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Supplemental Information

Substrate Reduction Therapy for Sandhoff Disease through Inhibition of Glucosylceramide Synthase Activity

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SUPPLEMENTAL FIGURE S1

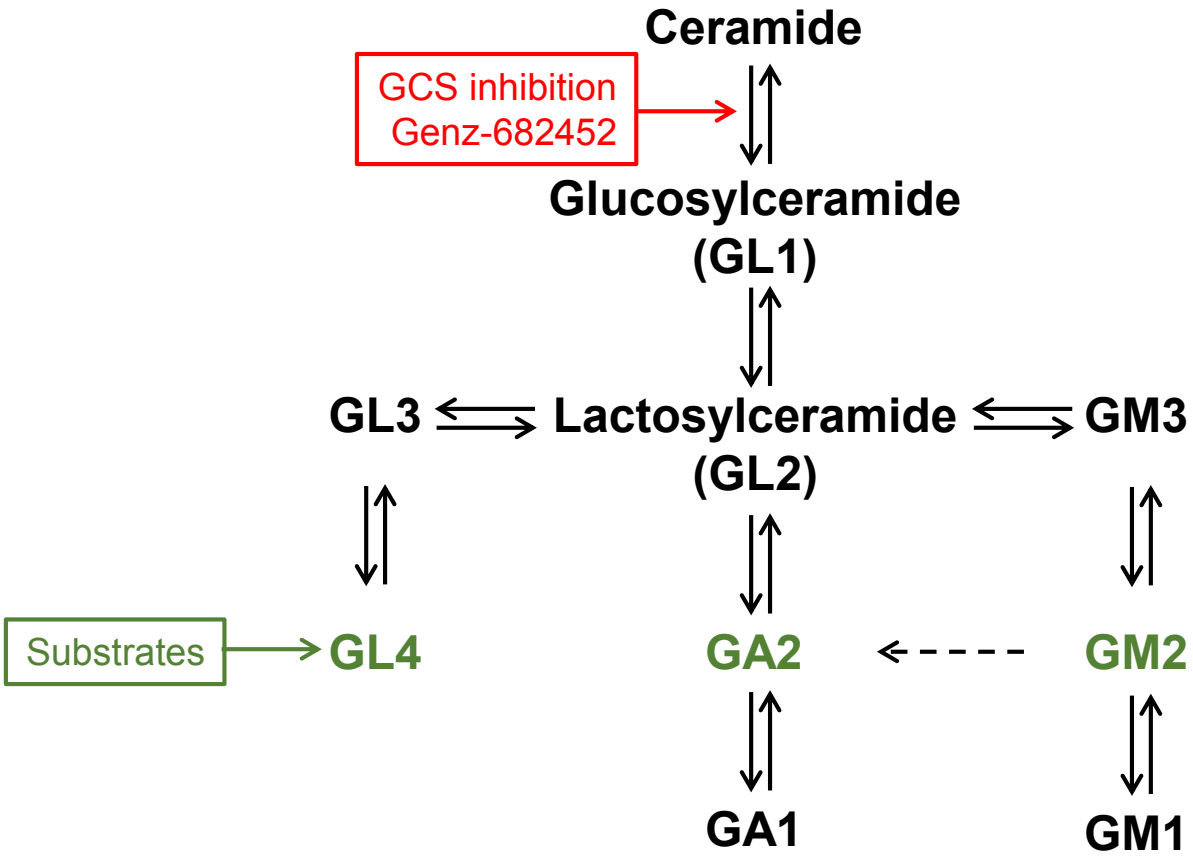

Figure S1. Attenuated schematic of the glucosphingolipid pathway
An abbreviated glucosphingolipid biosynthetic pathway beginning with the glucosylation of ceramide by glucosylceramide synthase. This enzyme is inhibited by Genz-682452 as indicated. The anabolic processes occur primarily in the Golgi and the catabolic processes can occur in the lysosome. The glucosphingolipid substrates of β-hexosaminidase are indicated in green.

