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 allogeneic 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 or chronic liver failure) and NASH. Non-alcoholic steatohepatitis (NASH), a severe form of non-alcoholic liver diseases (NASH), 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 promoting candidates to modulate the proinflammatory and pro-fibrogenic environment of chronic liver because of their immunosuppressive properties. Recent data obtained in preclinical models of early and advanced stage NASH provided significant evidences to open these new clinical studies in NASH.

Methods and Results

Figure 1: A liver disease patient’s journey

Figure 2: Current product pipeline for liver diseases

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 3: The current manufacturing process

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 JF1M 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 seeded train. POC runs in medium and large (560) systems yielded up to 1 billion cells per litre for the best combinations.

Conclusions

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 CDG 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.

Figure 7: The future manufacturing process

> 300,000 patients