CULTURES OF LIVER-DERIVED CELLS IN FLOW BIOREACTORS FOR EFFICIENT BIOARTIFICIAL LIVER

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Transplant of the whole organ is currently the only effective method to cure liver failure. Unfortunately, the main problem is a donors' shortage. This led to the development of the alternative methods based on cell therapies, eg. Bioartificial Liver (BAL). The most advanced BAL, a hybrid system used for liver failure bridging therapy, ELAD (Extracorporeal Liver Assist Device), utilizes human hepatoma-derived C3A cells seeded in a hollow fiber bioreactor. ELAD has recently failed to demonstrate its efficacy in clinical trials. Primarily, the C3A cells do not metabolize ammonia due to the non-functional urea cycle. On the other hand, the use of isolated human hepatocytes is currently impractical. The main problem with the primary human hepatocytes is dedifferentiation. The cells *in vitro* quickly lose their characteristic features, particularly protein production and the ability to neutralize the toxic substances.

We propose several strategies to solve these problems including the use of genetically modified hepatoma cells with restored urea cycle, the culture of hepatic cells in dynamic conditions (perfusion bioreactors), and coculture of liver-derived cells with genetically modified feeder layer cells. Our preliminary results show that such approaches have potential to achieve success in construction of effective BAL.

Modified hepatoma cells or isolated human hepatocytes will be seeded individually, or in coculture with human skin fibroblast producing additional amounts of growth factors, in hollow fiber bioreactors and cultivated under dynamic flow conditions. Consumption of glucose and urea production will be monitored using metabolic test. Synthesis of the albumin will be measured quantitatively with ELISA. The cells parameters, such as viability and phenotype will be analyzed by flow cytometry.