Challenges in developing an off-the-shelf cell therapy for ACLF and NASH

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Introduction

Promethera is a biopharma company focused on the research, development and commercialization of stem cell-based therapies and technologies for acute and chronic liver diseases. Our lead clinical program, an allogenic human liver derived mesenchymal stem cell product derived from our patented cell technology platform HepaStem, is currently being used in Phase IIa clinical trials for ACLF (acute on chronic liver failure) and NASH. Non-alcoholic steatohepatitis (NASH), a severe form of non-alcoholic liver diseases (NAFLD), is one of the prominent liver diseases worldwide. There is currently no approved drug for its treatment and liver transplantation is the only therapeutic approach for advanced NASH. Mesenchymal stem cells (MSCs) are promising candidates to modulate the proinflammatory and pro-fibrogenic environment of chronic liver because of their immunomodulatory properties. Recent data obtained in preclinical models of early and advanced stage NASH provided significant evidences to open these new clinical studies in NASH.

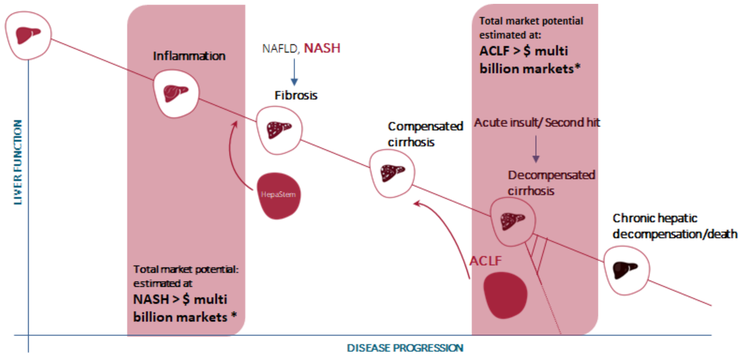


Figure 1: A liver disease patient's journey

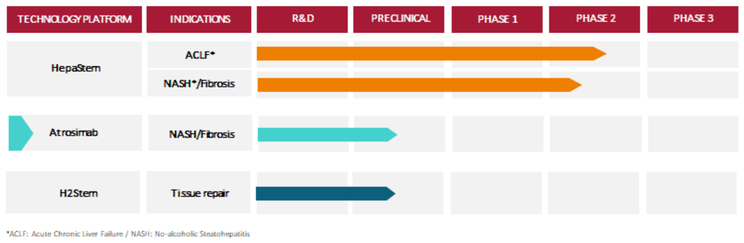


Figure 2: Current product pipeline for liver diseases

The dosing for these indications is likely to be in the order of 100 million cells per infusion. Large numbers of cells thus need to be manufactured and using standard cell culture techniques would make it too expensive and labour intensive. A standard expansion protocol in flasks or cell factories is an open process, and therefore run in expensive clean rooms to avoid the risk of contamination. We have explored several state-of-the art-bioreactor systems, and various types of microcarriers in stirred tanks from different manufacturers. We have tested these systems to optimize the complete workflow of HepaStem culture, including stem cell isolation from livers and expansion up to the scale of many clinical doses. Quality control and comparability studies were performed to verify that the characteristics of HepaStem cells harvested from the different procedures were maintained.

Methods and Results

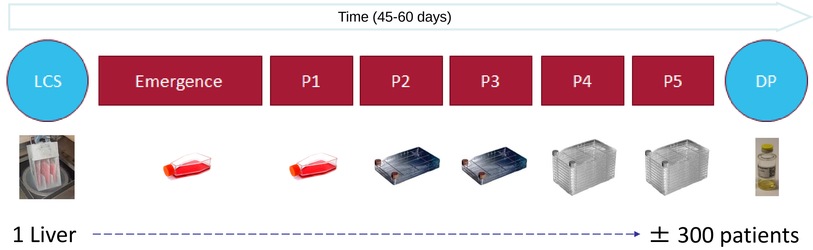


Figure 3: The current manufacturing process

The current manufacturing process starts with plating a liver cell suspension under conditions that stimulate the emergence of the HepaStem cells. The media contain 9% foetal bovine serum. The GMP process is executed over 6 open steps, needing grade A in B which is expensive and labour intensive. The liver cell suspension (LCS) prepared from one liver can generate material to treat about 300 patients.

