ZDSD Rat Factsheet

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The most translational rat model for metabolic syndrome, obesity, diabetes, and diabetic complications

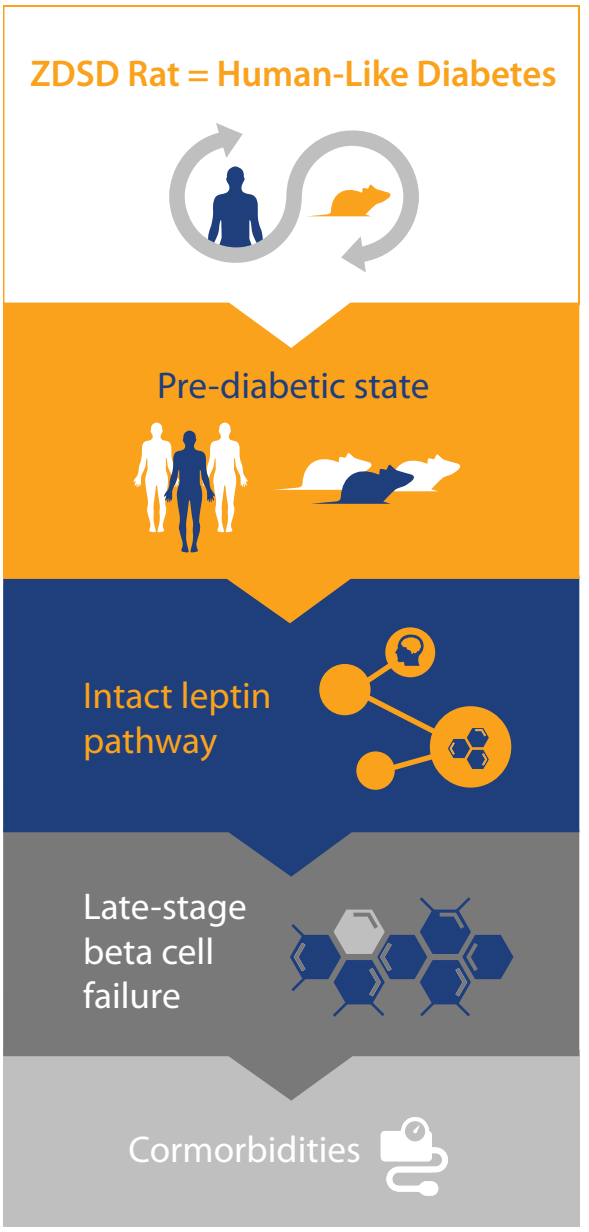
Progress your preclinical studies with the ZDSD rat, which more closely mimics human diabetes than other rodent models.

Currently available rodent models for diabetes and metabolic syndrome lack translatability to the human condition. To allow evaluation of agents which control multiple disease risk factors and can prevent the manifestation of pathology, more translational models are required.

CrownBio has developed the ZDSD rat model, the most translatable rodent model for metabolic syndrome, diabetes, and obesity.

Human-Like Diabetes Progression:

- Polygenic model with an intact leptin pathway as in humans, but unlike conventional rodent models of diabetes and obesity.
- More closely resembling the human pre-diabetic state with elevated biomarkers, diabetes progression, and diabetic complications, unlike any other rodent model.
- Allowing the evaluation of pharmacological intervention at different disease stages.
- Responds to anti-diabetic standard of care treatments like humans.
- Used to evaluate antilipogenic and antihypertensive agents, as well as diabetic nephropathy therapies.



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ZDSD Rat Key Facts

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CrownBio provides the ZDSD rat, the most translatable rodent model for metabolic syndrome, diabetes, and obesity:

- Developed by crossing the *ZDF* rat (Lean +/+) with the *CD(SD)* rat, then selectively bred for obesity and diabetes traits, followed by inbreeding for more than 35 generations.
- Polygenic model of diabetes and obesity, with an intact leptin pathway.
- Progressively develops many human-like features of diabetes and metabolic syndrome while on a normal chow diet, including a clear pre-diabetic state as well as hyperglycemia, impaired glucose disposal and tolerance, and insulin resistance.
- Allows evaluation of anti-diabetic agents at different points during disease progression, and responds to agents such as metformin, rosiglitazone, exenatide, and sitagliptin.
- Development of cormorbidities allows assessment of therapies treating hypertension, dyslipidemia (e.g. niacin), and diabetic nephropathy (e.g. ACE inhibitor lisinopril).

