An Apple A Day – Why Galectin Therapeutics ($GALT) is Worthless and will drop 99%

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Executive Summary

Galectin Therapeutics (GALT) is a publicly traded company with one drug. That drug, belapectin, does not work. Nevertheless, the fully diluted market capitalization of Galectin is $132 million, with an enterprise value of $209 million. This will change shortly, when the Phase III clinical trial results for belapectin are reported.

Galectin's drug, bela***pectin*** is made from ***pectin***. Pectin is found in fruit peel. Galectin takes the fruit peel's pectin and makes an intravenous formulation for patients with liver fibrosis. They don't have a patent. They have proven that this "drug" does not work, in a definitive Phase II trial. Despite that, they are conducting a new trial based on a "finding" from a post-hoc subgroup of the failed Phase II trial.

Fruit pectin is not the cure for HIV, cancer, fibrosis or COVID-19. But Galectin's founders, who invented belapectin, are obsessed with the supposed power of this carbohydrate. Unfortunately, sugars have never been medicines and never will be. The molecular basis for belapectin has been disproven. While the company has claimed belapectin is a "galectin-3 inhibitor", the most sophisticated work conducted suggests that it is **not** a galectin-3 inhibitor.

Galectin has very little cash left. By their own admission, the company has funding until May. The brilliant Richard Uihlein, who I share political views with, is the primary backer of Galectin. Uihlein is not the first and will not be the last billionaire backer of biotech who walks away burned. There is no turning around for Galectin without abandoning belapectin and doing something brand new. I wish Mr. Uihlein would have consulted with sharper biotech minds before making the investment he has in Galectin, and I hope this was a small loss for him that he doesn't allow to turn into a bigger one.

Principally, Galectin sought to show belapectin reduced portal hypertension, ideally by 2mmHg. Portal hypertension happens when the portal vein's blood pressure is above normal, and it is concomitant or causal to liver fibrosis. Reducing this pressure would have been ideal for advancing belapectin into definitive Phase III trials. Belapectin failed to reduce portal hypertension at all. Nor was belapectin able to reduce liver fibrosis. Nevertheless, the company irresponsibly progressed belapectin to an even larger study. Why?

In the Phase II study, belapectin 2mg/kg (but not 8mg/kg) demonstrated that patients without varices (fluid retention) at baseline did do better than placebo. As we've seen in so many short sales of biotech stocks, post-hoc subgroup findings are almost never reliable. They are literally never reliable if they don't have any element of causality. Here, the giveaway is the lack of efficacy in 8mg/kg. There is no pharmaceutical agent that I am aware of which defies the laws of pharmacology and works *better* when less drug is given. There is also no agent I'm aware of that *doesn't work at all* when a higher dose is given.

Galectin's results are due in December 2024. The entire company boils down to this moment. With yet another failed study of belapectin, the company must abandon this asset and focus on something else. Unfortunately, the company has very little cash left, and no other assets.

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A. Introduction and Overview

Liver Fibrosis

As we accumulate injury to our organs, because of disease or simply aging, our organs undergo fibrosis. What is this fibrotic process? How exactly does it limit the function of our organs on a biochemical level? Can we interrupt the process medically?

So far, the only known way to limit or reverse fibrosis is to stop the underlying cause of the fibrosis-causing disease. In the case of some disease—including some liver fibrosis—that is possible. But, for most diseases, reversing fibrosis has proven elusive. Part of the reason for this is fibrosis is a natural response to organ injury. Stopping the process would not restore organ function and result in further injury. Another reason is our organs come with a variety of self-repair capacity, most of which are limited.

We will take a deep dive into the world of liver fibrosis. The liver is the main metabolism organ—designed to take reactive, foreign substances and metabolize them into neutral compounds for excretion. The liver sees a lot of toxicity over its lifetime. But disease processes caused by alcohol, hepatitis C and genetic diseases accelerate liver damage, and we can learn from these diseases as we examine more general forms of liver fibrosis.

B. Tortured story of Galectin

Galectin started life in 2011 as “Pro-Pharmaceuticals”. The initial goal of Galectin was to combine carbohydrates (also known as sugars) with chemotherapy to lessen the harmful effects of chemo. At first, the company focused on mannose. Drs. David Platt and Anatole Klyosov were the original management team of Galectin. Dr. Platt is a chemist with a long history in carbohydrates. His career has been a frustrating ride of small company entrepreneurship, having led nowhere. He is particularly important to the Galectin story.

Platt’s life begins in Israel, where he earns a PhD in chemistry. He moves to the US, becoming a fellow at another Israeli’s lab, Dr. Avraham Raz. In 1992, the duo published their seminal paper, which would guide Platt for more than 30 years. Dr. Raz began publishing on lectins in 1981 (Raz, 1981). Pectins have become a sort of scientific conspiracy theory. They have never proven an effect in humans, but work continues by “true believers” nevertheless.

