New Treatment for Type-2 Diabetes Id1 Inhibition

Inhibition of Id1 in type-2 diabetes:

- Directly targets pancreatic β-cells
- Reduces or prevents glucose intolerance
- Increases insulin levels
- Improves glucose-stimulated insulin secretion
- Reduces islet stress
- Complimentary to existing therapies

Inhibitor of DNA Binding, Id1, is a member of a family of proteins that are capable of inhibiting differentiation. Its expression is normally suppressed in healthy adult cells, however, it is progressively upregulated in human β-cells in conditions of type-2 diabetes. In these cells, Id1 plays an essential role in the etiology of glucose intolerance, insulin secretory dysfunction and β-cell dedifferentiation under conditions of chronic lipid oversupply. Furthermore, Id1 knock-out mice appear normal and healthy, consistent with normal suppression of Id1 expression. Inhibiting Id1 therefore represents a novel approach to treating type-2 diabetes by directly targeting dysfunction of the β-cell unlike existing therapeutics.

Id1 Inhibition Increases Insulin Secretion

- Id1 knock-out mice secrete more insulin in response to glucose compared to wild-type mice, particularly after high-fat feeding (Figure 1)
- Islets from Id1 knock-out mice display enhanced insulin secretion.
- Id1 deletion does not affect β cell mass, islet number or insulin action
- Enhanced insulin secretion is associated with reduced stress gene expression and protection from lipid-mediated β-cell dedifferentiation

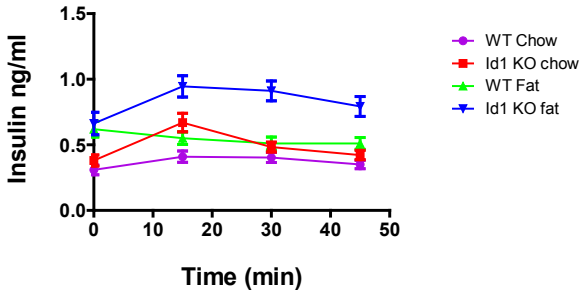

Figure 1. *Intraperitoneal Glucose Tolerance Test (2g/kg body weight)*

Wild-type vs Id1 knock-out fat 2-way ANOVA genotype effect p<0.001

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Id1 Inhibition Enhances Glucose Tolerance

Id1 knock-out mice have increased glucose tolerance and are protected against fat diet-induced glucose tolerance compared to wild-type mice.

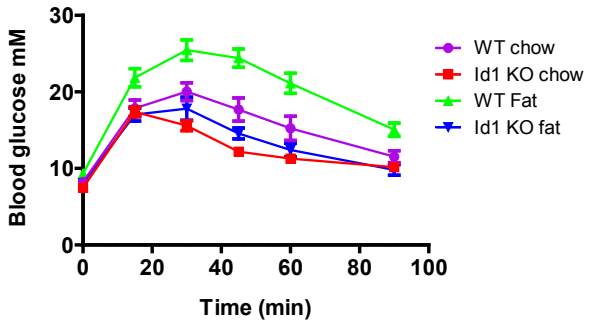

Figure 2. *Intraperitoneal Glucose Tolerance Test (2g/kg body weight)*

Wild-type vs Id1 knock-out fat 2-way ANOVA genotype effect p<0.0001

siRNA Knock-Down Protects Insulin Secretion

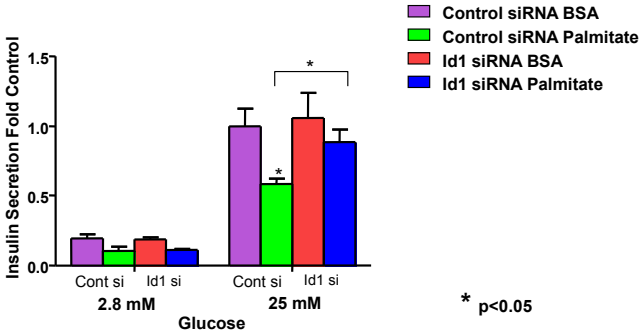

Figure 3. *Insulin Secretion*

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Intellectual Property: PCT/AU2011/000806 Pending in AU & US

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Opportunity: Licensing or research collaboration. Proposed therapeutic approach: gene silencing using pancreas-specific delivery

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