CLINICAL SCALE MANUFACTURING OF AUTOLOGOUS INSULIN PRODUCING LIVER CELLS FOR THE TREATMENT OF DIABETES

Rachel Legmann, Pall Life Sciences
Rachel_legmann@pall.com
Andy Reniers, Pall Life Sciences
Nicholas Kohlstrom, Pall Life Sciences
Brian Gardell, Pall Life Sciences
Fabien Moncaubeig, Pall Life Sciences
Vered Aviv, Orgenesis Ltd
Keren Shternhall-Ron, Orgenesis Ltd
Irit Meivar-Levy, Orgenesis,Ltd
Sarah Ferber, Orgenesis, Ltd

Key Words: Adenoviral vector, fixed bed bioreactor, Diabetes, cell culture, industrialization

Diabetes is a major global health problem with over 387 million diabetics causing 4.9 million deaths worldwide. Current therapies rely on recombinant insulin injection to the patients several times a day to control glucose levels but do not address the fundamental problem; the loss of insulin producing cells of the pancreas. Orgenesis developed a cell therapy to replace these cells by taking a small biopsy from a patient's liver; growing the cells in flatware treating; and transdifferentiating these cells with adenovirus vectors containing genes for insulin production. This approach allows the diabetic patient to be the donor of their own therapeutic tissue, overcoming both the shortage in cadaver tissue availability and immune suppression. To bring this cell therapy approach into the pre-clinical and clinical phases, Orgenesis and Pall combined their respective expertise to develop a manufacturing strategy for both viral vector and cell products at large scale with the added benefit of greater process control incorporating two single-use large scale bioreactors. The Xpansion® 200 single-use bioreactor was successfully used to scale-up the human adult liver-derived cells proliferation process. By using the Xpansion platform, Orgenesis now has a reliable process to amplify their cells from 10-25 million up to 1.8-2 billion cells required for curing a diabetic patient. The cell mass generated by the bioreactor preserves their viability and potential for trans-differentiation. As a result of this successful co-development partnership, Orgenesis is moving forward with their process to large-scale clinical studies for GMP-compliant commercial manufacturing of AIP cell for transplantation. For large scale viral production we used the packed-bed iCellis® 500 disposable bioreactor that provides 3D matrix in a controlled system with low shear stress for adherent cells. In this study, we have optimized manufacturing for three adenovirus serotype 5 using the predictive small scale iCellis® nano and the manufacture scale iCellis® 500 bioreactor with cultivation area of 66 m^2. By optimizing culture and infection parameters such as HEK293 cell seeding density, multiplicity of infection, time of infection, day of harvest, and media circulation parameters, yield was increased to $5.6x10^{15}$ infectious virus particle per batch (iCellis 500_{66}). These cells and viral vector yields make the Xpansion® 200 and the iCellis® promising scalable technologies for the production of adenovirus products. The purified adenovirus hPDX-1, hNeuroD and hMafA were fully functional and successfully transduced the target liver derived cells. Next step of the study is to incorporate the viral trans-differentiation step into the developed cGMP cell expansion process.

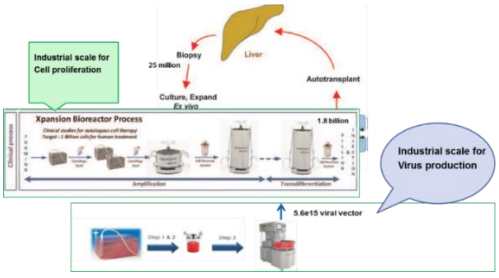

Figure 1 – Liver cells-based autologous cell therapy schema