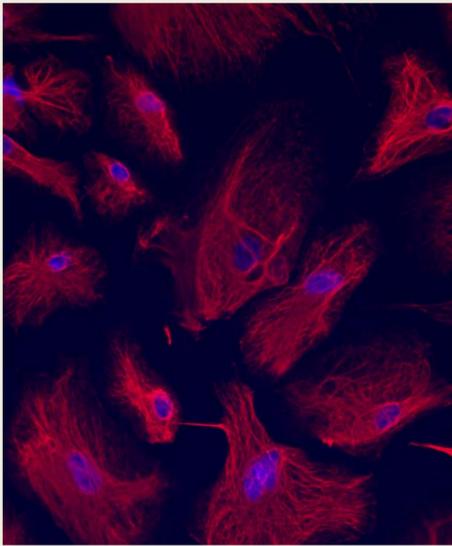


Human liver-derived cell therapy for Immuno-mediated and inflammatory liver diseases

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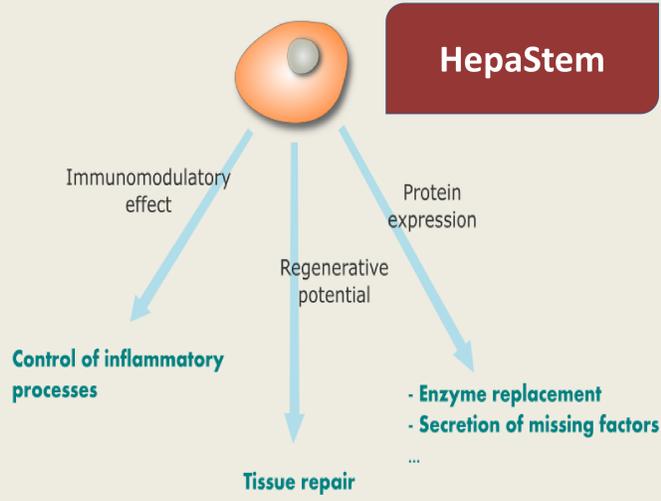
Organization: (1) Promethera Biosciences, 11 rue Granbonpré, 1435 Mont-Saint-Guibert, Belgium. (2) Pôle de Pédiatrie (PEDI), UCL, Avenue Hippocrate 10 bte B2, 1200 Woluwe-Saint-Lambert, Belgium (3) UCL, Institute for Liver and Digestive Health. Division of Medicine, Royal Free Campus, Rowland Hill Street, London NW3 2PF London, UK



HepaStem is a cell suspension constituted of Heterologous Human Adult Liver-derived Progenitor Cells isolated from normal adult human liver tissue.

A cell suspension predominantly constituted of liver parenchymal cells, is isolated by a proprietary process and further expanded in appropriate culture conditions to obtain billions of liver cells. Cryopreserved liver cells are then cultured, progressively resulting in the emergence of a homogeneous progenitor cell population expressing both mesenchymal and hepatocytic markers.

These cells can be used to treat a wide variety of liver diseases, from rare inborn metabolic diseases to acquired deficiencies such as acute alcoholic hepatitis or nonalcoholic steatohepatitis in adults.

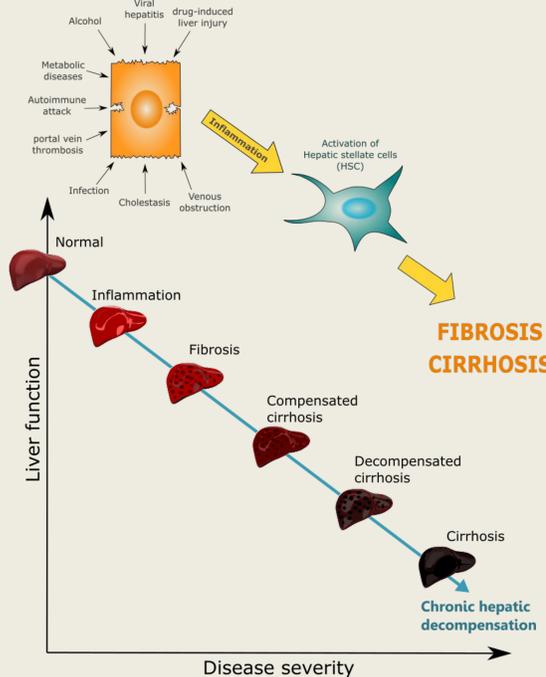


HepaStem is a human liver derived progenitor cell manufactured under GMP conditions by Promethera Biosciences. A phase I/II clinical trial already showed the cell therapy was safe and well tolerated in 20 paediatric patients. The cell's metabolic properties were used to treat genetic diseases like urea cycle disorder, but as mesenchymal stem cells, HepaStem has been shown to have immunomodulatory properties.

