Outline of Presentation Contents

1. Introduction
2. Spontaneous or Synchronous Diabetes
3. Metabolic Syndrome Elements
   A. Visceral Obesity
   B. Insulin Resistance
   C. Clamp Study
   D. Dyslipidemia
   E. Hypertension
4. Eating Behavior
5. Beta cell Failure
6. Renal Injury
   A. Urinary biomarkers, Exp. 1, 2
   B. RBM Biomarkers – Renal, Exp 3
   C. Glomerular Pathology, EM, Exp 4
   D. Synchronized Nephropathy, Exp 5
7. Osteoporosis
8. Wound Healing
9. RBM Biomarkers – Pro-Thrombotic
10. RBM Biomarkers - Inflammation
11. Therapeutic Efficacy
   A. Common Anti-diabetic Compounds
   B. Rimonabant
   C. Niacin
12. Summary
Characteristics of Metabolic Syndrome Seen in the ZDSD Rat

- Increased body weight with increased abdominal fat
- Insulin resistance / Glucose intolerance
- Hyper-lipidemia
- Increased blood pressure / Hypertension
- Increased Serum BioMarkers of Coagulation inflammation and Vascular Disease
- Increased fed and fasting glucose and HbA1c levels
Rimonabrant in ZDSD (11-14 weeks old)

Slower weight gain with high dose Rimonabrant (5008 chow).
Anti-diabetic Drug Treatment Prevents Diabetes and Weight Loss in ZDSD Rats (5008 Chow)

- **Glucose**
  - Metformin 150mg/Kg BID (N=7)
  - Vehicle BID (N=4/6)
  - Rosiglitazone 3mg/Kg BID (N=7)
  - Exenatide 1µg/rat BID (N=6)

- **Weight**
  - Metformin 150mg/Kg BID (N=7)
  - Vehicle BID (N=6)
  - Rosiglitazone 3mg/Kg BID (N=7)
  - Exenatide 1µg/rat BID (N=6)
Diabetic Nephropathy in the ZDSD Rat

- Increased kidney weight
- Increased urinary markers for kidney disease
- Increased serum markers for kidney disease
- Glomerular sclerosis
- Nodular sclerosis, KW nodules
- Thickening basement membrane of glomerular capillaries
- Podocyte effacement on glomerular capillaries
The **ZDSD** Rat: One rodent – Many Models

ZDSD
Obesity
Metabolic Syndrome
Diabetes

- Obesity Model before diabetes develops, 5-16 weeks of age
- Metabolic Syndrome
  - Insulin Resistance
  - Hyperlipidemia
  - Obesity
  - Hypertension
- Diabetes Model
  - Natural/Spontaneous Development (LabDiet 5008)
    - Slower & more random
  - Diet Synchronized (RD D12468 or Purina Test Diet 5SCA)
    - Diabetic Nephropathy
    - Osteoporosis
    - Cardiovascular Complications
Summary of **ZDSD** Characteristics

- Conforms to the FDA’s guidelines for development of therapeutics for obesity, metabolic syndrome, and type II diabetes.

- Intact leptin pathway.

- Insulin resistance, elevated glucose levels and glucose intolerance develop early.

- Mirrors the progression of type II diabetes in humans.

- Progresses through Insulin resistance, hypertension, dyslipidemia, obesity & diabetes.

- Diet sensitive.

- Responsive to: TZDs, Metformin, Exenatide, Sitaglipin, Niacin, Rimonabant & Glyburide.

- Exhibits diabetic complications: nephropathy, osteoporosis and cardiovascular.

- Complications of diabetes develop over reasonable timeframes.