Use of Gene Expression Signature technology to identify VVP808, a novel insulin sensitiser with efficacy in vitro and in vivo

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Background and Aims: The aims of the current study were to develop a new small molecule library screening strategy based on gene expression signature (GES) technology, and to utilise this screen to identify new insulin sensitising agents.
Material and Methods: Differentiated 3T3-L1 adipocytes were rendered insulin-resistant using TNFα (3 ng/ml for 72h), and insulin sensitivity was restored by adding a cocktail of known antidiabetic agents for the last 24h. Mouse cDNA microarrays were used to establish gene expression profiles for the insulin resistant cells, and the cells with insulin sensitivity restored. Bayesian linear model selection was performed to find the optimal set of 11 genes (the GES) that best defined the difference between the two cell states. Insulin resistant 3T3-L1 cells were then treated with a library of ~1500 compounds, and analysed for similarity of expression of the 11 GES genes. Hit compounds were selected for further testing *in vitro* and *in vivo*.
Results: Using the GES, we identified a family of compounds that dose-dependently improved insulin stimulated glucose transport and incorporation into lipid in 3T3-L1 adipocytes ($p=9x10^{-7}$). The lead compound, designated VVP808, was further tested in animal models of insulin resistance and diabetes. Treatment of *db/db* mice with VVP808 for 7 days resulted in a dose-dependent reduction in fasting blood glucose concentration (up to 65% reduction at 50 mg/kg/d, Day 0: 24.7±1.8 vs Day 7: 9.5 ±1.0 mmol/L, p=0.00004). The improvement in glycemia was associated with a 7% reduction in body weight (p=0.002), however a subsequent pair-feeding study showed that the reduction in blood glucose concentration was independent of body weight loss. Treatment of diet-induced obese (DIO) C57Bl/6 mice with VVP808 for 21 days resulted in a dose-dependent improvement in glucose tolerance and reduction in fasting blood glucose concentration. The area under the blood glucose curve during an ipGTT was reduced by up to 28% (p=0.037), while fasting blood glucose was significantly reduced at doses from 20-100 mg/kg/d ($p<0.05$). These effects were accompanied by a dose-dependent decrease in body weight of 5-11% ($p<0.05$).
Conclusion: The GES screening strategy successfully identified a family of compounds with insulin sensitising and antidiabetic effects *in vitro* and *in vivo*. VVP808 is a novel insulin sensitiser that also causes moderate loss of body weight in obese animals, and therefore has excellent potential for development as an antidiabetic agent. A clinical study evaluating the safety and efficacy of VVP808 in type 2 diabetic patients is planned for the second half of this year.