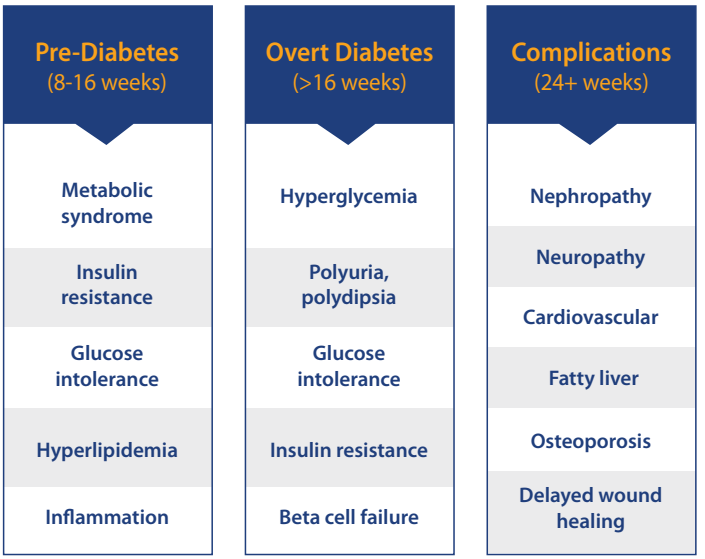
What is the ZDSD Rat?

The ZDSD rat is an inbred polygenic model for metabolic syndrome, obesity, diabetes, and diabetic complications. Unlike other rodent models of metabolic disease, the ZDSD rat does not rely on monogenic leptin or leptin receptor mutations for development of obesity and Type 2 diabetes, which more closely mimics human disease development. This results in a more translatable choice for evaluating your therapeutic agents.

The ZDSD rat was developed by crossing the *ZDF* rat (Lean +/+) with the *CD(SD)* rat and selectively bred for obesity and diabetes traits, followed by inbreeding for more than 35 generations. The resulting ZDSD rat model displays:

- Type 2 diabetes progression similar to the human disease: pre-diabetes (8-16 weeks of age), through overt diabetes (>16 weeks of age), to diabetic complications (24+ weeks of age)
- diabetic complications including nephropathy, neuropathy, cardiovascular disease, delayed wound healing, fatty liver, etc.
- metabolic syndrome characteristics including increased body weight with abdominal fat, insulin resistance, dyslipidemia, and hypertension (**Figure 1**).

Figure 1: Human-Like Metabolic Syndrome and Diabetes Progression in the ZDSD Rat



The ZDSD Rat More Closely Mirrors the Human Metabolic Syndrome Phenotype than Conventional Rodent Models

Most rodent models of Type 2 diabetes have a monogenic mutation that is responsible for the initiation of obesity and subsequent insulin resistance. The two most common obesity-causing mutations involve:

- the leptin receptor, observed in
  - Zucker Fatty (ZF) rat
  - Zucker Diabetic Fatty (ZDF) rat
  - *db/db* mouse
- the leptin molecule, observed in
  - *ob/ob* mouse

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However, both leptin and leptin receptor mutations are rare in humans. The ZDSD rat does not rely on these leptin receptor mutations, and instead has an early onset of polygenic obesity in the absence of a high calorie diet by two months of age, with early onset diabetes starting around 4 months of age (**Figure 2**). This more closely mirrors the human metabolic syndrome than conventional rodent models (a comparison of the ZDSD rat with conventional rodent models is shown in **Table 1**). The ZDSD rat also displays hyperglycemia, impaired glucose disposal and tolerance, and insulin resistance (**Figure 2**), with a slower progression to overt diabetes when compared with the ZDF rat, due to a slower deterioration of beta cell function. Insulin levels also decline as the diabetic phenotype progresses (**Figure 3**), similar to the human disease, and diabetic complications occur.

