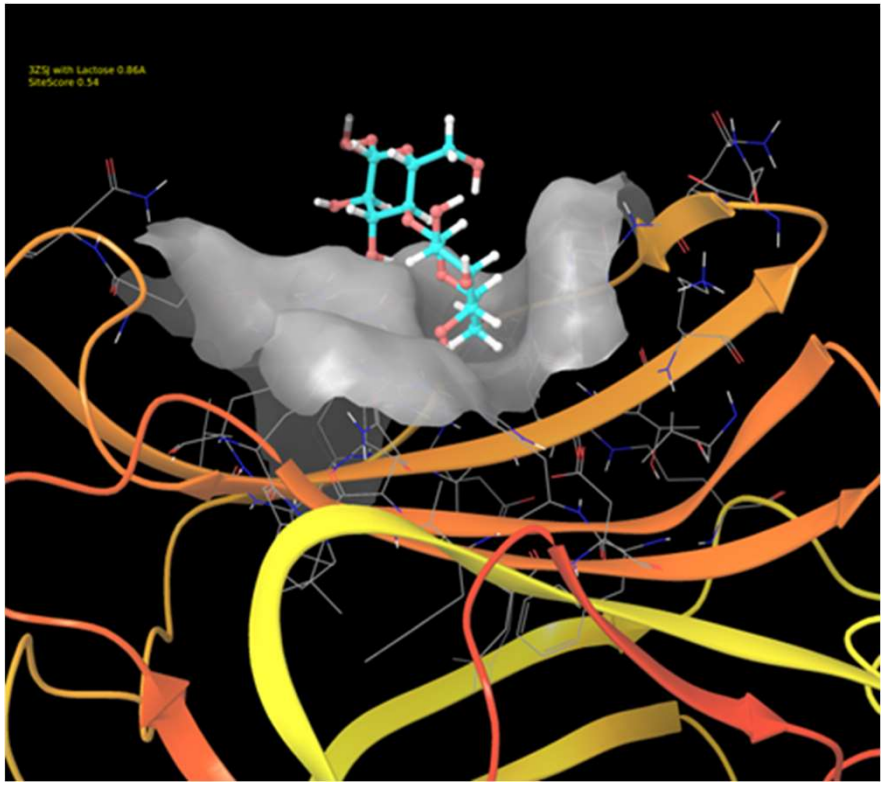
# Galectin-3 CRD Druggability Is Poor

**Druggability** evaluates suitability of the binding site for small molecules under the Lipinski's Rule of 5 [Druggable=1 / Undruggable=0].

Correlates with binding site hydrophobicity and curvature (Cheng, Nat. Comp. Biol. 2007).

**Galectin-3 Carbohydrate Receptor Domain (CRD), is shallow and polar.**

**Analysis with Schrodinger SiteMap also suggests poor druggability!**



# Commercial Positioning:

## Targeting Galectin-3 Inhibition as Therapeutic for Unmet Medical Need

| | |
|---|---|
| **Organ Fibrosis / Inflammation** | • Targeting pathologies with elevated tissue Gal-3 and fatty liver disease[1]<br>• Lead pathology is liver fibrosis<br>• Other fibrotic diseases with elevated Gal-3 e.g. cardiovascular, kidney failure, and neurodegenerative diseases<br>• Animal models: Disease models indicative use for veterinarian applications. |
| **Systemic Insulin Resistance** in Obesity related Diabetes | • Targeting systemic insulin resistance where elevated Gal-3 impairs insulin action in myocytes, adipocytes, and hepatocytes<br>• Targeting elevated Gal-3 in Diabetic nephropathy, the most common complications of diabetes mellitus and chronic obesity. |
| **Cancer** Immunotherapy | • Focus on aggressive and metastatic cancers<br>• Combination treatment with immunotherapy drugs |

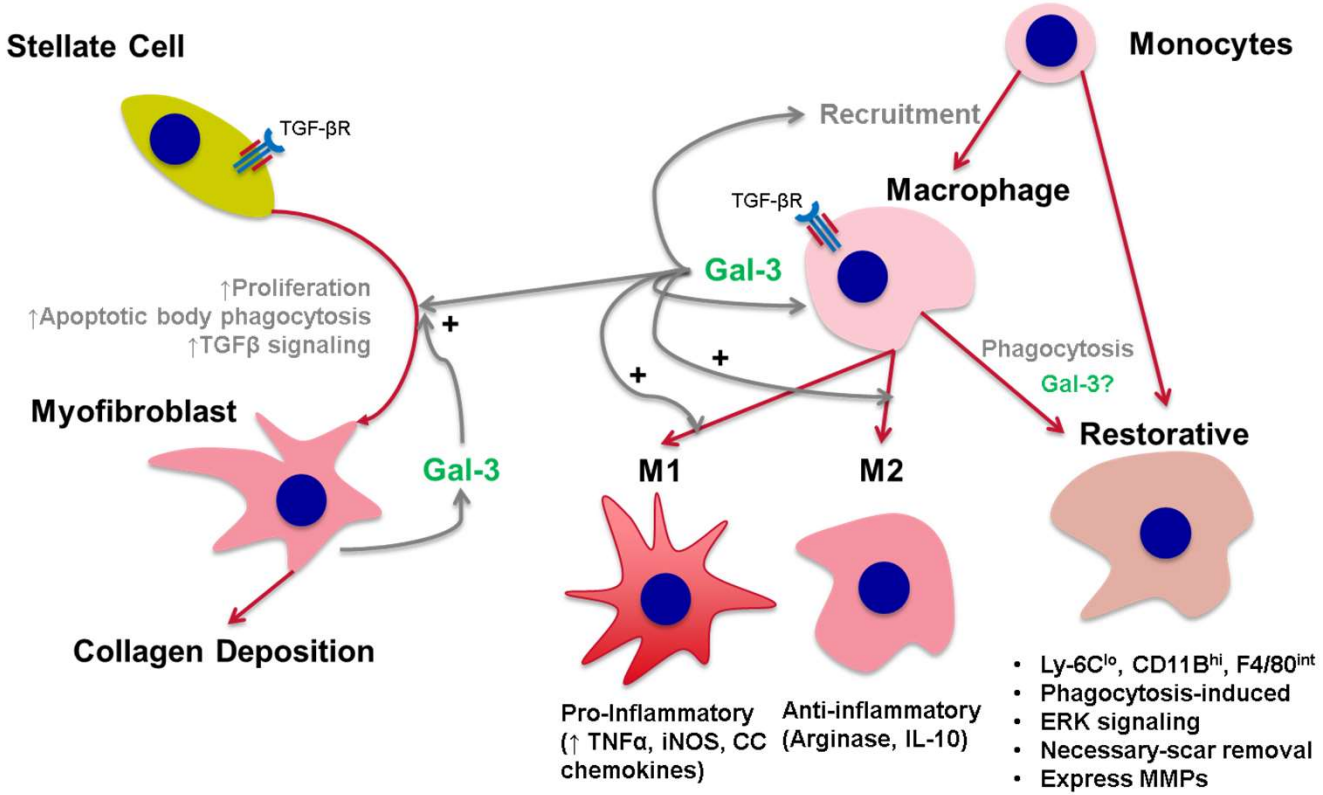
1. 75% of all liver disease in U.S, .Younossi, et al. Clin. Gasto. Hepatol. 2011;9:524-530

# Galectin Therapeutics Pharmaceutical Initial Development Plan

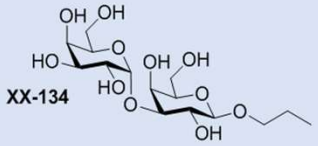
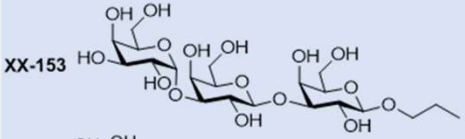
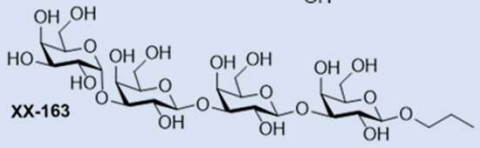
- Optimize initial chemical processing of active poly-galactoside (GR-MD-02) to enhance therapeutic effects in Liver Fibrosis where Gal-3 plays an important role in disease progression

- Establish discovery program for new anti-galectin molecules with potential oral delivery
  - Synthetic carbohydrates of small oligo-galactosides composition in collaboration with UGA
  - Evaluation of small modified oligo-galactosides from natural sources
  - Evaluate synthetic non-carbohydrate compounds in collaboration with SBH Sciences