Platt decides to take Dr. Raz’s work and start a company. He calls it

SafeScience changed its name to Glycogenesys.

Platt then started Pro-Pharmaceuticals, which would inevitably become Galectin.

α-D-galactose
α-D-galactopyranose

D-galactose
(linear)

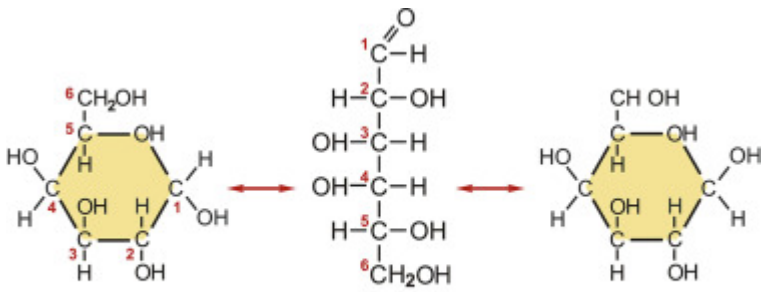
β-D-galactose
β-D-galactopyranose

Belapectin MOA

Galectin is developing belapectin as a “galectin-3 inhibitor”. Galectin-3 is a lectin, a protein that detects carbohydrates. Belapectin is made from apples—specifically, apple pomace. What is pomace? It’s everything that is left after you juice an apple—the peel, the seeds, the core, etc.

The belapectin story might be plausible, except for one detail. Belapectin doesn’t bind galectin-3! As I have written previously, for every single drug, I always want to under the ‘binding event’ that is purportedly taking place. This is akin to photo evidence, on the nanometer scale, of course. If you can’t take a picture of it—is it even happening? Well, some effort was put into this, and the results were ugly (Stegmayr, 2016). This should have been the end of Galectin Therapeutics.

Lectins, such as galectin-3, are proteins which recognize galactose residues on macromolecules.



As you can see, galactose can be described in its closed (galactopyranose) or linear form. Galactose is almost identical to glucose. Technically, an isomer, glucose only differs from galactose in its fourth carbon’s hydroxyl group (the hydroxyl is on the left in glucose).

Clinical Trials

NASH backgrounder

Non-alcoholic steatoic hepatitis (NASH) looks very confusing at first. What is the difference between NASH and non-alcoholic fatty liver disease? What does fibrosis have to do with this? What *about* alcoholics? I will make it easy for you.

The best way to understand NASH is to ignore all the jargon and start with portal hypertension. You are undoubtedly familiar with **essential hypertension** itself: 120/80 is the ideal systolic/diastolic pressure, for instance. If you've followed pharmaceuticals, you've undoubtedly come across PAH and pulmonary hypertension. In this case, a specific vasculature has a different pressure than the rest of the circulation. NASH/NAFLD and other liver diseases are no different. Here, the portal vein is the vasculature we're focused on. In NASH/NAFLD we often see HVPG of over 10 mmHg, which is very worrisome clinically.

What is NASH and NAFLD? These are histological findings in the liver. Histology is the art of looking at a biopsy under a microscope and analyzing the findings for clinical relevance. We must do this because other methods of studying the liver are difficult. Portal hypertension is practically the only non-invasive way to monitor liver health. Liver enzymes can be helpful to watch, but are often non-specific and difficult to monitor. Bilirubin.

A Phase II clinical trial proved convincingly that belapectin does not work in NASH (Chalasani, 2020). This 162 patient trial tested two doses of belapectin in NASH patients, 2mg/kg and 8mg/kg against a placebo. The primary endpoint was HVPG. The drug and placebo had no effect on HVPG. Baseline HVPG was around 12.2. Drug moved in the right direction by -0.3mmHg and placebo went up by 0.1mmHg, which is around one half of one standard deviation. The p-value given by the company for this is 1.0, the worst possible. The company was hoping for 2mmHg according to the study protocol (Galectin Therapeutics, 2015).

The company rationalized moving forward with the drug by revealing an unplanned subgroup analysis in the 2mg/kg group. As we've discussed many times, almost no drugs have an inverse dose response. This is not how basic pharmacology behaves, and you must be suspicious of any drug with a supposed inverse dose response. The alternative hypothesis is far easier to accept: the drug does not work.

In the 2mg/kg dose group, *in patients without varices at baseline*, belapectin improved HVPG by ~1mmHg and 0% of patients developed varices vs. placebo's 18%. This spurious finding is incidental and not worth pursuing due its inverse dose response and lack of even a trend in portal hypertension.

Sources