Figure 2: Development of Obesity, Hyperglycemia, Impaired Glucose Disposal and Tolerance, and Insulin Resistance in the ZDSD and SD Rat

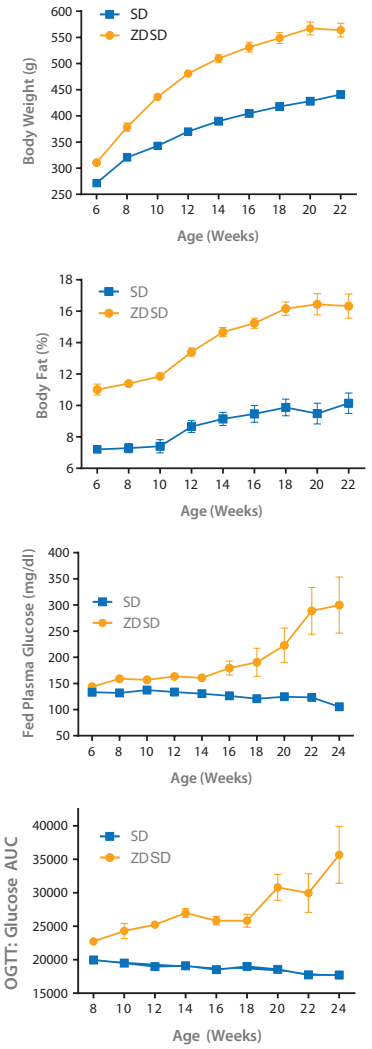


Figure 2: *continuation..*

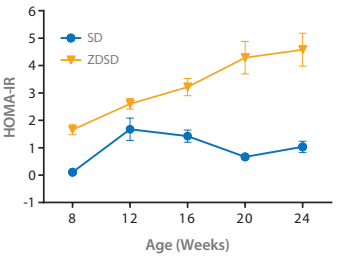
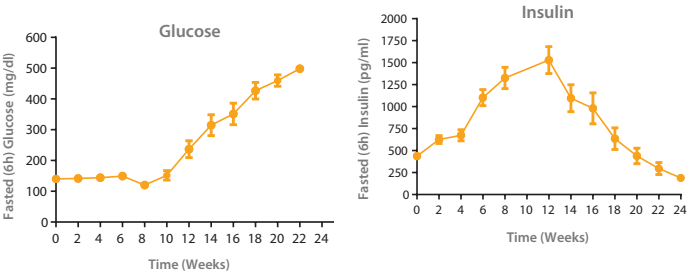


Table 1: The ZDSD Rat vs Conventional Murine Models

	Human	ZDSD Rat	ZDF	Zucker	DIO Rat
Polygenic Disease	●	●			●
Intact Leptin Pathway	●	●			●
Pre-Diabetic State	●	●			●
Glucose Intolerance on Normal Diet	●	●	●	●	
Weight Gain on Normal Diet	●	●	●	●	
Hyperglycemia	●	●	●		
Comorbidities	●	●	●		
Cardiac Dysfunction	●	●	●		
Nephropathy	●	●	●		
Hypertension	●	●		●	●

Figure 3: Insulin Levels Decline as Diabetes Progresses in the ZDSD Rat

Rats are 7 weeks of age at Time 0.



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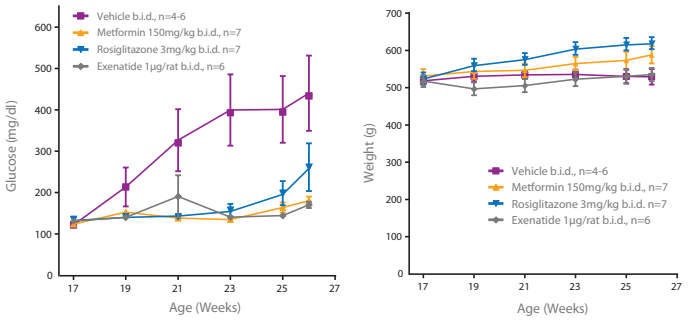
The ZDSD Rat Responds to Anti-Diabetic Therapies

The ZDSD rat has been shown to respond to a variety of anti-diabetic therapies. Agents including metformin, rosiglitazone, and exenatide prevented diabetes in ZDSD rats (**Figure 4**). Rosiglitazone has been shown to improve insulin sensitivity in ZDSD rats, with sitagliptin shown to improve glucose tolerance.