# Liver Fibrosis - Galectin-3 effects macrophages and stellate cells



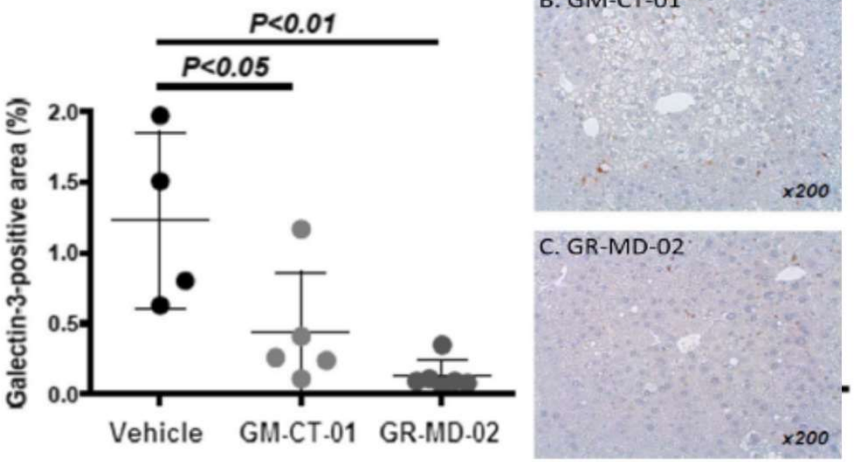
# Optimized Process by Evaluating the Effect of Synthetic Oligo-galactosides* Chain Structures in Galectin-3 Binding Kd

| Oligosaccharide | Integrin aMB2 Binding | Fluorescence Polarization | Biacore |
|---|---|---|---|
| | $IC_{50}$ (µg/ml) | $IC_{50}$ (µg/ml) | $K_D$ (µM) |
|  XX-134 | >50 | >75 | >4000 |
|  XX-153 | 43 | 10 | 474 |
|  XX-163 | 48 | | 21 |

* In collaboration with Prof. Geert-Jan Boons, UGA

# Therapy of experimental NASH and fibrosis with galectin inhibitors model[2]

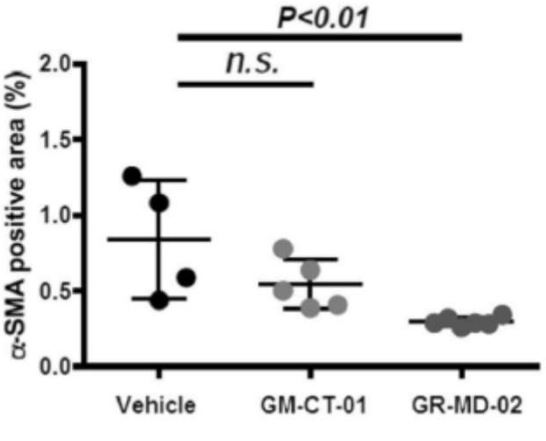
**Study compared two leading poly-galactose compositions In Murine NASH with Fibrosis on liver Gal-3**

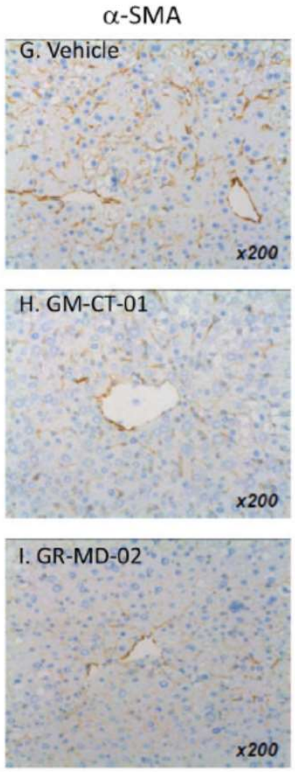






**Study compared two leading poly-galactose compositions for Inhibition of Fibrosis biomarker α-SMA**

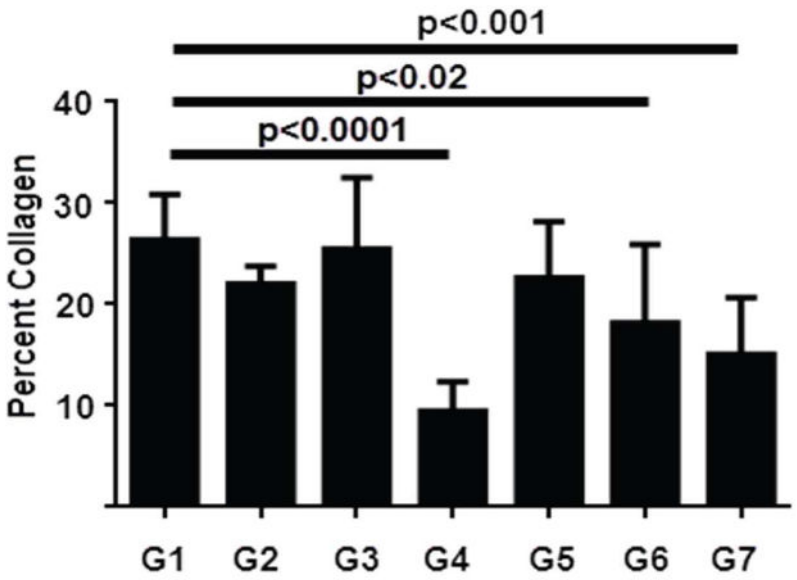



[2] *Traber PG, Zomer E.PLoS One. 2013; 8(12):e83481*

# Regression of fibrosis and reversal of cirrhosis in rats by galectin inhibitors in thioacetamide-induced liver disease[3].

**Study Dose optimization for two leading poly-galactose compositions In Murine Model with Advanced Cirrhosis**



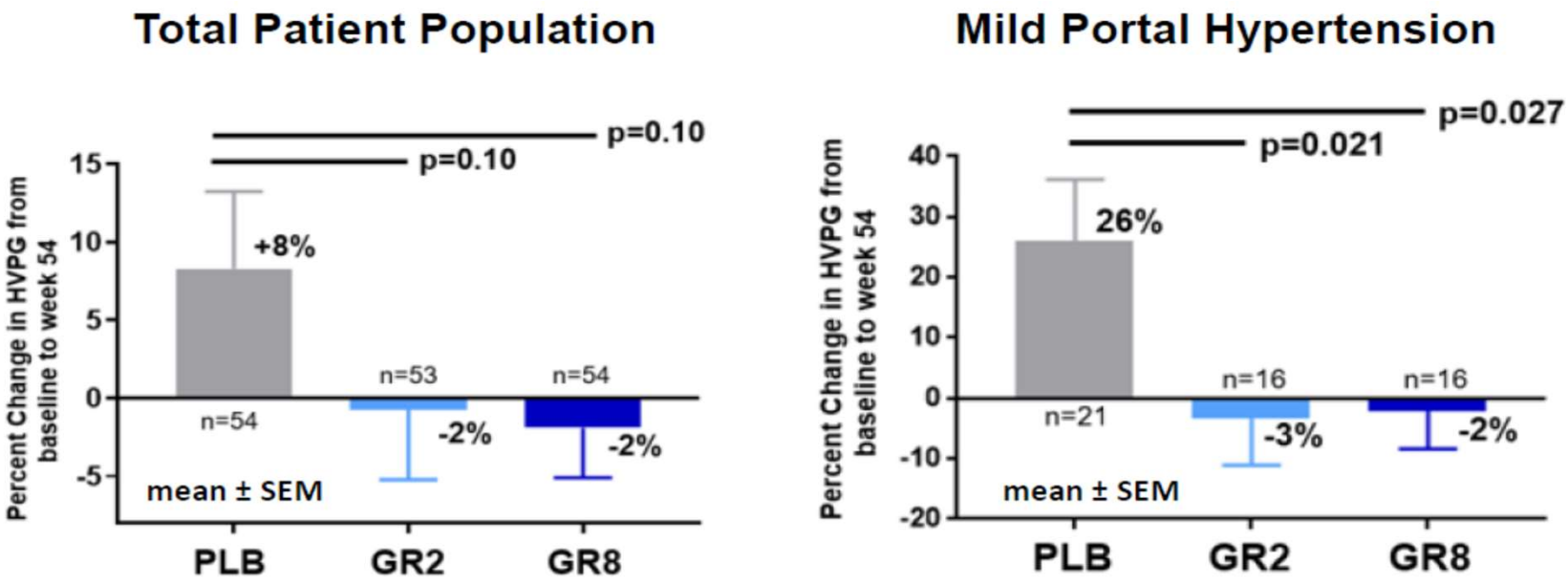

[3]*Traber PG et al. PLoS One. 2013; 8(10):e75361.*

**Hepatic venous pressure gradient** (HVPG)

| Treatments | Mean (SE) |
|---|---|
| Group 1: Vehicle Control | 20.3 (2.4) |
| Group 2: GR-MD-02 | 15.7 (2.9)* |
| Group 3: GR-MD-02 | 18.9 (1.4) |
| Group 4: GR-MD-02 | 17.1 (2.4)* |
| Group 5: GM-CT-01 | 20.8 (1.9) |
| Group 6: GM-CT-01 | 19.6 (2.4) |
| Group 7: GM-CT-01 | 18.5 (3.7) |
| Normal Rats | 10.5 (2.4)** |

.P values compared to vehicle control (control 0.9% NaCl).
*$p<0.05$;
**$p<0.001$.

