**Trodamusquemine (MSI-1436) Enhances Glucose Tolerance in a Murine Model of Insulin Resistance**

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**Abstract**

Trodamusquemine (MSI-1436) is an allosteric inhibitor of protein tyrosine phosphatase 1B (PTP1B) which has been shown to elicit weight loss and improve glucose tolerance in a diet-induced model of obesity and genetically obese models. Trodamusquemine has also been shown to improve fasting and postprandial blood glucose levels. To further characterize this glucose tolerance enhancement, AKR/J mice were treated with rapamycin (2 mg/kg daily, IP) to induce a glucose intolerant state. The mice were treated with either MSI-1436 (5 mg/kg, q3dx3, IP) or vehicle and OGTTs were performed 24 days after the last treatment. MSI-1436 corrected the rapamycin-induced glucose dysmetabolism. Trodamusquemine shows potent improvement in glucose tolerance and supports development as an anti-diabetic therapy.

**Introduction**

Trodamusquemine (MSI-1436)

- Trodamusquemine is a small molecule that causes weight loss in wild type, genetically obese, and diet-induced, obese animal models.
- Phase I clinical trials for obesity were initiated in May of 2007.
- Trodamusquemine is a selective PTP1B inhibitor (>150 fold specificity over the highly homologous enzyme, TCPTP). PTP1B is a negative regulator of insulin signaling.

**Objective**

To characterize the anti-diabetic properties of trodamusquemine. To assess the effect of trodamusquemine treatment on glucose tolerance and insulin sensitivity.

**Figure 1: Study Design, AKR/J Mice**

Timeline

- Daily Rapamycin/Vehicle Tx
- Trodamusquemine/Vehicle Tx

**Figure 2: Trodamusquemine Alleviates Rapamycin-Induced Glucose Intolerance**

**Objective**

- To characterize the anti-diabetic properties of trodamusquemine. To assess the effect of trodamusquemine treatment on glucose tolerance and insulin sensitivity.

**Figure 4: Trodamusquemine Improves Fasting Blood Glucose**

Plasma Insulin (µg/L)

- Female ob/ob mice were treated with 5 mg/kg (p.o.) trodamusquemine on Days 0, 3, 6, and 9. On Day 21, overnight fasting blood glucose levels were measured (upper right panel). On Day 30 and following an overnight fast, an oral glucose tolerance test revealed improved glucose tolerance as compared to vehicle control. Data shown is Mean + SEM, n=2-4 mice/group.

**Figure 5: Extended Improvement of Glucose Tolerance**

Plasma Insulin (µg/L)

- Female ob/ob mice were treated with trodamusquemine (5 mg/kg) on Days 0, 7, and 14, followed by weekly doses of 1 mg/kg from Days 35-65, and 5 mg/kg on Days 105, 112, and 119) or saline. An OGTT (Day 122) confirmed that improved glucose tolerance is maintained over time. Data shown is Mean + SEM, n=5-7 mice/group.

**Conclusions**

- Trodamusquemine improves insulin sensitivity in mice.
- Trodamusquemine lowers plasma insulin levels.
- Trodamusquemine treatment improves fasting blood glucose and glucose tolerance in hyperglycemic animal models and these effects are maintained over time.

**References**

