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

**Author Block:** M. Imamura1,2, M. Matsunami3, S. Maeda1,2;
1Department of Advanced Genomic and Laboratory Medicine, Graduate School of Medicine, University of the Ryukyus, Nishihara, Japan, 2Division of Clinical Laboratory and Blood Transfusion, University of the Ryukyus Hospital, Nishihara, Japan.

**Abstract:**
**Background and aims:** Genome-wide association studies (GWAS) have identified more than 200 genetic loci associated with susceptibility for type 2 diabetes (T2D). We have previously proposed several new potential pharmacological targets for T2D treatments using systematic bioinformatics approach integrating the findings of GWAS for T2D, and biological or pharmacological information from various databases. KIF11 is one of the potential therapeutic targets identified by the in silico pipeline. However, its therapeutic effect for T2D has not been evaluated by in vivo study. Here, we aimed to investigate the therapeutic effect of a KIF11 inhibitor on T2D using diabetic mice model.

**Materials and methods:** C57BL/6J (B6J) mice (n=8/group) and BKS.Cg-Dock7m+/+Lepdb/J (db/db) mice (n=3/group) under normal chow diet 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. Intra peritoneal glucose tolerance test (IPGTT), insulin tolerance test (IPITT), and pyruvate tolerance test (IPPTT) were performed after 3, 4 and 6-7 times of SB743921 administration respectively. Total RNAs of liver tissues from SB-db or C-db (n=3/group) were extracted for subsequent gene expression analysis using Clariom™ S Assay for mouse (Thermo Fisher Scientific Inc. MA, U.S.A.).

**Results:** The KIF11 inhibitor increased insulin sensitivity (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 (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 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). No difference in body weight gain was observed between C-db and SB-db until 13 weeks of age. As a result of microarray analysis, we
identified 355 differentially expressed genes between SB-db and C-db mouses (t-test, P<0.05 and expression changes, >1.5-fold or <0.67-fold), and gene set enrichment analysis indicated that gene sets “mitotic spindle”, “notch signaling” and “Wnt beta catenin signaling” were down-regulated in the SB-db liver (FDR q<0.05). The results of the IPGTT and IPITT on SB743921-administrated B6J mice (C-B6J vs SB-B6J; AUC-IPGTT, 39718±4569 vs 35796±4803, P=0.13; AUC-IPITT, 6701±1028 vs 5896±764, P=0.13) indicated SB743921 did not significantly affect glucose metabolism under normal conditions.

**Conclusion:** We have demonstrated that administration of KIF11 inhibitor ameliorated impaired glucose tolerance on db/db mice through increasing the insulin sensitivity and suppressing hepatic glucose production. The results suggest that our GWAS-based drug discovery platform is useful to identify novel drug targets for the treatment of common diseases, such as T2D.