Novel Compounds for the Treatment of Liver Fibrosis/Cirrhosis

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Categories	Therapeutic Composition , Liver Fibrosis, Fibrosis, drug	
Development Stage	Preclinical	
Patent Status	Pending	
THM Reference	2016045	

Abstract

In the normal liver, hepatic stellate cells (HSCs) constitute quiescent, vitamin A-storing cell. Upon activation by specific stimuli released by an injured liver, HSCs undergo activation''or trans-differentiation, yielding a myo-fibroblast-like cell. Stellate cell activation is a tightly programmed response occurring in a reproducible sequence. Nevertheless, it has been demonstrated that fibrosis and even cirrhosis can be reversible if the underlying cause is successfully eliminated. Furthermore, it was demonstrated the HSCs themselves can undergo regression from differentiated myo-fibroblast like to quiescent cell.

As of today, no compound has been thoroughly validated as a therapy for fibrosis. The most effective therapy for treating hepatic fibrosis to date is still to remove the causative agent. This approach is successful in achieving the regression of fibrosis in some patients, mainly in patients with chronic hepatitis C, and partially in patients with chronic hepatitis B. However, there is no available treatment for patients with alcoholic and nonalcoholic fatty liver disease. In highly selected patients, liver transplantation is often indicated as the only effective therapy today. However, liver transplantation being a major abdominal surgery has many risks and complications.

The Need

Fibrosis is a wound-healing response of the liver to injury, caused by the excess production and accumulation of extracellular matrix (ECM) proteins, resulting from chronic, non-resolving inflammation and impaired regenerative capacity.

Fibrosis progression toward cirrhosis, is the major cause of liver-related morbidity and mortality. Patient with cirrhosis are more prone to develop liver failure, portal hypertension and its complications and are at higher risk of developing hepatocellular carcinoma (HCC). Fibrosis and even cirrhosis is reversible in some patients if the underlying cause is successfully eliminated. However, for some patients with cirrhosis and patients, which already developed HCC, liver transplantation is the treatment of choice.

We believe that our findings will lead to the development of new compounds for the treatment of liver fibrosis/cirrhosis that will successfully limit and even reverse the progression of the disease.

These compounds will allow accelerate repair and enhance liver regeneration in patients with chronic liver disease.

The Technology

Novel Composition to treat liver Fibrosis - we have studied the mechanism of liver fibrosis; our novel composition is based on a central pathway that maintain liver homeostasis.

Our main finding includes:

Characterization of a novel and unique mechanism and approach where liver cells can inhibit/reverse HSCs activation

We have developed a novel Composition and demonstrated its activity with respect to its potential to inhibit and reverse liver fibrosis

Novel Mechanism of action: Biological induced resolution of HSCs activation and liver fibrosis

Applications

Hepatic fibrosis

Might be applicable to other fibrotic tissues as lung and kidney

Advantages

Suitable to all etiologies in liver fibrosis

Treat the fibrosis mechanism of action as a whole

No or very low toxicity

The Market

According to the American Liver Foundation , about 30 percent of people in the U.S. now suffer from fatty liver diseases, such as NASH (nonalcoholic steatohepatitis), fueled by obesity, diabetes and over-indulgent lifestyles,. Without treatment, sufferers can develop advanced damage, including the scarring known as fibrosis; cirrhosis, which destroys liver function; and even cancer.

Liver fibrosis and its end-stage sequela of cirrhosis resulting from chronic liver injury are major causes of morbidity and mortality worldwide. Among the etiologies of hepatic fibrosis, viral infection is most common (e.g. hepatitis B and C), and currently affects 1-2% (5.3 million) of the US population, with cirrhosis projected to reach 45% of those infected with hepatitis C virus (HCV) patients in 2030. In addition, the consequences of precipitously rising obesity rates worldwide have accelerated the risk of liver injury due to nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH); at least 20% of patients with NASH progress to cirrhosis. Other etiologies of chronic liver injury include alcohol-induced disease, drug-induced toxicity, other liver infections (e.g. schistosomiasis), immune-mediated liver diseases (e.g. autoimmune hepatitis), metabolic disorders (e.g. lipid, glycogen, or metal storage disorders) and cholestasis (e.g. secondary biliary cirrhosis). Complications of cirrhosis are well characterized, and include ascites, portal hypertension, encephalopathy, liver failure, and accelerated risk of hepatocellular carcinoma (HCC). In particular, HCC has the fastest rising cancer incidence of any neoplasm in the USA and Europe.

Now that new medicines promise to cure millions of hepatitis C patients in coming years, drugmakers are turning their attention to other liver diseases, with a potential market that could rival the success of statins, which generated more than $30 billion a year in sales at their peak.

Fatty liver conditions caused by rising obesity, which without treatment could affect half of all Americans by 2030, will be the primary cause for Liver Fibrosis and liver cancer. Liver fibrosis and cirrhosis are causing the scarring that virtually all liver diseases cause without effective treatments.

Based on the ongoing obesity epidemic in the US and its direct correlation to NAFLD prevalence, recent research by GlobalData estimates the current market opportunity in liver fibrosis to be worth $83BN, as 70% of obese people are diagnosed with NAFLD.

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