Correlation of gene expression and cellular pathways in insulin-expressing mouse liver cells transduced with an integrating adeno-associated viral vector (AAV)

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Gene therapy is being considered as a treatment/cure for type 1 diabetes (T1D). Previously we used a clinically applicable AAV to deliver furin cleavable insulin (INS-FUR) to the livers of diabetic non-obese diabetic mice. The traditional AAV8 that allows predominantly episomal expression, and the hybrid AAV8/piggyBac that results in transgene integration into the host genome were used. Euglycaemia was achieved in mice (n=4) that received AAV8/piggyBac-INS-FUR, but not in mice that received AAV8-INS-FUR. In the current study global transcriptomic profiling was carried out, by total RNA sequencing, to compare the key pathways modulated in hepatocytes that reversed diabetes with those that did not. Using Qiagen CLC Workbench, significant genes were identified based on fold change expression cut offs of, and a false discovery rate (FDR) p-value of < 0.05.

Selected genes were mapped onto the various cellular pathways using Qiagen Ingenuity Pathway Analysis (IPA) software to determine trends in pathway activation/ inactivation related to the altered gene expression. IPA analysis showed that the canonical pathways identified between the treatments remained largely the same, however their downstream biological processes differed. Key canonical pathways identified include pathways related to insulin signalling, glucose, and lipid metabolism. Key pathway players identified as significantly altered in the comparative treatments included insulin, major histocompatibility complex class I, A, glucose-6-phosphatase catalytic subunit 1 and insulin like growth factor binding protein 1. The profile of AAV8/piggyBac-INS-FUR transduced mouse livers resembled that of a normal liver compared to livers transduced with AAV8-INS-FUR. This study confirms the correlation of transcriptomic data mapping and has identified differences in the cellular effects of both vector systems used to deliver INS-FUR for T1D treatment.