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# Industrialization of adenoviral vector production in fixed bed bioreactor and amplification of primary liver cells in Xpansion® bioreactor: Autologous insulin producing cells for the treatment of diabetes, from bench to clinical scale

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# INDUSTRIALIZATION OF ADENOVIRAL VECTOR PRODUCTION IN FIXED BED BIOREACTOR AND AMPLIFICATION OF PRIMARY LIVER CELLS IN XPANSION® BIOREACTOR: AUTOLOGOUS INSULIN PRODUCING CELLS FOR THE TREATMENT OF DIABETES, FROM BENCH TO CLINICAL SCALE

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Diabetes is a major global health problem with over 370 million diabetics and an estimated 550 million by 2030. Current therapies rely on recombinant insulin injection to the patients several times a day to control glucose level 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 these cells with adenovirus vectors containing the genes required to transdifferentiate them to insulin producing cells. This approach allows the diabetic patient to be also the donor of his own therapeutic tissue, overcoming both the shortage in tissues availability from cadaver and also the immune suppression. To bring this cell therapeutic approach into the pre-clinical and clinical phases, Orgenesis and Pall combined their respective expertise to develop a strategy to manufacture both viral and cells products at large scale and with greater control by the usage of two single-use large scale bioreactors. For large scale viral production we used packed-bed iCellis® 500 disposable bioreactor that provides 3D controlled, perfusable system with low shear stress for adherent cells. The Xpansion 200 single-use bioreactor was used for growing the primary human liver cells under controlled culture conditions to generate cell mass required for curing a diabetic patient.In this study, we have optimized adenovirus serotype 5 manufacturing using the iCellis Nano bioreactor with different cultivation area up to 4 $m^2$. HEK293 cell cultivation, infection and harvest of the virus in an adherent environment proved possible reaching total virus yield of 3.4e14 IU/batch. We have successfully scaled up the cell amplification process to the fully closed Xpansion platform technology. Results showed that 1-2 gr of patient's liver biopsy was expanded to around 1.8 Billion cells in Xpansion 200 bioreactor representing more than the targeted dose requirement of 1 Billion cells per patient. Next step of the study is to focus on develop purified viral stocks, incorporating the viral trans-differentiation step into the developed cGMP cell expansion process.

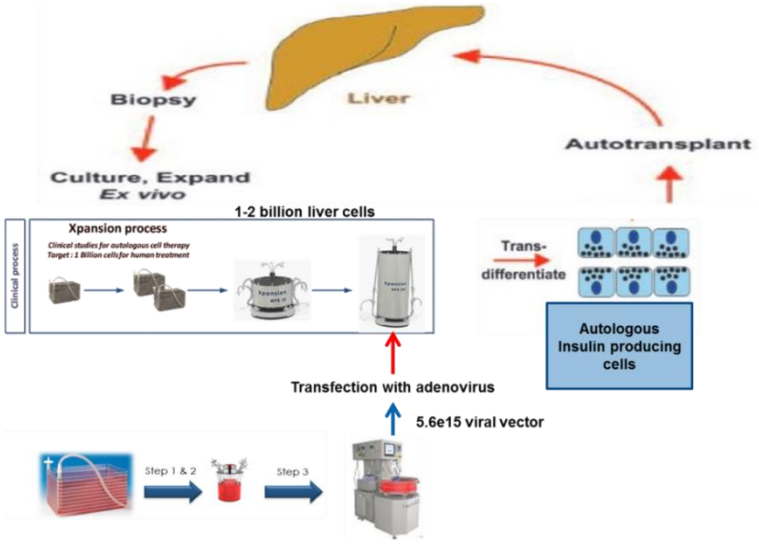


*Figure 1* – Liver cells-based autologous cell therapy schema