Title: *In vivo* evaluation of a novel therapeutic target for type 2 diabetes identified through genome wide association study-based drug discovery

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Abstract:
We have previously proposed several new potential pharmacological targets for type 2 diabetes (T2D) treatments using systematic bioinformatics approach integrating the findings of genome-wide association studies (GWAS), and biological or pharmacological information from databases. KIF11 is one of the potential therapeutic targets for T2D identified by the *in silico* pipeline. Here, we aimed to investigate the therapeutic effect of a KIF11 inhibitor on T2D using diabetic mice model. C57BL/6J (B6J) mice and BKS.Cg-Dock7m+/+Leprdb/J (db/db) mice were treated with either KIF11 inhibitor (SB743921, 5mg/kg body weight, ip, SB-B6J or SB-db) or vehicle (C-B6J or C-db) every 4-5 days from 7-8 weeks of age. The KIF11 inhibitor increased insulin sensitivity [insulin tolerance test (IPITT)-area under the curve (AUC); 23423±2273 vs. 13620±551, C-db vs SB-db respectively, P<0.005], and reduced hepatic glucose production [pyruvate tolerance test (IPPTT)-AUC; 66830±7763 vs. 47430±5690, C-db vs SB-db, P<0.05] in db/db mice. AUC for blood glucose levels during intra peritoneal glucose tolerance test (IPGTT)of SB-db was lower than that of C-db (59268±5097 vs. 49370±383, C-db vs SB-db), although the difference was not attained statistically significant level (P=0.09). SB743921 did not significantly affect glucose metabolism in non-obese mice (C-B6J vs SB-B6J; AUC-IPGTT, 39718±4569 vs 35796± 4803, P>0.05; AUC-IPITT, 6701±1028 vs 5896±764, P>0.05). We next analyzed gene expression profile of liver tissues isolated from SB-db or C-db using Clariom™ S Assay for mouse (Thermo Fisher Scientific Inc. MA, U.S.A.). The result of gene set enrichment analysis indicated gene sets “mitotic spindle”, “notch signaling” and “ Wnt beta catenin signaling” were down-regulated in the SB-db liver (FDR q<0.05).

In conclusion, we have demonstrated that administration of KIF11 inhibitor ameliorated impaired glucose tolerance of db/db mice through increasing the insulin sensitivity and suppressing hepatic glucose production. The results suggest our GWAS-based drug discovery platform is useful to identify novel therapeutic targets for common diseases.