Rodent Models of Renal Disease

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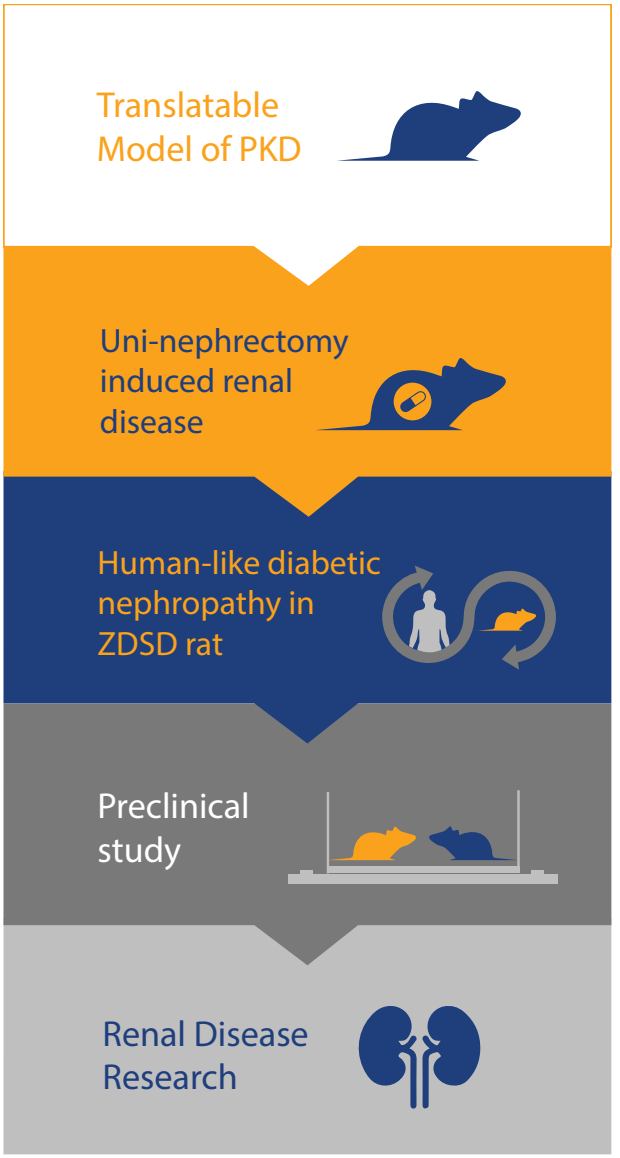
Translate your research into the clinic using our human disease-relevant models

Discover how our wide-ranging panel of rodent models, covering different forms of renal disease, can progress your preclinical research.

Models are validated with standard of care treatment data, and have robust study designs available.

CrownBio provides a comprehensive platform of rodent renal disease models to accelerate preclinical research. These include:

- A highly translatable model of PKD, the *pcy* mouse, which develops renal disease associated with a gene that causes human disease.
- Uni-nephrectomy, aldosterone-induced renal disease in SD rats, the standard model for evaluating mineralocorticoid receptor antagonists.
- Type 2 diabetic nephropathy observed in the polygenic ZDSD rat model, closely mimicking human disease development.



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Rodent Models of Renal Disease
Key Facts

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Our comprehensive rodent renal disease research platform is used to progress novel agents treating a variety of kidney diseases:

- Polycystic kidney disease, through the highly translatable *pcy* mouse, which develops renal disease associated with a gene that causes human disease:
  - Fully validated with positive standard of care treatment controls.
  - Variety of endpoints including cyst volume and fibrosis in kidney, kidney weight, and renal disease biomarkers.
- Uni-nephrectomy, aldosterone-induced renal disease in SD rats, which develop renal injury and hypertension with aldosterone treatment post-surgery.
  - Suitable model for kidney disease research, validated through mineralocorticoid receptor antagonist eplerenone administration.
  - Range of endpoints including urinary albumin levels and kidney weight.
- Type 2 diabetic nephropathy in the ZDSD rat.
  - Highly translatable polygenic model of dysmetabolism, which spontaneously develops Type 2 diabetes and complications, closely mimicking human disease.
  - With validated histological changes in the glomerulus, including basement membrane thickening and podocyte effacement.

PKD in the *pcy* Mouse

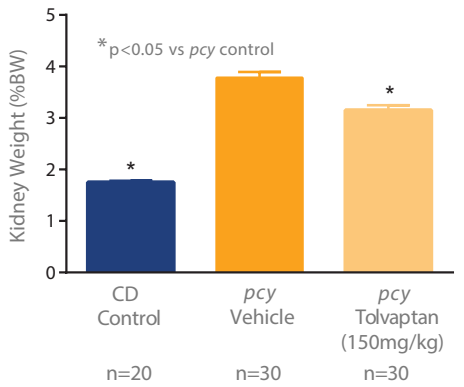
The highly translatable *pcy* mouse, rodent strain CD-1-pcy^{lusm}, develops renal disease associated with the same gene that causes human nephronophthisis type 3. Renal cystic disease slowly develops in this model, with cysts developing in the collecting tubules, and other segments of the nephron becoming cystic during disease progression. Both male and female mice are similarly affected by the disease.

