RenaSci: Streptozotocin Model of Type 2 Diabetes in Animals on High Fat Diet

- **Rats or mice**
  - Diabetic phenotype dependent on dose of the β-cell toxin, STZ. Higher doses increase urinary albumin excretion and are relevant to the study of diabetic nephropathy
  - Mouse model validated with DPP-IV inhibitors
- **Bespoke study design**
  - Chronic compound dosing up to 140 days by various routes eg po, sc, ip
  - Assessment of glucose tolerance at key stages during the procedure. Glucose and insulin determinations at all timepoints
  - Measurement of blood HbA1c, plasma fructosamine, ketone bodies, urinary glucose excretion and a variety of other metabolic parameters and biomarkers
  - Sampling for PK analysis
  - Pancreatic insulin determination
  - Immunohistochemistry and histology service: eg preparation of pancreatic tissue sections for immunohistochemical staining for insulin and glucagon or determination of β-cell mass (out-of-house)
- **Experimental design/consultation, statistical analysis by a qualified statistician, fully audited data pack and written report to regulatory standards if required**

### Impaired Glucose Tolerance

**Plasma glucose (Day 11)**

![Graph showing plasma glucose levels](image)

**Plasma insulin (Day 11)**

![Graph showing plasma insulin levels](image)

Animals on high fat diet develop insulin resistance and display impaired glucose tolerance following glucose (2 g/kg po at baseline (B)) compared to animals on control diet. STZ increases fasting plasma glucose at B (at higher doses or longer dosing periods) and produces a degree of fasting hyperinsulinaemia compared to controls on standard chow. However, STZ markedly blunts insulin secretion and elevates plasma glucose for up to 3 h post-glucose. n=8-9. (Mouse data).

### Reduced Pancreatic Insulin

- **Vehicle**: Insulin (x10)
- **45 mg/kg STZ**: Insulin (x10)

Animals given STZ (ip) exhibit markedly reduced pancreatic insulin, consistent with the destruction of insulin-secreting β cells. (Rat data).

### Immunohistochemistry and Histology

- **Vehicle:**
  - Insulin (x10)
- **45 mg/kg STZ:**
  - Insulin (x10)

All animals on HFD. A reduction of insulin-positive islets is observed following STZ treatment (ip). (Rat data).

DPP-IV inhibitors such as saxagliptin and sitagliptin are effective in the model with significant improvements in glucose tolerance and β-cell mass observed subsequent to STZ treatment (for data from the RenaSci model see: Poucher et al. 2012. Diabetes Obes Metab. 14(10): 918-926). This model may be especially relevant for testing compounds modifying the GLP-1 axis since GLP-1 increases islet neogenesis and modulates β-cell mass.

Significant differences vs HFD control group are denoted by "p<0.05, **p<0.01, ***p<0.001."

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