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**).

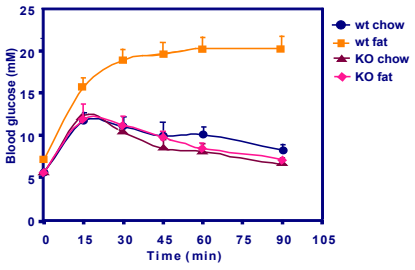

Figure 1. *Glucose levels during i.p. glucose tolerance test in wild-type and PKCε knock-out mice.*

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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.

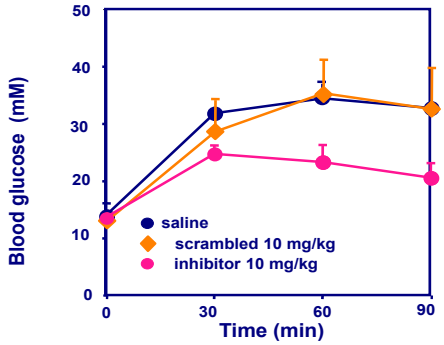

Figure 2. *Glucose levels during i.p. glucose tolerance test in db/db mice*

PKCε Inhibition Reconstitutes Glucose-Stimulated Insulin Secretion (GSIS)

- β-cell responsiveness was increased in the high-fat fed PKCε knock-out mice compared to their wild-type controls (**Fig 3**)
- No significant difference in GSIS is observed in the chow-fed animals
- Diabetic mice treated with a PKCε inhibitor displayed a marked enhancement in β-cell function.
- Functional ablation of PKCε selectively enhanced insulin release ex vivo from only diabetic or lipid-pretreated islets with no effect on healthy islets.
- PKCε inhibition specifically targets the defect in insulin secretion that characterises type-2 diabetes

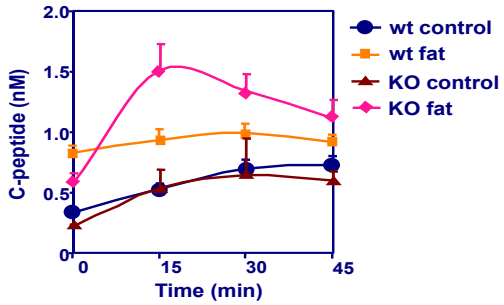

Figure 2. *Insulin levels during i.p. glucose tolerance test in wild-type and PKCε knock-out mice.*

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**).

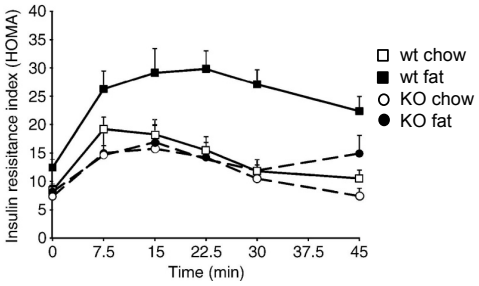

Figure 4. *Insulin resistance index during i.p. glucose tolerance test in wild-type and PKCε knock-out mice.*

Intellectual Property: PCT/AU2004/001255
Granted in AU, pending in EP & US

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Diabetologia 2011,54(6), 1447-1456

Opportunity: Licensing or Collaborative Research

Scientists: Prof Trevor Biden &
Dr Carsten Schmitz-Peiffer

Contact: Dr Katrina Frankcombe
Senior Business Development Manager
k.frankcombe@garvan.org.au

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