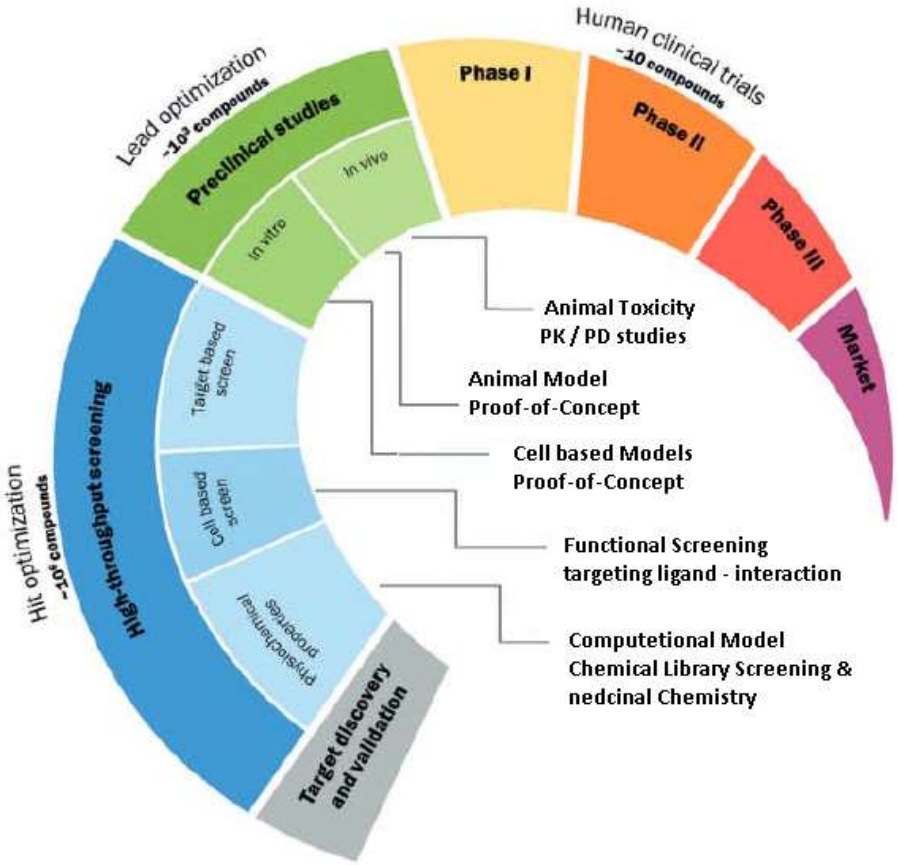
# A multicenter, randomized, double-blind, placebo-controlled trial of Galectin-3 inhibitor (GR-MD-02) for one year in patients with NASH cirrhosis and portal hypertension The NASH-CX Trial[4]




ITT with LOCF (last observation carried forward); ANOVA with LSD (least squared difference)

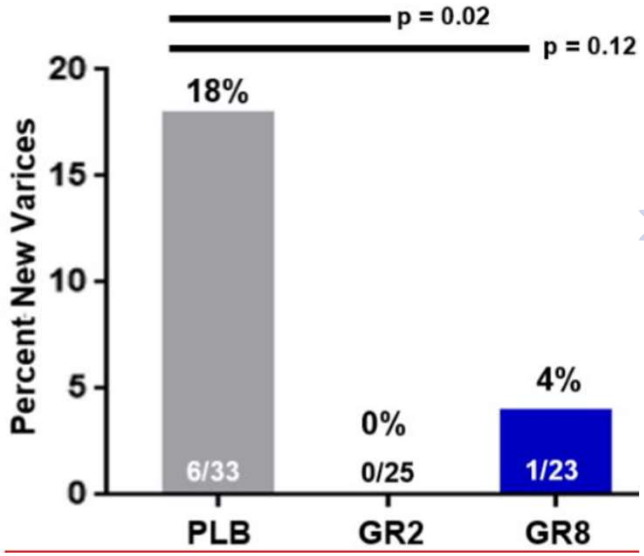
[4]Naga Chalasani et al. EASL2018 Presentation

# From Target to Market



# Phase III Targets Compensated Liver Cirrhosis without Varices[5]

**Disease progression as indicated by Development of Varices in The Phase II**




**Primary End point for Phase III**

- Development of Varices

[5]Naga Chalasani et al. EASL2018 Presentation

# Galectin Sciences, LLC

**Galectin Therapeutics (NASDAQ: GALT) ~80%**
**SBH Sciences (private) ~ 20%**

In January 2014, Galectin Therapeutics and SBH Sciences formed GALECTIN SCIENCES, LLC, a collaborative venture to research and develop Galectin inhibitors for oral administration.

Objectives:

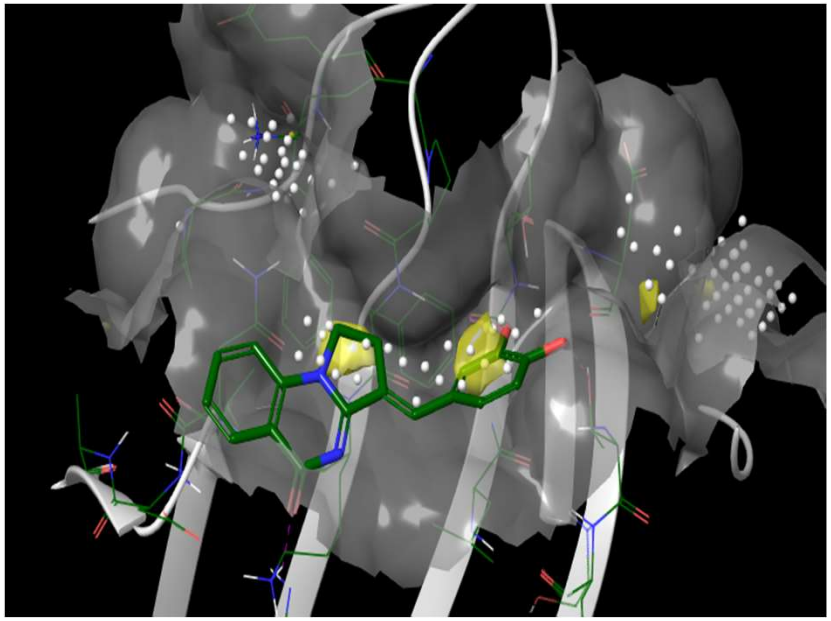
- Explore new analytical methods to identify interaction sites that modulate and enhance the Gal-3 binding to diversified ligands (affecting pathologies of unmet medical needs)
- Make use of SBH Sciences' library of cell based disease models, computational in-silico analysis, and array of bioanalytical methods to screen potential compositions

# Screening Program:

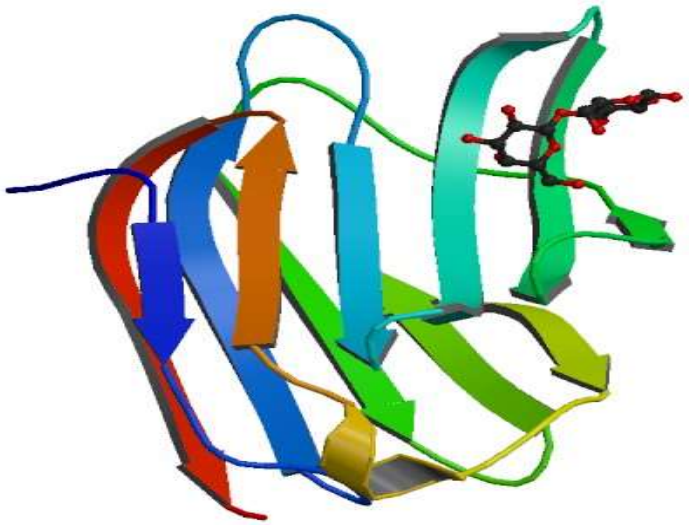
- ***First line: Computational In-silico libraries screening to identify chemicals effecting Ligand Interaction sites***
- ***Second line: Analysis of chemicals on Gal-3 interaction with synthetic & biological ligands***
  - Di-Gal-FITC, Integrins, Gal-3 BP, insulin receptor, TGF-β1-Receptor1 etc.
- ***Third line: Effects on* Cell-Based Anti-inflammatory / fibrosis models**
  - Inflammation – THP-1 macrophage, fibrosis – LX-2 Hu-Hepatic Stellate Cell, Lung Fibrosis – Beas-2B cell using biomarkers and Flow Cytometry.
- **Forth line : Validation of sites through $^{15}$N-enriched Gal-3 protein HSQC spectra overlays**
- **Initiate Non-clinical *in-vitro* ADME (absorption, distribution, metabolism, and excretion)**
  - Non-Clinical In-Vitro Microsomal Drug Metabolism & Plasma interaction
  - Non-Clinical In-Vitro Bioavailability & PK and Toxicology

# Galectin-3 Multi-Faces – Computational In-silico Screening for Identification of Potential Sites Effecting Ligand Interaction