Figure 4: Anti-Diabetic Drug Treatment Prevents Diabetes and Weight Loss in ZDSD Rats



Dyslipidemia – Why Choose the ZDSD Rat to Evaluate Antilipogenic Compounds?

Patients with Type 2 diabetes and metabolic syndrome often present with dyslipidemia, displaying elevated cholesterol and triglycerides, and decreased HDLc, which has been shown to impact on cardiovascular and renal comorbidities. In ZDSD rats on a normal diet, hypertriglyceridemia manifests as early as 12 weeks of age, and levels progress up to 500mg/dl by 15 weeks of age. Increases in cholesterol are not as dramatic as triglycerides, and may be induced by feeding a high fat diet (a comparison of the ZDSD rat with the ZDF rat is shown in **Figure 5**). The ZDSD model responds to classic reference agents including rosiglitazone, and response to treatment with niacin is shown in **Figure 6**.

Figure 5: Comparison of ZDSD Rat with Available Dyslipidemic Models

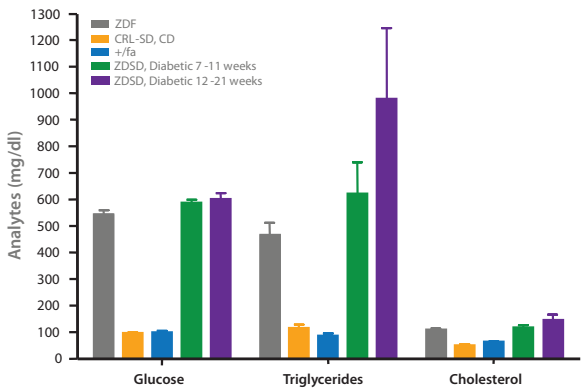
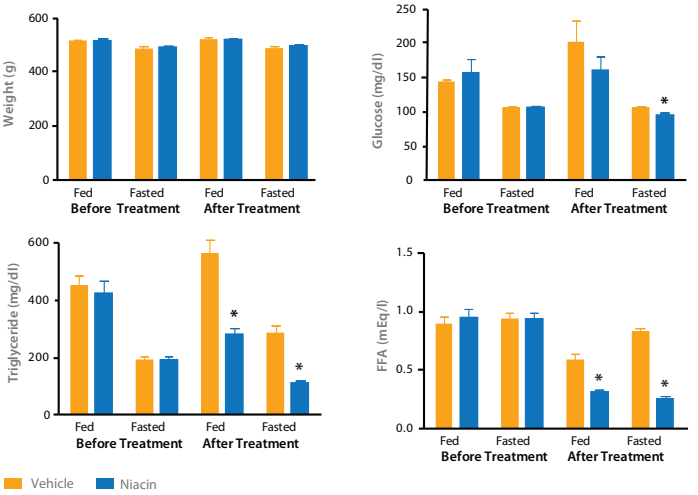


Figure 6: ZDSD Rat Responds to Niacin Treatment

Treatment: 100mg/kg, q.d. for 7 days.



Hypertension – An Integral Component of Metabolic Syndrome

High blood pressure is a key symptom of metabolic syndrome and is a major contributor to the increased risk of cardiovascular disease, kidney disease, and ischemic stroke seen in these patients. Examination of the interactions of all the components of the syndrome in rats is complicated by the absence of high blood pressure in current models (e.g. the ZF rat). ZDSD rats present elevated biomarkers for an activated renin–angiotensin–aldosterone system (RAAS), endothelial dysfunction, and aberrant vasoconstriction and direct evidence of hypertension has been confirmed in the pre-diabetic state via the tail-cuff method as well as telemetry.

Renal Injury (Nephropathy) – Why Choose the ZDSD Rat to Evaluate Diabetic Nephropathy Therapies?