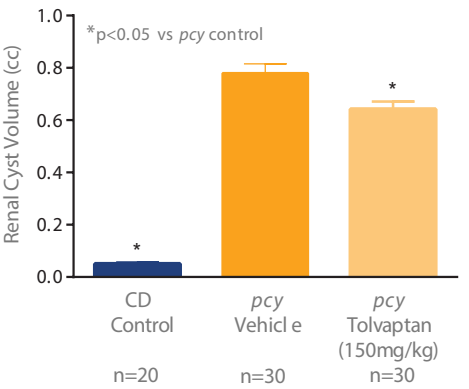
The close correlation with human disease makes the *pcy* mouse highly relevant for use in novel efficacy evaluation. Study design, endpoints, and positive controls are shown in to **Table 1** for this model, and example data for the positive control used within studies are shown in **Figure 1**.

Table 1: *pcy* Mouse Study Design Overview

Model	*pcy* Mouse
Rodent Age	5 weeks
Test Substance Administration Route	Admixed in diet
Typical Dosing Length	15 weeks
Endpoints	Cyst volume and fibrosis in kidney, including histological verification Kidney weight Serum BUN Concentration of test article in the blood Other analyses relevant to the target may be included Body weight and food intake recorded weekly
Positive Control	Vasopressin receptor-2 (V2) antagonist tolvaptan

Figure 1: The *pcy* Mouse Responds to Tolvaptan Treatment
Animals are 5 weeks old at study initiation, treatment for 15 weeks.





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Uni-Nephrectomy, Aldosterone-Induced Renal Disease

Renal disease can be induced in Sprague-Dawley (SD) rats by uni-nephrectomy, and the resulting model is used as a standard for evaluating mineralocorticoid receptor antagonists. Male SD rats are subjected to aseptic uni-nephrectomy (at CRL), and following one week acclimation at CrownBio, animals are implanted with an Alzet mini-pump containing aldosterone (0.75µg/h) for 28 days. Drinking water is supplemented with 0.3% KCl to prevent hypokalemia and a standard diet is admixed with 6% NaCl for the study duration. As the models salt intake is increased, stress on the remaining kidney also increases, leading to the animal developing renal injury and hypertension (detailed in our Rodent Models of Cardiovascular Disease Factsheet).

The resulting model is suitable for kidney disease research and has been validated with the administration of the clinically approved, mineralocorticoid receptor antagonist eplerenone (30 or 100mg/kg q.d., via oral gavage).

Collection of 24 hour urine samples is performed at baseline, 2, and 4 weeks following pump implantation, with the urine analyzed for creatinine and albumin. Kidney and heart samples are also fixed for histological analysis at study termination. Eplerenone is shown to:

- Prevent a rise in urinary albumin seen with vehicle treatment (with no major effect on creatinine changes; **Figure 2**)
- Inhibit the increase in kidney weight of the remaining kidney, as well as inhibiting the increase of heart mass (**Figure 3**)
- Inhibit changes in renal and cardiac pathology (verified by histology; **Figure 4**)

Figure 2: Eplerenone Prevents a Rise in Urinary Albumin in Uni-Nephrectomy, Aldosterone-Induced Renal Disease

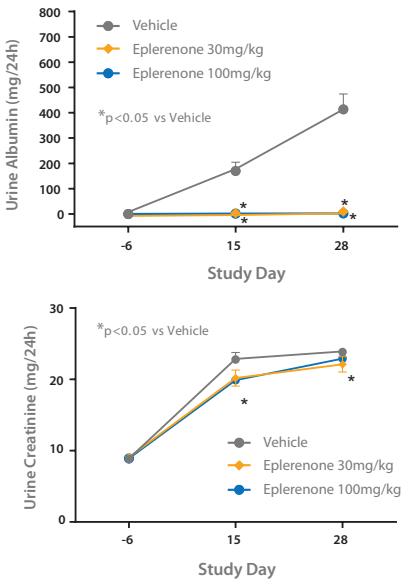


Figure 3: Eplerenone Preserves Kidney and Heart Weight in Uni-Nephrectomy, Aldosterone-Induced Renal Disease