## Non-CRD Site

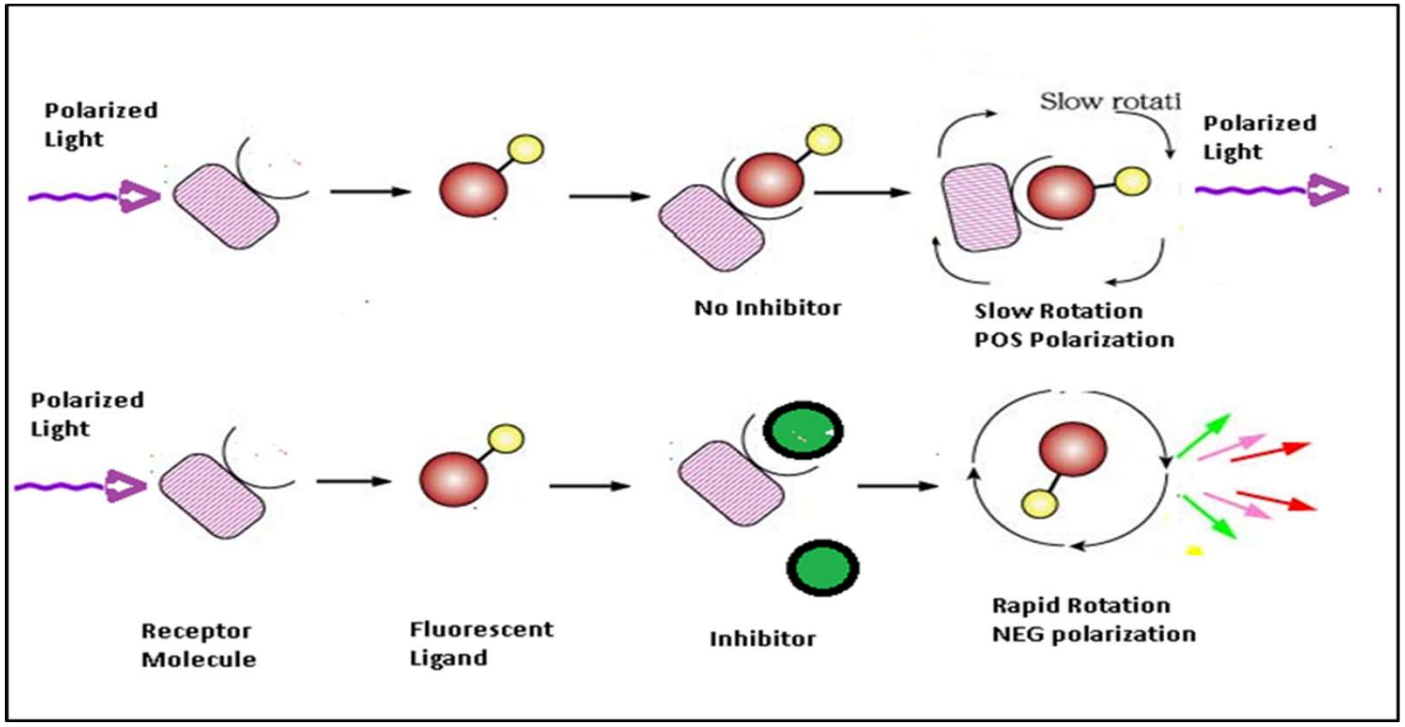


## CRD Site



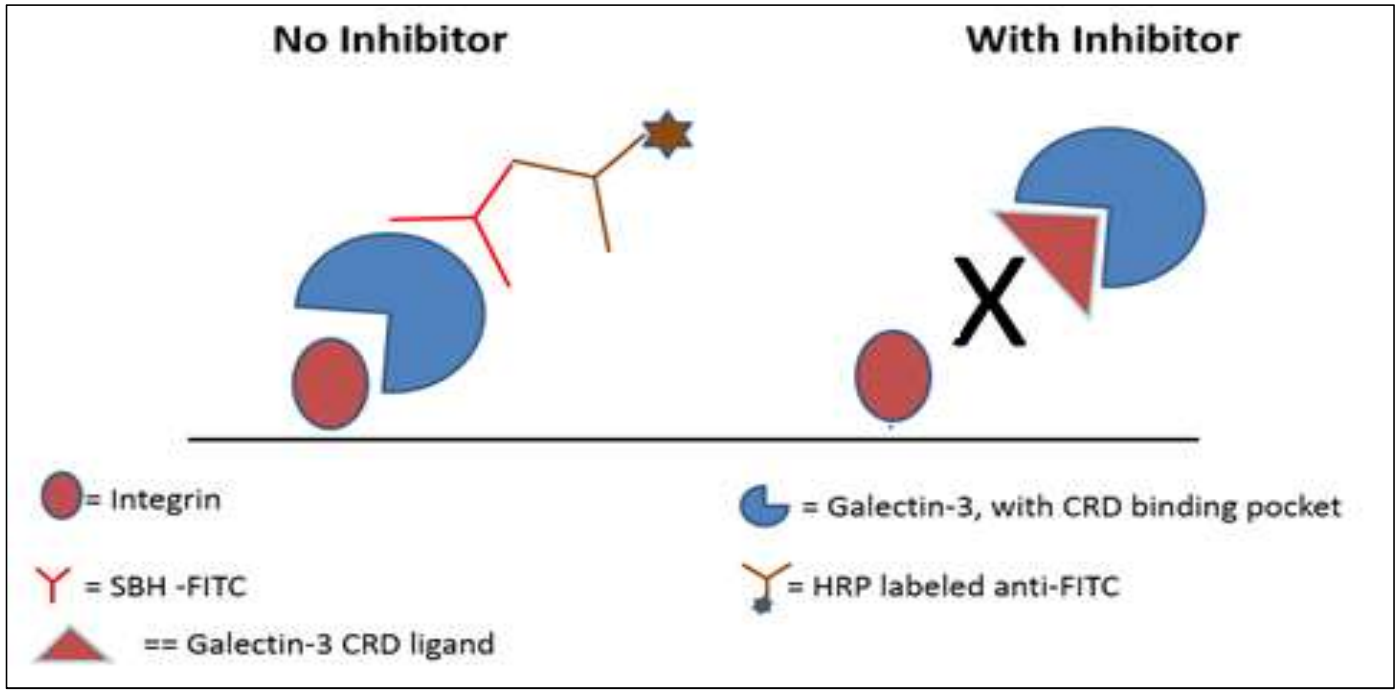
# In-vitro Gal-3 Carbohydrate Recognition Domain (CRD) Binding Screening Assays

Fluorescent Polarization Assay: Uses a galactoside fluorescent probe that specifically binds to the Gal-3 CRD site.

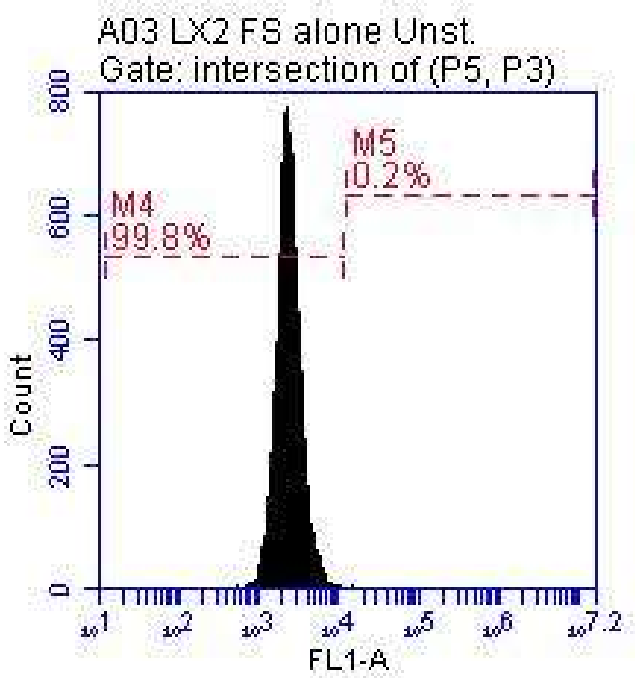


# In-vitro Gal-3 Binding to Functional Ligands

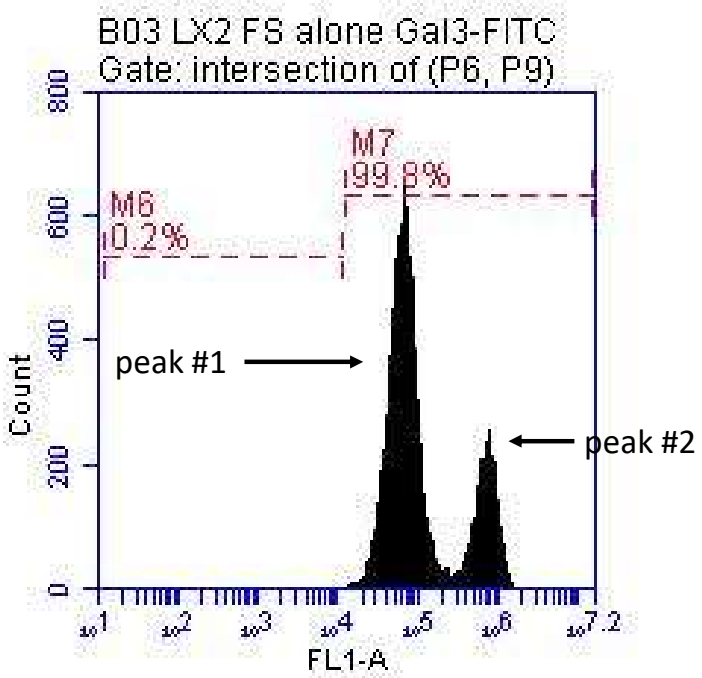
Functional ELISA assay measures the interaction of Gal-3 to Glycoproteins ligands like Integrin aVB6, Galectin-3 BP, Insulin Receptor, TGF-β1-R1, and others, reported to be essential in the pathology of a variety of diseases.



