

**P001** De-differentiation facilitates hepato-pancreatic transdifferentiation.

**S. Thowfeequ, W.-C. Li, K.E. O'Neill, D. Eberhard, J.M.W. Slack and D.Tosh.**

*Centre for Regenerative Medicine, University of Bath, Bath, United Kingdom*

Several recent studies have suggested that hepatocytes can be converted to pancreatic beta-cells with varying degrees of success. However, the main drawback of culturing hepatocytes in vitro has been their limited life span and their rapid de-differentiation in culture. This de-differentiation is accompanied by a progressive diminution in the transcription levels of liver-specific genes. By using a novel culture system in which the differentiated state of hepatocytes can be maintained long term, a direct comparison between differentiated and de-differentiated hepatocytes is possible. We have shown that the de-differentiation of hepatocytes, and the loss of their hepatic phenotype is in fact associated with a concomitant induction of a pancreatic gene expression profile, including the expression of Pdx-1, insulin 1 and 2, SUR1 and Kir6.2. In this 'primed' state, it is possible to transdifferentiate or convert these cells more efficiently into beta-like cells by the transduction of the pancreatic master switch gene, Pdx-1. These results were confirmed in rat, mouse and human hepatocytes. Hepatocytes can therefore be induced to express a pancreatic phenotype when maintained under de-differentiating conditions and then further matured into functional beta-cells by the over-expression of key regulatory pancreatic transcription factors or by the application of specific growth factors.