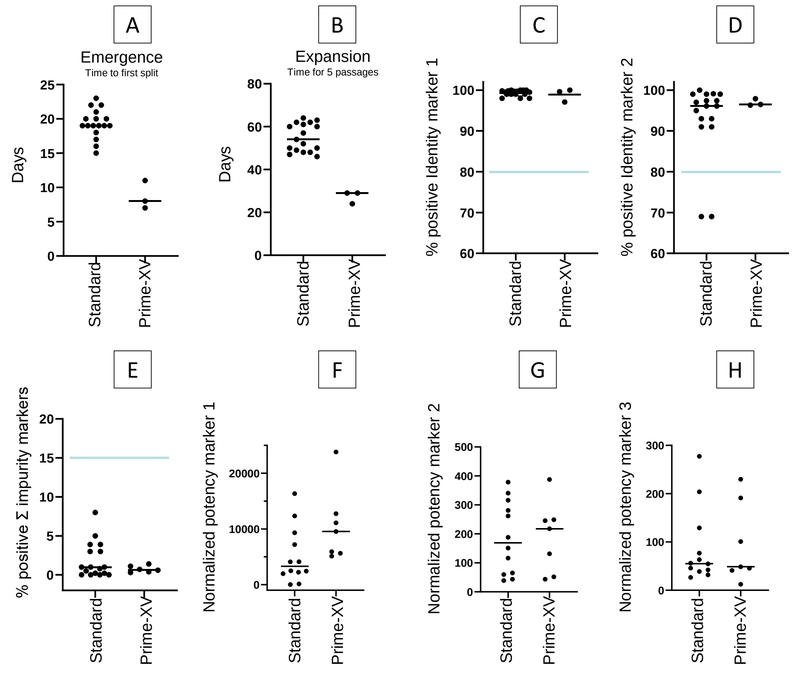
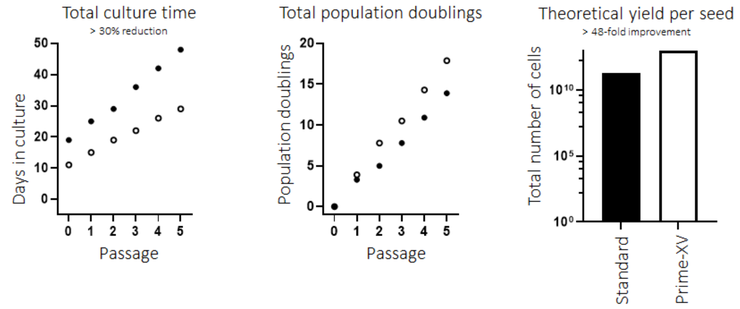


Figure 4: Performance and quality parameters of xenofree culture

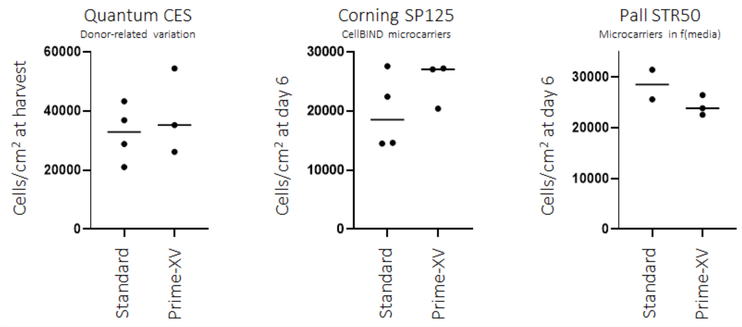
Transition of the current manufacturing process to a new process using xenofree media in bioreactors starts with evaluating xenofree media for emergence (A) and expansion (B) in the 2D process. Control of identity parameters (C, D and E) and confirmation of potency (F, G and H) are part of the comparability exercise. As an example, results with the Fujifilm Irvine Scientific Prime-XV MSC XSFM Medium are shown but some other media were also successful.

Figure 5: Performance in manufacturing



The application of xenofree media throughout the process was transferred to manufacturing to check feasibility and performance. The combination of faster emergence and growth, resulted in more than 30% reduction in time for the process and a theoretical 48-fold increase in yield.

Figure 6: Proof of concept studies in bioreactors



Several bioreactors and bioreactor-microcarrier combinations were evaluated for expansion of the product in xenofree media after emergence on flatware. Several combinations worked as well or better with xenofree media and this leaves choice to build a seeding train. POC runs in medium and large (50L) systems yielded up to > 1 billion cells per litre for the best combinations.

Conclusions

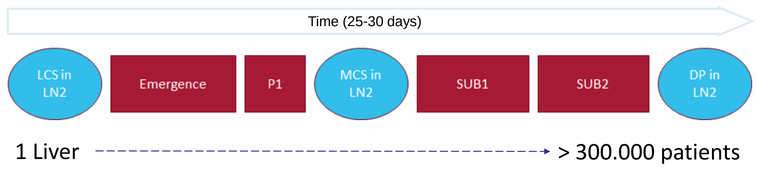


Figure 7: The future manufacturing process

By combining all the improvements related to the use of xenofree media, the implementation of a Master Cell Stock and the use of Single Use Bioreactors (SUB), the COGS will drop dramatically while the overall yield per liver will increase > 1000 fold. This will render the process suitable for late stage development and commercialisation for ACLF and NASH.