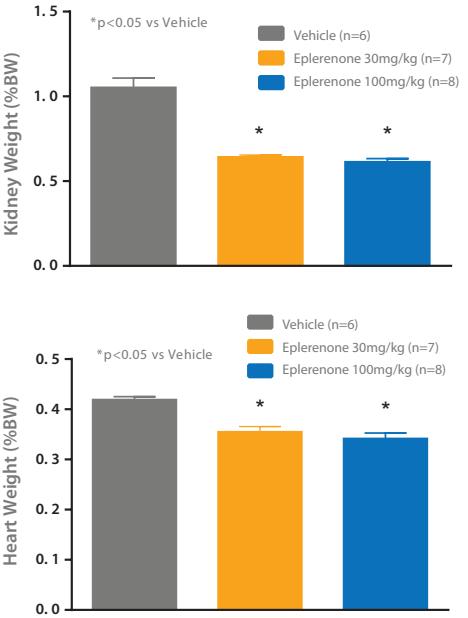
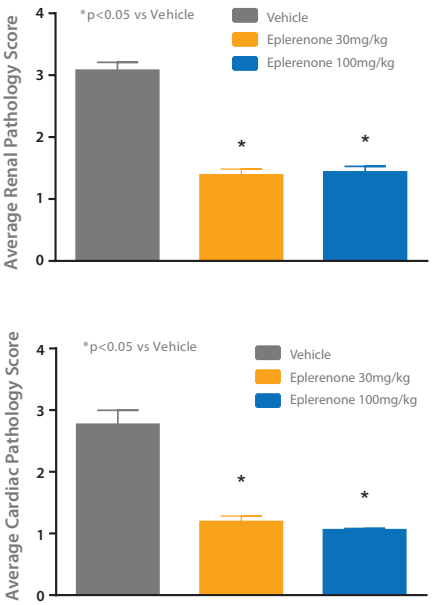


Figure 4: Eplerenone Preserves Renal and Cardiac Pathology in Uni-Nephrectomy, Aldosterone-Induced Renal Disease



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Type 2 Diabetic Nephropathy in 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 mono-genetic 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 model displays 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) including nephropathy, neuropathy, and fatty liver. Full background details on the ZDSD rat are included within a standalone factsheet on this model.

To study diabetic nephropathy, male ZDSD rats are allowed to become spontaneously diabetic. Control SD rats and ZDSD rats that have been diabetic from 12 to 13 weeks, and 16 to 17 weeks are terminated and perfused fixed at approximately 35 weeks of age. Glomerular capillaries and basement membrane (BM) are imaged and endpoints analyzed include measuring GBM thickness and evaluation of podocyte morphology.

Histology verifies that diabetic nephropathy induces changes in the kidney glomeruli (**Figure 5**). Control animals have a normal glomerulus with even staining, whereas animals with diabetic nephropathy display atrophy, separation of the glomerulus from the capsule, and have fibrous material within the mesangium. Transmission electron micrography (TEM) demonstrates that the thickness of the glomerular capillary BM is increased as the diabetic state progresses (**Figure 6**). Podocytes can also be evaluated using TEM. In control animals, podocytes are discrete and attached to the basement membrane; however, in an animal with diabetic nephropathy they display podocyte effacement, appearing flattened out, nucleated, and irregular (**Figure 6**).

Figure 5: Histological Changes in the Kidney Glomeruli of the Diabetic Nephropathy ZDSD Rat

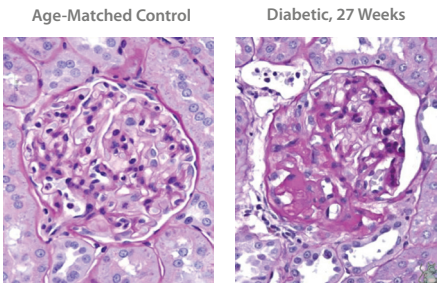
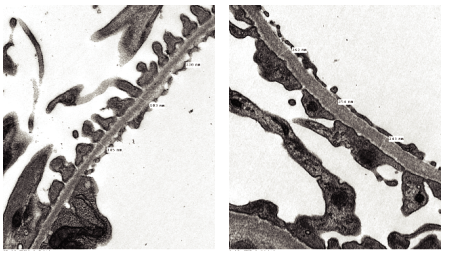
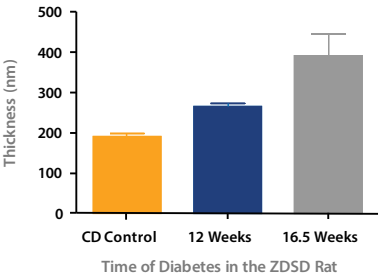


Figure 6: Diabetic Nephropathy Increases the Glomerular Capillary Basement Membrane Thickness in the ZDSD Rat





Summary

Renal disease exists in many forms including genetic diseases of the kidney (e.g. PKD) and as complications from other disorders (e.g. diabetic nephropathy). CrownBio provides a range of models and study designs for preclinical evaluation of agents to treat these diseases.

Our highly translatable model of PKD, the *pcy* mouse, develops renal disease associated with a gene that causes human disease, providing a translatable rodent model that closely mirrors human PKD development. We have validated positive controls for this model for inclusion in study designs.

Clients can also study renal disease in uni-nephrectomized SD rats, with aldosterone induction of disease. Our model is validated with eplerenone which is shown to prevent renal disease development.

To study and evaluate agents in type 2 diabetic nephropathy, CrownBio provides the highly translatable ZDSD rat model which displays diabetes progression similar to the human disease and also develops diabetic complications including nephropathy, neuropathy, and fatty liver. As the model closely mirrors human disease it is ideal for preclinical agent evaluation.

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