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## Immunoprivileged: why liver-derived stem cells are the key to allogeneic cell therapies

Promethera is developing HepaStem, a unique cell therapy that expresses mesenchymal stem cells with immunomodulatory properties suitable for the treatment of a number of hepatic diseases.

Immunogenicity is critical to the success of allogeneic cell therapy products. If the immune system identifies cells as foreign, the host will attack them, diminishing their efficacy. Mesenchymal stem cells (MSCs) once looked likely to avoid such attacks. However, recent studies have shown that some MSCs are more immunogenic than others. Liver-derived MSCs, such as Promethera Biosciences' HepaStem, emerged from these studies with an immunogenic advantage.

HepaStem is an allogeneic cell therapy based on liver-derived progenitor cells that express MSCs and hepatocytic markers. The HepaStem cells have immunomodulatory properties, similar to other MSCs, and act on the hepatic stellate cells that drive hepatic fibrosis.

These immunomodulatory, antifibrotic, and liver-specific features make HepaStem cells well-suited to the treatment of hepatic diseases characterized by cirrhosis, fibrosis, and inflammation, such as acute-on-chronic liver failure (ACLF) and nonalcoholic steatohepatitis (NASH). Promethera has advanced HepaStem into clinical development based on the strength of preclinical data that support this hypothesis.

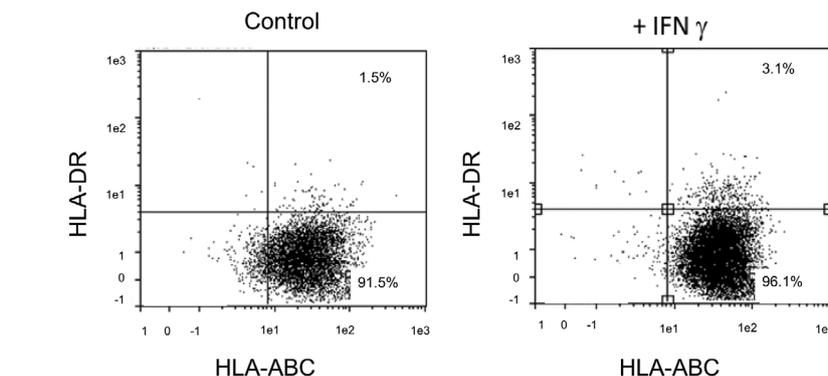
Promethera has also characterized the immunogenic profile of HepaStem, which indicates that it is free from the immunogenicity problems described for other MSCs and can bring the efficacy of cell therapies to major diseases.

### Why some MSCs trigger immune responses

Cell therapies can have dramatic efficacy but many of them create problems for drug manufacturers and health-care systems. Autologous cell therapies that use a patient's own cells pose the logistical challenge of shipping cells back and forth between a hospital and a manufacturing plant. These tasks drive up the cost of the therapy and delay treatment. Furthermore, the donor's own health status may impair the quality of the derived MSCs.

Allogeneic therapies, in contrast, use cells taken from other human donors, not the patient himself (the recipient). This means health-care facilities can buy in supplies of off-the-shelf therapies. Patients receive the treatment as soon as the physician decides the patient needs it, without any of the costly logistical issues. Cells taken from one healthy suitable donor can be used to treat multiple patients.

These factors make allogeneic cell therapies preferable to autologous products on many logistical, commercial, and therapeutic grounds. However, allogeneic cell therapies risk immune rejection. The cells originated in another person, and as such can



**Fig. 1 | Expression of HLA-ABC and HLA-DR by HepaStem and effect of the proinflammatory cytokine IFN $\gamma$ .** HepaStem cells were cultured in presence or absence of interferon- $\gamma$  (IFN $\gamma$ ). After 24 h, cells were harvested and stained with the antibodies specific for the cell surface markers human leukocyte antigen (HLA)-ABC and HLA-DR. Expression was analyzed by flow cytometry.

carry markers that allow them to be identifiable as invaders by the immune system, which attacks the cells in a similar manner to an attack on an invading virus or bacterium. Allogeneic cell therapies must avoid this fate to be effective.

In the early 2000s, researchers showed that MSCs derived from bone, cartilage, or adipose tissue expressed low levels of human leukocyte antigen (HLA) class I proteins—HLA-A, HLA-B, and HLA-C—and no HLA class II proteins, even when pretreated with the proinflammatory cytokine interferon- $\gamma$  (IFN $\gamma$ ). As the expression of HLA proteins is a key factor in immunogenicity, the findings raised hopes that MSCs could be safely taken from one patient and given to another.

However, later studies found that MSCs derived from bone marrow, adipose, and other tissues do express an HLA class II protein—HLA-DR—when exposed to IFN $\gamma$  (Fig. 1). This is a potentially critical shortcoming in the context of allogeneic cell therapies. The expression of HLA-DR could activate allo-specific CD4<sup>+</sup> T cells, leading to an immune reaction that renders the therapy ineffective.

### The immunogenic advantage of liver-derived cells

The most widely used sources of MSCs yield cells that express HLA-DR in the presence of IFN $\gamma$ . However, studies run by Promethera and academic partners show that cells derived from the liver do not express HLA-DR even in the presence of IFN $\gamma$ . This provides HepaStem with a big advantage over other sources of MSCs, which may produce cells that are rejected by the immune system unless given in combination with immunosuppressants.

Promethera's finding is in keeping with knowledge of the immunoprivileged status of the liver. Most of the blood supply to the liver is transferred along veins from the gut. This blood is loaded with the products of the microbial degradation that takes place in the gut. The immune cells in most organs would react to these products, resulting in unnecessary and potentially harmful attacks. The liver, in contrast, features tolerance mechanisms that stop the immune system from overreacting.

HepaStem cells come from this unique, immunoprivileged environment. When the cells are taken from this environment, processed, and administered to a different person, they retain some of the features shaped by their original niche, enabling them to cope better in hosts than other types of MSC.

The finding is a boost for Promethera and patients. Promethera is testing HepaStem in a phase 2 ACLF trial and is preparing to start human studies in NASH. These are the types of widespread disease in which scalable, allogeneic cell therapies are needed. Supported by the immunogenicity data, Promethera has strong reasons to position HepaStem as such a therapy.

contact

Alexandra Schiettekatte,  
Senior Communications Manager  
& Spokesperson  
PROMETHERA Biosciences S.A./N.V.  
Mont-Saint-Guibert, Belgium  
Tel: +32 (0)10 39 43 00  
Email: alexandra.schiettekatte@  
promethera.com