A Crossed Hollow Fiber Membrane Bioreactor for Liver Tissue Engineering as a Tool for Drug Testing and Toxicology

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Tissue or organ physiological model can be a reproducible and economical tool for the in vitro study alternatively to animal models and for the human enzyme expression prediction. A crossed hollow fiber membrane bioreactor was developed to support the long-term maintenance and differentiation of human hepatocytes. The bioreactor consists of two types of hollow fiber (HF) membranes with different molecular weight (MW) cut-off and physico-chemical properties cross assembled in alternating manner: modified polyetheretherketone (PEEK-WC) and polyethersulfone (PES), used for the medium inflow and outflow, respectively. The combination of these two fiber set produces an extracapillary network for the adhesion of cells and a high mass exchange through the cross flow of culture medium.

Primary human hepatocytes were cultured in the extraluminal compartment among the PEEK-WC HFs, devoted to provide the cells oxygenated medium containing nutrients and metabolites, and the PES HFs devoted to remove from cell compartment catabolites and cell specific products. In this way the two HF membrane systems mimic the in vivo arterious and venous blood vessels. In the bioreactor human hepatocyte maintened their differentiated specific functions at high levels up to 18 days of culture and re-established their polygonal morphological behaviour with an high level of cell adhesion on the fibers surrounded by an extracellular matrix-like structure. The individual cytochrome P450 isoenzymes involved in the diazepam metabolism were expressed at high levels and the same metabolites found in humans were produced in the bioreactor.

The good performance of the bioreactor demonstrated its workability as device with a controlled environment that may provide an inexpensive and reliable in vitro physiological model for in vitro study on engineered human liver tissue constructs.