# Gal-3 Detection in Two Distinct Populations: Flow Cytometer Analysis of Stressed LX-2 Hepatic Stellate Cells



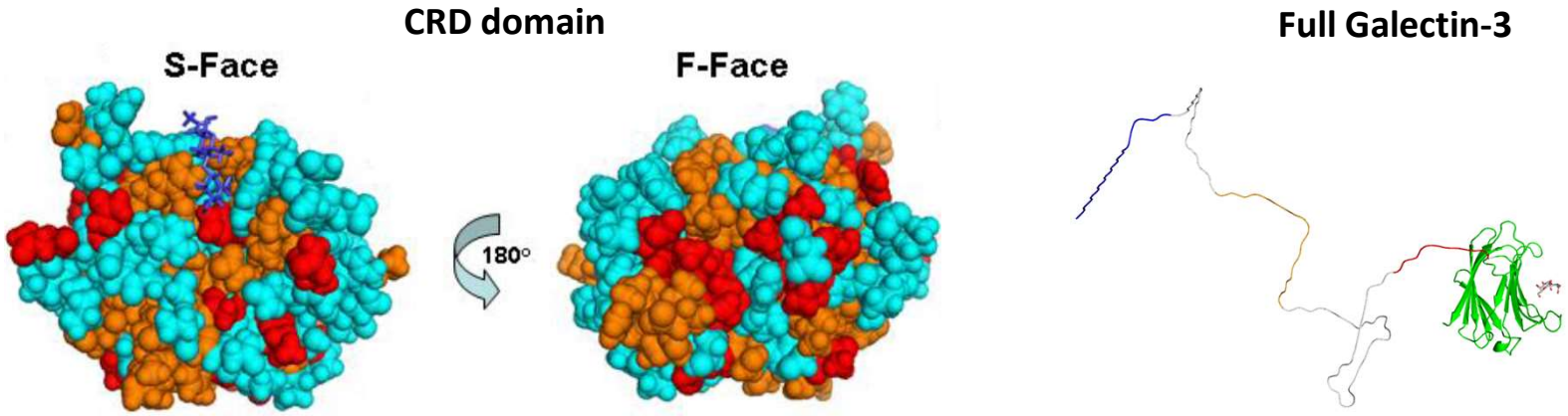

Unstained




FS alone

| Sample | Treatment | Gal3 stain (Y/N) | mean FL1 | % peak1 | FL1 peak 1 | % peak 2 | FL1 peak 2 |
|---|---|---|---|---|---|---|---|
| FS | Alone | Y | 237,922 | 75.4% | 69,537 | 24.6% | 756,288 |

# Galectin-3 Multi-Face Analysis by NMR-HSQC (Heteronuclear Single Quantum Coherence)

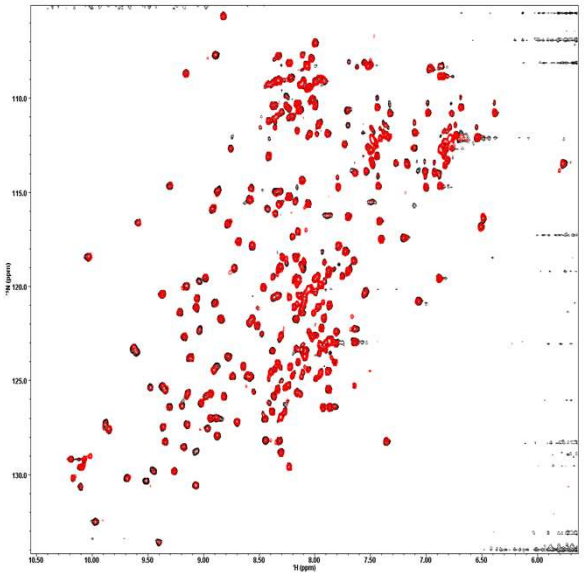



- Site Target 1:The CRD (the canonical Carbohydrate Recognition Domain) at the S-face has few NMR specific resonances that shift upon interaction with ligands.
- Site Target 2:Published data suggests an independent site that may sterically interfere with the CRD binding specificity. Further studies suggest interaction between the N-terminal domain (AA 91–113) and the CRD domain (AA 114–245) may affect the CRD – ligand interaction.*

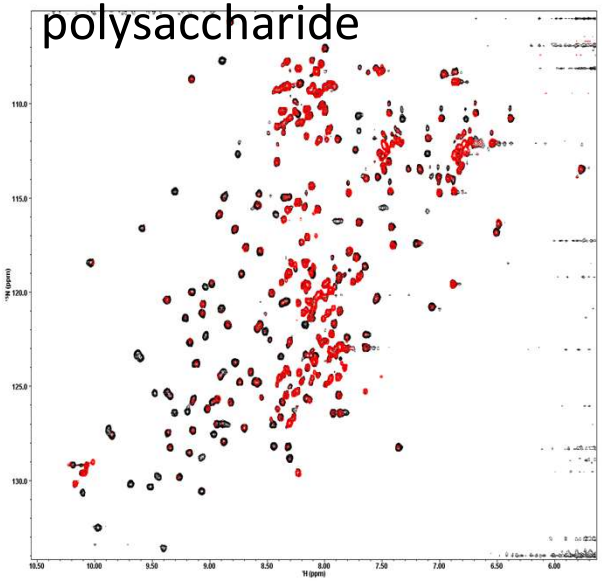
* Erminia A. M. Barboni et al. Glycobiology (2000) 10 (11): 1201-1208

# NMR Interaction Using $^{15}$N-enriched Gal-3 Protein*
# HSQC Spectra Overlays Convey Interacting Sites (black spot)

$^{15}$N-protein + low



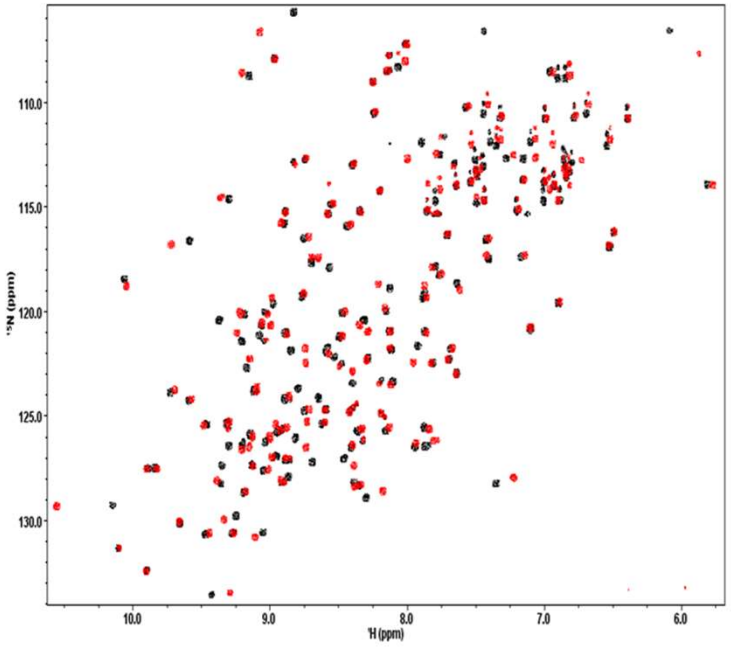
$^{15}$N-protein + more polysaccharide



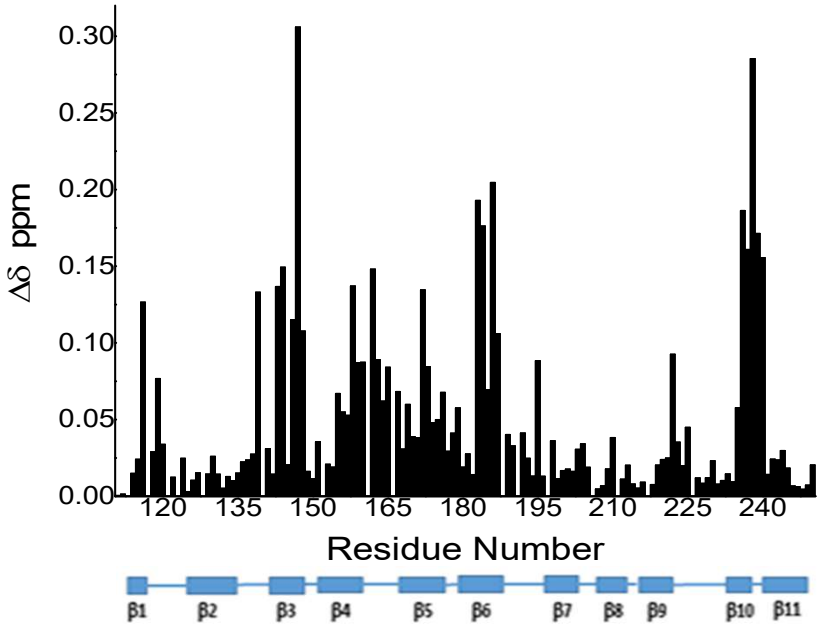
* In collaboration with Prof. Kevin H. Mayo, Univ. of Minnesota