Obesity and metabolic syndrome are clear predictors of chronic kidney disease, largely due to the potentiation of chronic inflammation by insulin resistance. In addition, the lipoprotein abnormalities, increased hemodynamics, hypercoagulability, and vascular dysfunction associated with metabolic syndrome have all been implicated as causative factors in renal disease. Biomarkers for renal dysfunction (i.e. IL6, TNF-α, NGAL, KIM-1, VEGF etc.) as well as significant albuminuria, elevated free fatty acids with oxidative stress, and histological analysis have shown the ZDSD rat to exhibit nephropathy that closely mimics that observed in obese, insulin resistant patients (**Figure 7**). The ACE inhibitor lisinopril was shown to significantly decrease urinary albumin in diabetic ZDSD rats (**Figure 8**).

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Figure 7: Diabetic Nephropathy in the ZDSD Rat

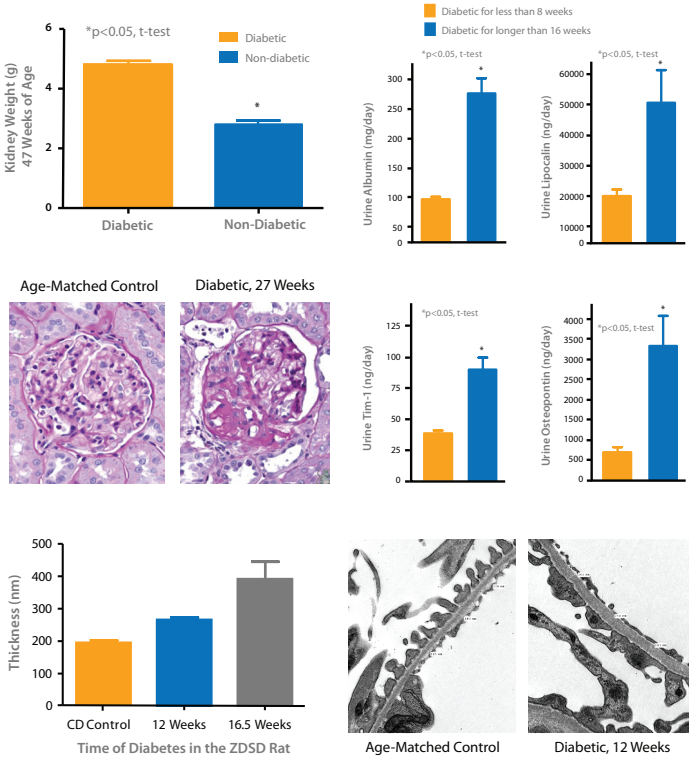
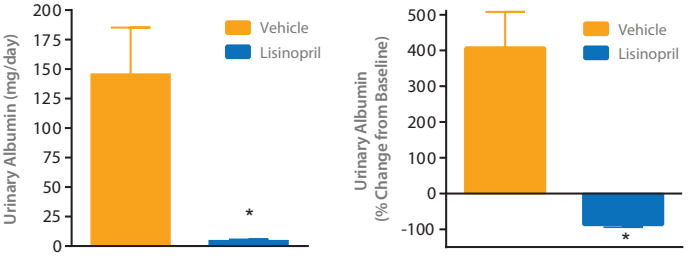


Figure 8: Lisinopril Decreases Urinary Albumin in ZDSD Rats



Summary

The ZDSD rat is a more translatable rat model for obesity, metabolic syndrome, diabetes, and diabetic complications. With an intact leptin pathway, more closely mimicking human disease initiation, the ZDSD rat displays insulin resistance, elevated glucose levels, and glucose intolerance from an early age, providing a *bona fide* pre-diabetic state that lasts for two months. The progression of human Type 2 diabetes is mirrored in this model, with advancement through insulin resistance, hypertension, dyslipidemia, obesity, and overt diabetes, and with diabetic complications such as nephropathy, osteoporosis, delayed wound healing, neuropathy, and increased cardiovascular/ inflammatory markers developing over a reasonable timeframe. Response to a range of agents such as TZDs, metformin, GLP-1 agonists, sitagliptin, niacin, ACE inhibitors, rimonabant, and glyburide has also been observed in the ZDSD rat, showing the model to be highly translatable to the human condition.