New Target for Insulin Resistance & Type-2 Diabetes: PKCε

Inhibition of PKCε corrects multiple dysfunctions associated with type-2 diabetes with minimal side effects, providing unique benefits over existing therapies:

- Increases insulin availability via increased glucose stimulated insulin secretion and reduced hepatic clearance
- Enhances glucose tolerance
- Targets β-cell secretory defect of type-2 diabetes directly
- Minimal risk of over-stimulation and hypoglycemia
- Complimentary to existing therapies

In type-2 diabetes, the pancreatic β-cells fail to secrete sufficient insulin to overcome peripheral insulin resistance. The lipid-regulated protein kinase C isoform, PKCε, has a central role in this β-cell dysfunction and inhibition of PKCε results in significant improvements in β-cell defects. Importantly, PKCε inhibition has no effect on non-defective β-cells, indicating that it acts selectively under conditions of secretory compromise to increase insulin secretion with minimal risk of over-stimulation and hypoglycaemia. The increase in glucose-stimulated insulin secretion is complimented by a decrease in hepatic clearance of insulin which results in a substantial increase in circulating insulin. There is also a positive effect on insulin action in target tissues. Supportive proof of concept data has been established using a peptide PKCε antagonist and PKCε knock-out animals using two independent models for type-2 diabetes. Garvan has substantial expertise and is seeking to apply its assays and animal models to the generation of novel PKCε inhibitors.

PKCε Inhibition Enhances Glucose Tolerance
Glucose tolerance was normalised in PKCε knock-out mice on a high-fat diet with no difference observed on the control chow diet (Fig 1).

Figure 1. Glucose levels during i.p. glucose tolerance test in wild-type and PKCε knock-out mice.
Use of a peptide selective inhibitor of PKCε increased glucose tolerance in the db/db mouse model (Fig 2), demonstrating successful treatment of pre-existing diabetes by PKCε inhibition.

**PKCε Inhibition Reduces Hepatic Insulin Clearance**

PKCε knock-out mice display increased insulin levels following injection of a large bolus of insulin compared to wild-type controls which is attributed to inhibition of insulin internalisation by hepatocytes.

**PKCε Inhibition Reduces Insulin Resistance**

PKCε deletion promotes insulin action in high-fat fed mice compared to wild-type controls (Fig 4).

**Intellectual Property:** PCT/AU2004/001255

Grant in AU, pending in EP & US

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**Opportunity:** Licensing or Collaborative Research

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![Graph showing glucose levels during i.p. glucose tolerance test in db/db mice.](image)

**Figure 2.** Glucose levels during i.p. glucose tolerance test in db/db mice

![Graph showing insulin levels during i.p. glucose tolerance test in wild-type and PKCε knock-out mice.](image)

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