# $^{15}$N-Gal-3 CRD (44 μM) + TD-139 (250 mM)

**Gal-3 + TD-139 (250 μM):**
**HSQC Spectra overlays convey many Interacting Sites (black spot)**



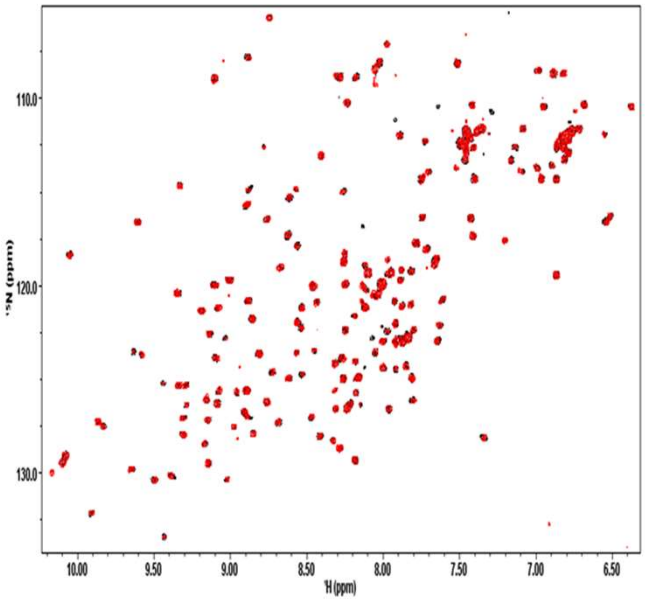

**Gal-3 + TD-139: Gave strong intensity for the interaction of specific aminoacids associated with the CRD site**



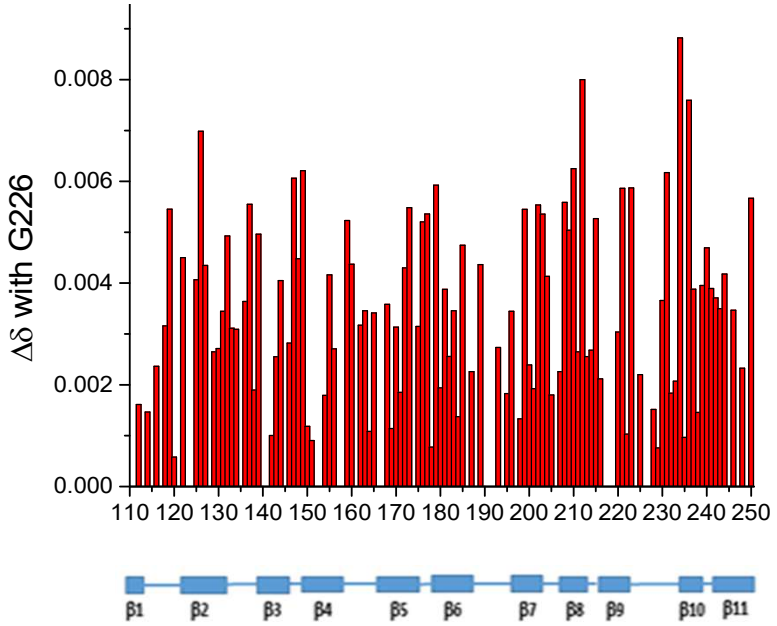
# $^{15}$N-Gal-3 FL (20 mM) + G226 (~800 mM)

## 20 mM Kphos, pH 6.9, 5% DMSO

**Gal-3 + G226 (~800 μM): HSQC Spectra overlays convey few Interacting Sites (black spot)**




**Gal-3 + G226: Gave Weak Intensity for the interaction of specific aminoacids associated with the CRD site**



# In-silico Screening Phase: Computational Analysis on 12 Libraries Using 3D Model of Gal-3

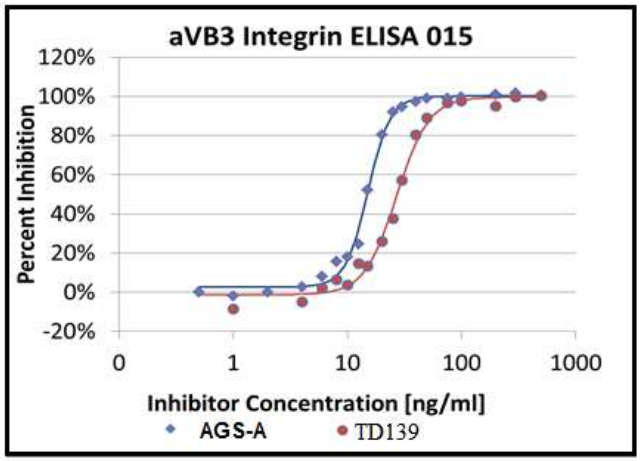
2 platforms identified and evaluated

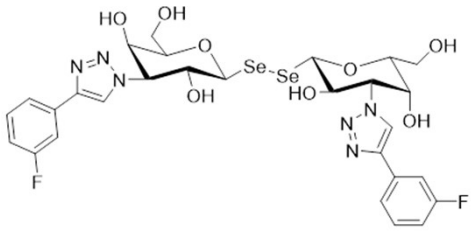
- Platform I: Carbohydrate mimics compounds
  - Polyhydroxyls with heterocycle substitutions and derivatives
  - Commercial libraries – identified limited & mostly unavailable compounds
  - 100 proprietary compounds synthesized and tested
  - >10 potential leading Gal-3 inhibitors identified

- Platform II: Organic non-carbohydrate heterocycles compounds
  - Commercial library – over 600 compounds identified and tested for potential structures
  - 60 proprietary compounds synthesized and tested
  - >10 potential allosteric inhibitors identified

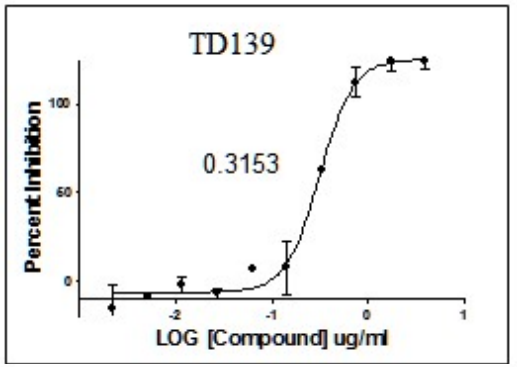
# Platform I: Carbohydrate Mimics
# Attenuating Gal-3 Ligand Binding through the CRD

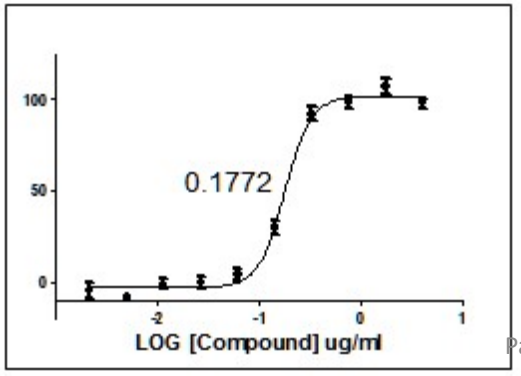
In an ELISA assay format inhibition of Gal-3 binding to integrin aVB3, Selenocarbohydrate heterocycle derivatives gave an IC50 of 30 nM




In a Fluorescent Polarization assay SelenoCarbohydrate heterocycle derivatives had 0.177 Kd.



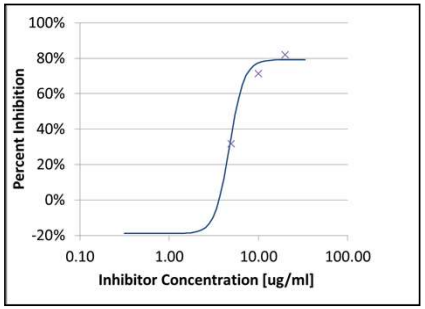



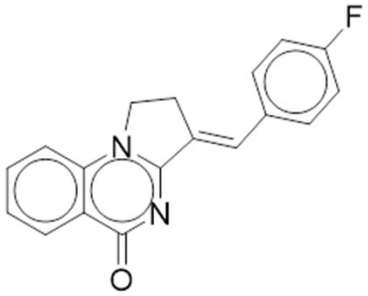
# Screening Platform II – Allosteric Compounds

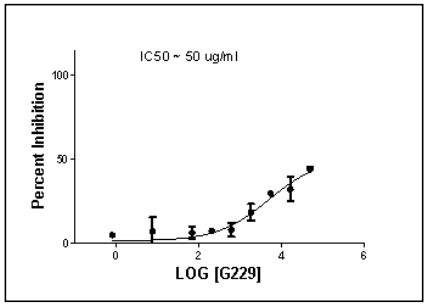
## Attenuating Gal-3 ligand specificity through a none CRD site interaction

AGS-229 – non-carbohydrate compound inhibits Gal-3 binding to integrin aMB2 at $IC_{50}$ (µg/mL) = 4.5.

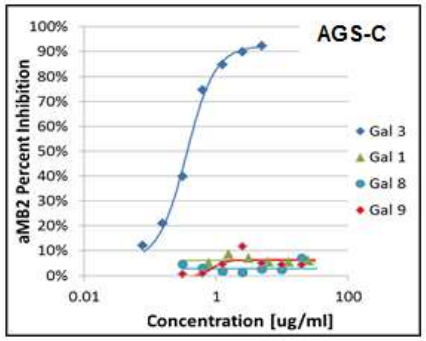
AGS-229 – In the Fluorescent Polarization assay the $IC_{50}$ (µg/mL) was > 50.

