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PROMETHERA BIOSCIENCES

# Targeting NASH and other devastating fibro-inflammatory liver diseases

**Promethera Biosciences is developing cell-based therapies to treat major acute and chronic liver diseases. Building on its research into immunomodulatory and antifibrotic allogeneic therapies, the biotech is running clinical development programs in acute-on-chronic liver failure (ACLF) and nonalcoholic steatohepatitis (NASH).**

The story begins with Etienne Sokal and Mustapha Najimi's discovery of liver-derived progenitor cells in 2005. Sokal and Najimi discovered liver-derived cells expressing mesenchymal stem cell (MSC) markers, as well as vimentin, alpha-smooth muscle actin, and other hepatic markers. Neither biliary markers, such as CK19, nor hematopoietic markers are expressed by the cells.

Further research showed the cells differentiate into hepatocyte-like cells, the main cell type found in the liver, and that they have desirable therapeutic properties. Like MSCs taken from bone marrow or adipose tissue, the cells are immunomodulators. Moreover, the cells act on hepatic stellate cells, a key driver of hepatic fibrosis. This gives such liver-derived progenitor cells anti-inflammatory and antifibrotic properties.

Recognizing the potential of their discovery, Sokal and Najimi founded Promethera in 2009. After initially developing the cells in rare diseases caused by enzyme deficiencies, Promethera expanded into more prevalent fibro-inflammatory liver diseases with the appointment of John Tchelingerian as CEO in 2015.

Since then, Promethera has turned a promising but preliminary prospect into a robust clinical-phase asset, HepaStem. Along the way, Promethera has further elucidated the potential of HepaStem. The therapy inhibits the inflammation that turns an injured liver fibrotic and blocks the hepatic stellate cell activation that leads to symptomatic cirrhosis (**Fig. 1**). That suggests HepaStem could act on the mechanisms of cirrhosis, fibrosis, and control the acute and sub chronic inflammation that respectively contributes to ACLF and NASH.

These are major indications and unmet medical needs. ACLF affects around one-third of patients with cirrhosis who are admitted to hospital. The short-term mortality rate in these patients is high. NASH is less deadly, particularly in its early stages, but affects a large and growing number of people. One estimate suggests NASH affects 13 million people in the United States.

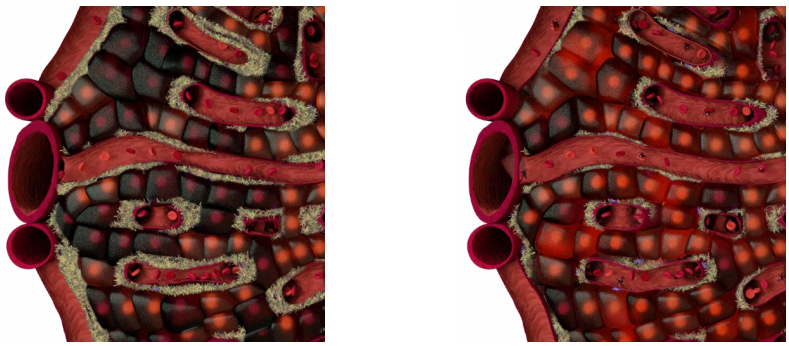

**Fig. 1 | HepaStem in 3D.** Images show hepatic tissue or lobule in a diseased state (fibrotic and inflamed) on the left and the expected state on the right after HepaStem treatment.

## Industrializing cell therapy supply

Promethera's targeting a severe segment of an indication as large as NASH means it needs an industrial, high-volume supply chain and production process to succeed. The basic idea of isolating and expanding liver cells ex vivo to create an off-the-shelf allogeneic cell therapy product was established in the early, academic phase of HepaStem's development but at that stage the process was ill suited to large-scale production.

That began to change in 2011, when Promethera transferred the process to its large-scale facility. Since then, Promethera has developed a good manufacturing practice (cGMP) process capable of producing treatments for about 300 patients (based on indications, in this case ACLF) from a single ethically-sourced healthy human liver.

Promethera has built a new production platform at Gosselies (Belgium), almost entirely in a closed system, to provide the large numbers of doses that would be needed for the treatment of severe NASH. The platform is modular and flexible to anticipate growing demands.

The biotech has spent as much time thinking about the supply chain steps either side of its facility. Upstream, Promethera has established relationships with tissue procurement centers in Europe and organ procurement organizations in the US (US-OPO's) to ensure a supply of healthy, ethically-sourced human livers. Coupled to work to increase per-liver output, these efforts have equipped Promethera to meet demand as it moves through advanced stages of clinical development and beyond.

The other supply chain considerations lie downstream of Promethera's facility. To ensure physicians and care takers can readily access HepaStem, Promethera cryopreserves the cells for reconstitution at hospitals. This extends the shelf-life of HepaStem—safeguarding availability while cutting costs and complexity—and means the last step in the supply chain is familiar to hospitals. HepaStem is taken out of its cryopreserved form like vaccines and other freeze-dried products.

Promethera has created this industrialized and scalable end-to-end cGMP supply chain without compromising the characteristics of HepaStem. The cell therapy has retained its therapeutic potency such as the immunomodulatory and antifibrotic properties.

## Clinically validating the concept

Promethera is now building on the platform it has established over the past decade. On the process development front, the biotech is implementing bioreactor-based scale-up technology to increase significantly the number of doses it generates from each liver.

Achieving that goal will position Promethera to easily scale up production of HepaStem as it moves into progressively larger clinical trials. Promethera is part way through a phase 2 ACLF trial designed to provide evidence of safety and preliminary indications of efficacy that will be pursued with a larger phase 2b trial. HepaStem is also advancing into the clinic in severe NASH.

These studies mark the culmination of more than a decade of work to discover and refine liver specific cell-based therapies with immunomodulatory and antifibrotic properties. Promethera has emerged from that period with a scalable cGMP process and evidence its cell therapies have the potential to treat devastating and major liver diseases.

Now, Promethera is poised to validate the concept in the clinic, opening the door to major markets and the widespread treatment of prevalent, life-threatening liver diseases with HepaStem.

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