SUPPLEMENTAL FIGURE S2

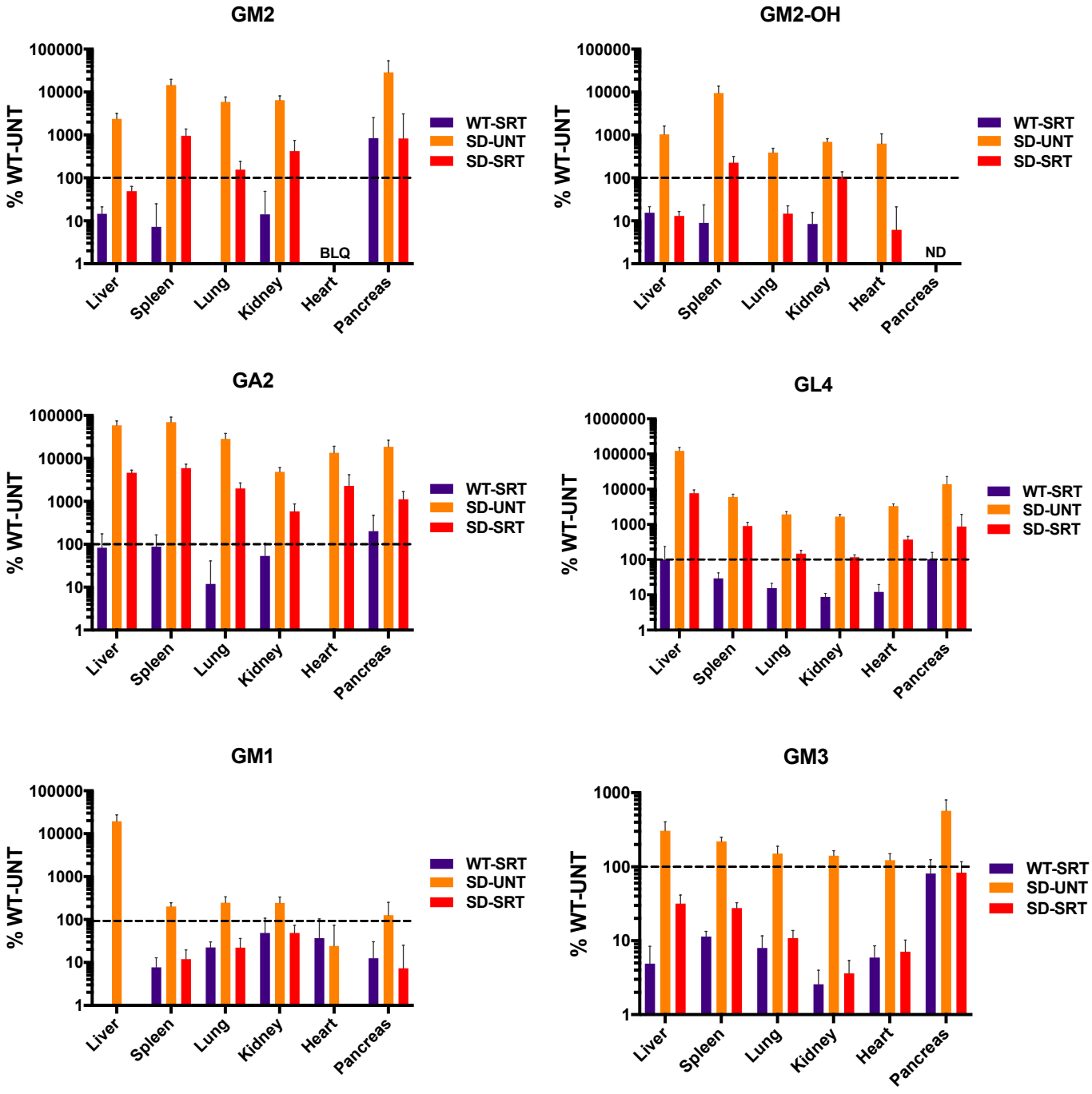

Figure S2. Genz-682452 attenuates glycosphingolipid accumulation in visceral tissues of *Hexb*$^{-/-}$ mice

Companion data for figures 1 and 2. Glycosphingolipids were analyzed in liver, spleen, lung, kidney, heart and pancreas from 112 day old mice. Glycosphingolipids GM2, 2-hydroxylated-GM2, GA2 and globoside GL4 are substrates of β-hexosaminidase. Gangliosides GM1 and GM3 were also evaluated. Data is presented as percent change from untreated *Hexb*$^{+/-}$ mice (WT-UNT) in each tissue (dashed line). Data from Genz-682452-treated *Hexb*$^{+/-}$ (WT-SRT), untreated *Hexb*$^{-/-}$ (SD-UNT) and Genz-682452-treated *Hexb*$^{-/-}$ mice (SD-SRT) are shown. BLQ = below the lower-level of quantitation; ND = not done. N = 6 per group.