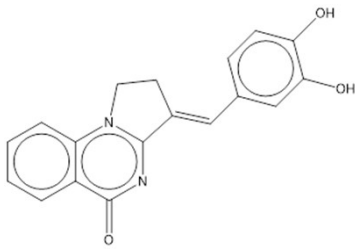


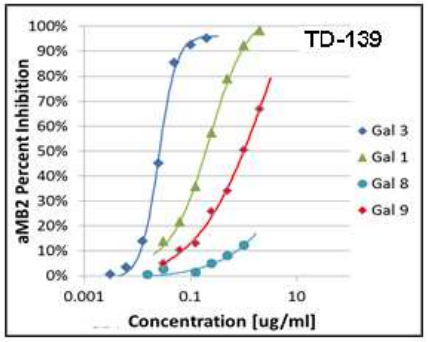



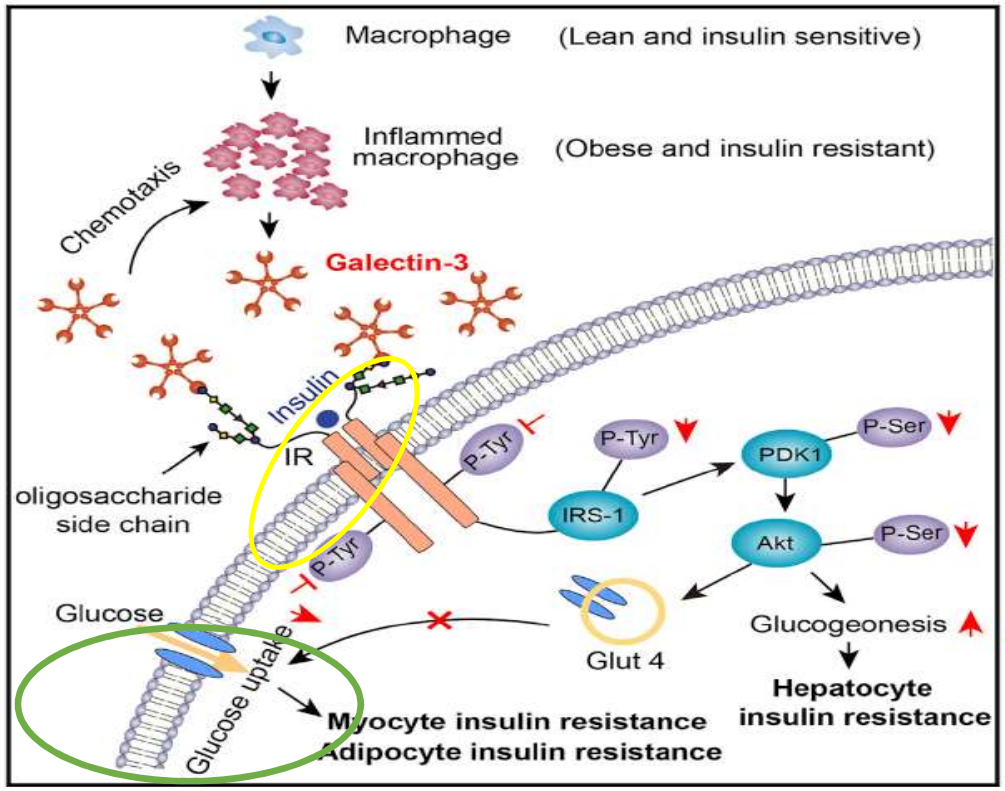

The allosteric compounds are specific to Gal-3 and have low binding to other galectins e.g. Gal-1, 8, and 9 as compared to TD-139 (A β-S-digalactoside derivatives).



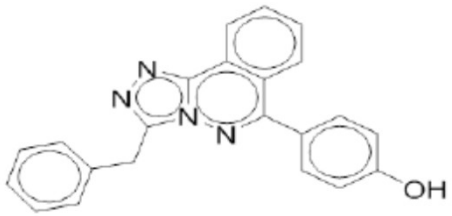
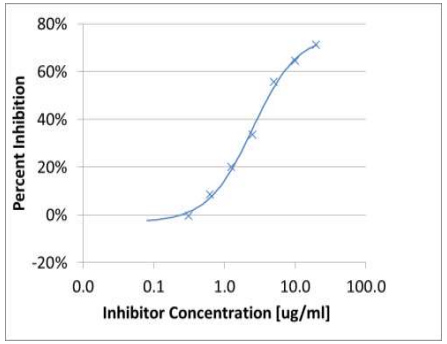
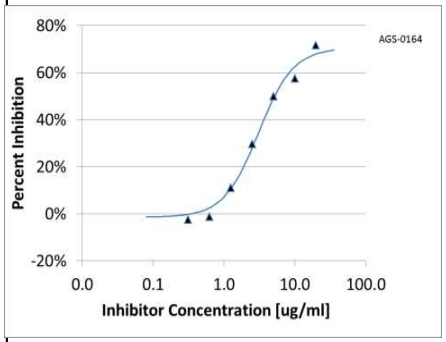
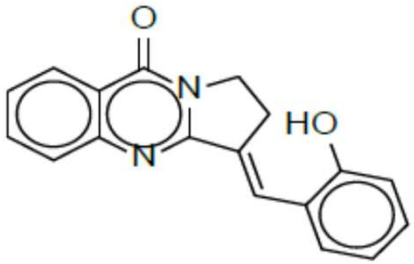
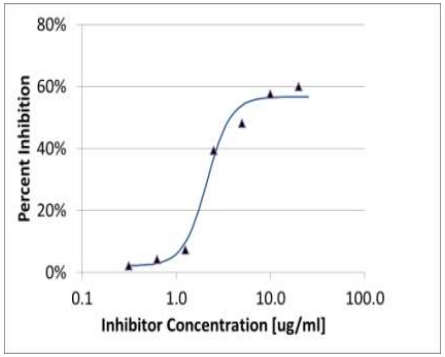
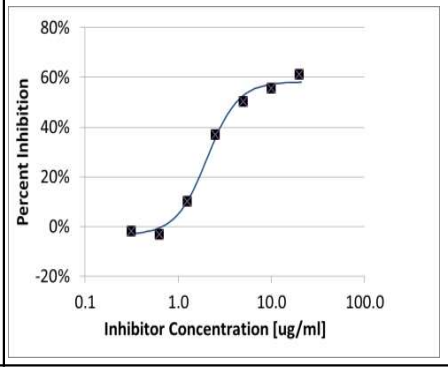



# Hematopoietic-Derived Galectin-3 Causes Cellular and Systemic Insulin Resistance[1]



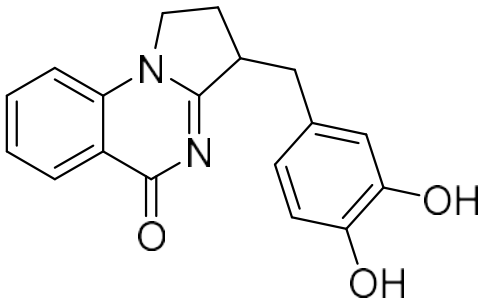

[1] Pingping Li, et al., Nov 3, 2016, v 167 (4), p 973–984.e12

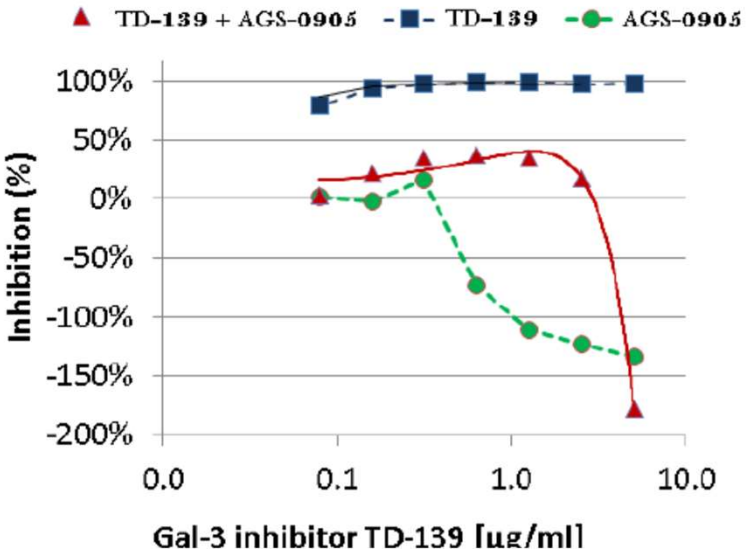
# Allosteric Compounds Attenuating Gal-3 Binding to Insulin Receptor and TGFb1-Receptor 1

| Code | Inhibition of Galectin-3 Binding to Insulin Receptor 1 | IC50 (ug/mL) | Inhibition of Galectin-3 binding to TGF-β1 Receptor-1 | IC50 (ug/mL) |
|---|---|---|---|---|
| **AGS-164**   |   | 4.3 |   | 5.1 |
| **AGS-155**   |   | 3.7 |   | 4.2 |