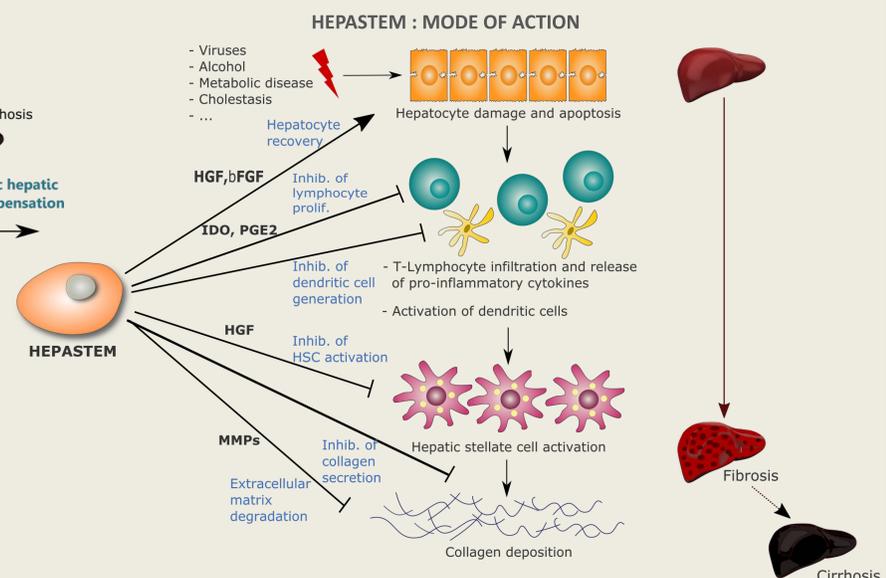
This immunomodulation will be now be applied in a clinical trial with patients suffering from acute-on-chronic-liver-failure (ACLF). They have a chronic liver fibrosis/cirrhosis, but are admitted to the hospital with an acute liver decompensation on top of the cirrhosis. ACLF is defined by an imbalance of the immune system, which progresses the diseases towards multiple organ failure. The survival of these ACLF patients drops below 50% in the first 3 months after hospital admission, but once ACLF progression is overturned, patients can return to a normal state, where the liver fibrosis is chronic only. Rebalancing the immune system, involved a complex mix of immuno-cytokines and cells.

HepaStem is liver derived and has shown to migrate towards the liver when infused in the peripheral vein, and a homing to inflamed body areas was observed; both helping the cells to migrate to the liver fibrotic areas that are the subject of this project.

Promethera is planning a clinical trial involving multiple centres spread over Europe, in which ACLF patients will receive several injections of HepaStem. Blood and tissue analysis will be evaluated to investigate the effect of the HepaStem modulation on the immune system and the ACLF progression of these patients.



HepaStem liver progenitor cells are able to suppress T lymphocyte activation and proliferation, by soluble factors. Cell-cell contact is thus not required for this inhibition to happen. Secreted cytokines like TGF- β , HGF, PGE2, IDO are involved in this mechanism. These molecules are all cytokines that are well secreted by HepaStem, affirming its immunomodulatory properties. Apart from the T-lymphocytes, dendritic cells (DCs) play a key role in the induction of immunity and tolerance, depending on the activation and maturation stage. MSCs have been demonstrated to interfere with DC differentiation, maturation and function. Even more, MSCs and our HepaStem cells lack surface expression of costimulatory molecules, such as CD80 and CD86, and it is believed that MSCs can render T cells anergic.



OFF-THE-SHELF ALLOGENIC PRODUCT



Sokal, Transplantation 2003

1 liver



Supply chain robustly mastered / off-the-shelf product directly delivered at patient's bedside
Simple and user friendly reconstitution at Hospital Pharmacy before infusion to patients

Promethera Biosciences was founded in 2009 by the Technology Transfer Office of the Université Catholique de Louvain and Prof Etienne Sokal, based on the discovery made by the research and clinical team at UCL. Prof Sokal is a leading expert in hepatology and cell therapy. The name of the Company was derived from the term "PROgenitor MEDicinal THERApies".

Promethera Biosciences has been funded by Venture Capital and grant and loans from the Walloon region (Belgium) since 2009 and a total of 67M Euros has been invested through three rounds of financing.

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