**RenaSci: Rat Model of Dietary-induced Obesity**

- Female Wistar rats exposed to a simplified cafeteria diet for 3-4 months to mirror human obesity
  - Weight-stable
  - Marked visceral adiposity
  - Insulin-resistant
- Bespoke study design
  - Acute, sub-chronic or chronic drug administration by a variety of routes including sc implanted osmotic minipumps
  - Daily body weight and food and water intake measurements
- Optional additional studies
  - Oral glucose tolerance tests at key stages to assess effects of drugs on glycaemic control
  - Blood-sampling for PK or to determine levels of comorbid risk factors/other biomarkers
  - Body composition analysis to confirm weight-loss due to selective fat loss
  - Necropsy and gross post mortem analysis
  - Immunohistochemistry and histopathology service
- Experimental design/consultation, statistical analysis by a qualified statistician, fully audited data pack and written report to regulatory standards if required

**Significant Weight-loss Produced by A Range of Drugs**

- Centrally-acting
  - Sibutramine 5 mg/kg po
  - Rimonabant 5 mg/kg po
- Peripherally-acting
  - Orlistat 20 mg/kg po bid
  - Sitagliptin 20 mg/kg po bid
- Peptides (osmotic minipump)
  - Exenatide 30 µg/kg/day sc

**Measurement of Food Intake**

- Daily food intake
- Average daily food intake
- Cumulative food intake

**Effect of Reference Antiobesity and Antidiabetic Agents**

<table>
<thead>
<tr>
<th>Name</th>
<th>Mode of action</th>
<th>Body weight</th>
<th>Adiposity</th>
<th>Insulin resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sibutramine</td>
<td>SNRI</td>
<td>↓ 11.4%</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Rimonabant</td>
<td>CB1 receptor antagonist</td>
<td>↓ 15.0%</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Orlistat</td>
<td>Gastric lipase inhibitor</td>
<td>↓ 7.3%</td>
<td>↓</td>
<td>↓/±</td>
</tr>
<tr>
<td>Exenatide</td>
<td>GLP-1 agonist</td>
<td>↓ 11.0%</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>DPP4-inhibitor</td>
<td>±</td>
<td>±</td>
<td>↓</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>PPARα agonist</td>
<td>↑ 5.5%</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

↓ = Decrease ↑ = Increase % Change in body weight vs controls on Day 29.

Some of this data has been published at Society for Neuroscience Meetings, 2004 and 2005. Available online at www.sfn.org. With thanks to Solvay and Speedel.

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Fully-validated DIO rat model with good predictive validity for therapeutic effects of novel antiobesity and antidiabetic drugs on body weight, adiposity and insulin resistance. Similar DIO male mouse model also available.