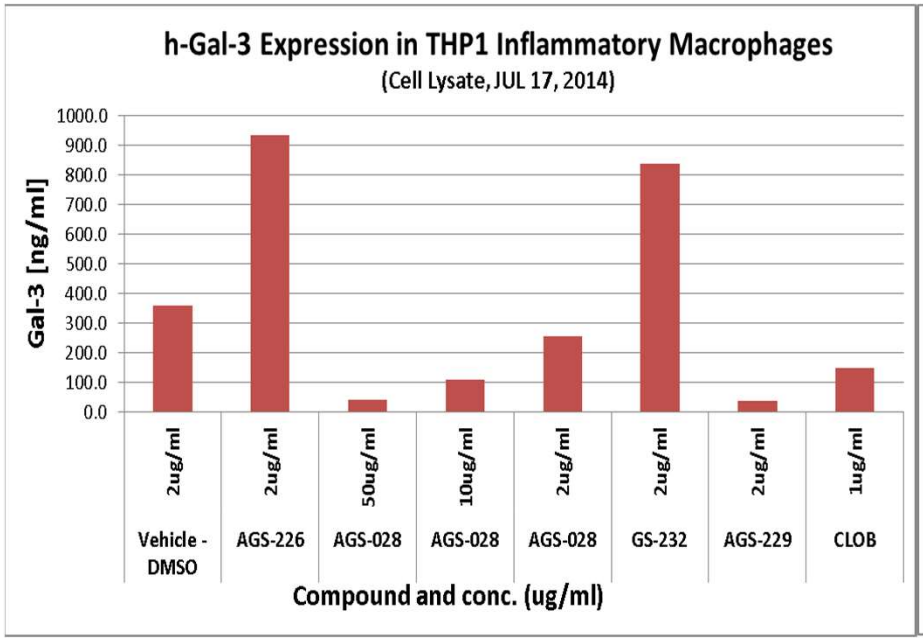
# Allosteric Compounds May Enhance Gal-3 Ligand Binding Kd through a None CRD Site Interaction

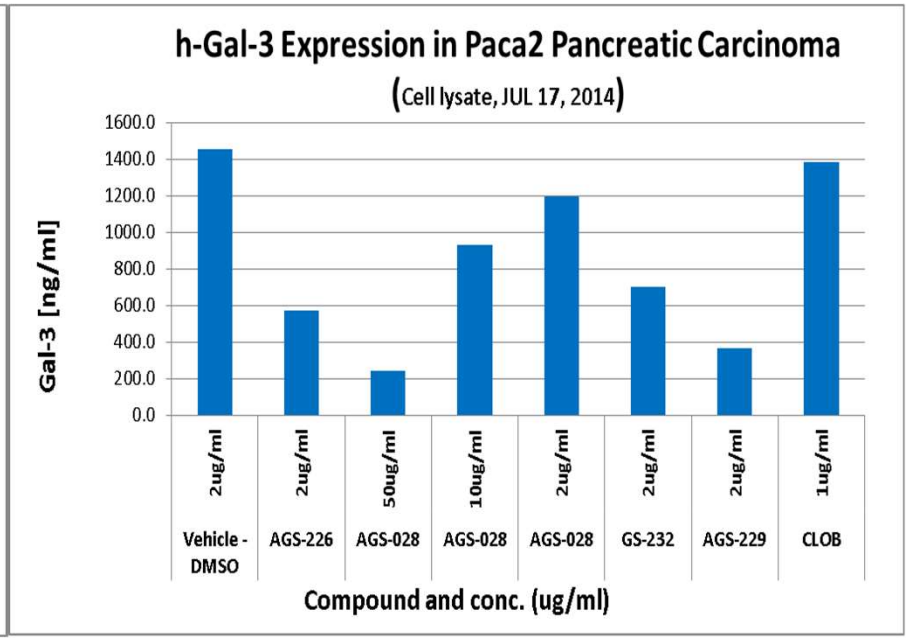
AGS-905 – non-carbohydrate compound enhanced Gal-3 binding to integrin aMB2 by 200%



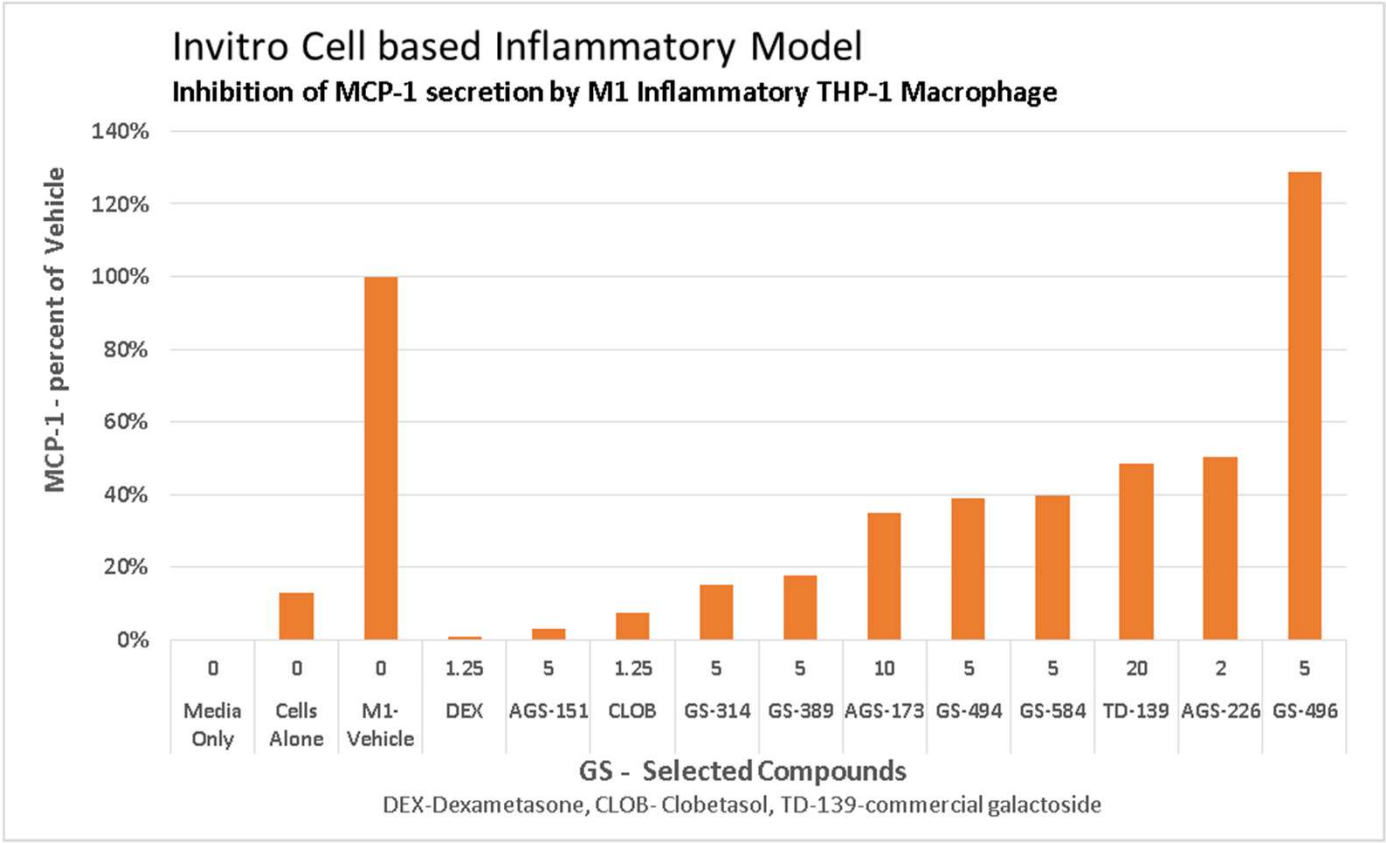



# Allosteric Compounds Attenuating Galectin-3 Expression in Inflammatory THP-1 Macrophage and Paca-2 Cell Model



# Allosteric Attenuating MCP-1 in Inflammatory THP-1 Macrophage



# Intellectual Property Portfolio

Building a Proprietary Family of Compositions and Use Patents:

1. Composition of matter, International PCT submitted March 2017
2. Composition of matter, 2nd International PCT submitted May 2018
3. Composition and use of matter, 3rd International PCT submitted May 2018
4. Composition and use of matter, 4th International PCT submitted Oct. 2018

   - All 4 PCT submissions received a written opinion indicating that the Searching Authority found the majority of claims to be novel, and have inventive chemistry and industrial applicability!
   - All patents are currently in US national phase and international applications!

5. Additional patents planned for 2019-2021 on methods of manufacturing and use

# Next Steps: CMC scale-up, COA Characterizations, and Animal model Proof of Concept

## API and Product manufactured

- Scale up of 2-3 leading compositions - Synthesis optimization – on going
- QC – Methods specifications and validation - on going
- Stability & Formulations - on going

## Proof of concept in animal models and Safety studies

- Disease model selection for unmet medical need – planned for 2020

## Pre-clinical Studies to Meet regulatory guide lines for IND

- Validate method for Pharmacokinetic / Pharmacodynamic – LC-MS in 2020
- Product formulation – Optimize oral bioavailability
- Initiate Pre-clinical tox studies – planned for 2021 with Pre-IND in 2023

# Thank You


- **Eliezer Zomer, Ph.D.**

  ***Galectin Therapeutics Inc.***

  ***VP Drug Discovery & Manufacturing***

  ***zomer@galectintherapeutics.com***

- **Raphael Nir, Ph.D.**

  ***SBH Sciences Inc.***

  ***President and Chief Scientific Officer***

  ***rnir@sbhsciences.com***