ADPKD Mouse Models

Mouse Models for Preclinical Trials

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### Core C: Mouse Models for Preclinical Trials

#### Summary

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<tr>
<th>Strain/Genotype</th>
<th>Inactivation</th>
<th>Survival</th>
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<td><strong>Constitutively Active Models</strong></td>
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<td>Pkd1/2cond; KspCre</td>
<td>Henle, distal and collecting segments of the nephron</td>
<td>~P15</td>
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<tr>
<td>Pkd1/2cond; Pkhd1Cre</td>
<td>distal segments of the nephron</td>
<td>~P30</td>
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<td><strong>Inducible Models</strong></td>
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<td>Pkd1/2cond; Pax8; Tet-O-Cre</td>
<td>Proximal and distal segment of the nephron</td>
<td>Early Onset ~P25</td>
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<td>Late Onset ~6 months</td>
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<td><strong>Hypomorphic Allele</strong></td>
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<td>Pkd1v/v</td>
<td>distal and collecting segments of the nephron</td>
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Constitutively Active Models

Cyst initiation and progression after Pkd1 inactivation in the Pkd1; KspCre line

Human Molecular Genetics, 2008, Vol.17, 11 1505-1516
Constitutively Active Models

Cyst formation after Pkd1 or Pkd2 inactivation in the Pkd1 or 2; Pkhd1Cre line
Inducible Models

Cyst initiation and progression after *Pkdl* inactivation in *Pax8; Tet-On-Cre* 10 days after born

Early Onset

A

P0  P10  P15  P20  P25

DOXYCYCLINE IP P10 P11

B

KHW/BW Ratio %

C

*Pkdl*\textsubscript{cond}; *Pax8; Tet-On-Cre* +

Group 1: P10>P15

Group 2: P10>P20

Group 3: P10>P25
Inducible Models

Cyst initiation and progression after \( B \) Pkd1 inactivation in Pax8; Tet-On-Cre 27 days after born

**A** Late Onset

**GROUP 1:** P27>P90

**GROUP 2:** P27>P130

**GROUP 3:** P27>P150

**KHW/BW Ratio %**

- \( P^0 \)
- P30
- P60
- P90
- P100
- P120
- P130
- P150
- P170

- P27
- P28
- P29
- P43
- P57

**DOXYCYCLINE**

**PKD1\textsuperscript{cond}; Pax8;Tet-On-Cre**

- **Female**
- **Male**

* 50% lethality

KHW/BW Ratio % graph with different colors for different groups.
Inducible Models

Cyst progression after *Pkd1* inactivation in the Tamoxifen Cre mouse model at P2 and harvested at P19 (a) or inactivation at P40 with kidneys harvested at P90 (b) and P180 (c).

**Early Onset**

- P2>P19
- ~P40>P90

**Late Onset**

- P40>P180

\( \text{Pkd}^{\text{v/v}} \text{ Hypomorphoric Allele} \)

Cyst initiation and progression in Pkd1 mutant mice (GPS mutation)

# Therapies to treat PKD

Example of some compounds successfully reducing cyst formation in Pkd models described above

<table>
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<th>Drugs</th>
<th>Target</th>
<th>Mouse Model</th>
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<tr>
<td><strong>Valproic acid (VPA)</strong></td>
<td>Pan-HDAC inhibitor</td>
<td>Rapid Progression: Pkd1flox/flox; Pkhd1-Cre</td>
<td>Proc Natl Acad Sci USA 2009; 106: 21819–21824</td>
</tr>
<tr>
<td><strong>Tubacin</strong></td>
<td>HDAC6 inhibitor</td>
<td>Rapid Progression: Pkd1flox/flox; Pax8; TET-On-Cre</td>
<td>Kidney Int 2016; 90: 90–99</td>
</tr>
<tr>
<td><strong>ACY</strong></td>
<td>HDAC6 inhibitor</td>
<td>Rapid Progression: Pkd1flox/flox; Pax8; TET-On-Cre</td>
<td>Am J Physiol Renal Physiol 2017; 313: F997–F1004</td>
</tr>
<tr>
<td><strong>anti-miR-17 oligonucleotide</strong></td>
<td>miRNA-17 inhibitor</td>
<td>Slow progression: Pkd1&lt;sup&gt;RC/RC&lt;/sup&gt;</td>
<td>Nat Commun 2017; 8: 1–15</td>
</tr>
<tr>
<td><strong>Venglustat</strong> *</td>
<td>Glucosylceramide Synthase inhibitor</td>
<td>Rapid Progression: Pkd1&lt;sup&gt;tm1Gztnt&lt;/sup&gt;</td>
<td>Nat Med 2010; 16: 788–792</td>
</tr>
<tr>
<td><strong>Metformin</strong> *</td>
<td>AMPK activator</td>
<td>Rapid Progression: Pkd1flox/−; Ksp-Cre and Pkd1flox/flox; pCx-CreER</td>
<td>Proc Natl Acad Sci USA 2011; 108: 2462–2467</td>
</tr>
<tr>
<td><strong>2DG</strong></td>
<td>Glycolysis inhibitor</td>
<td>Rapid Progression: Pkd1&lt;sup&gt;v/v&lt;/sup&gt;, Pkd1ΔC/flox; TmCre and Han:SPRD Cy/þ rat</td>
<td>1. Nat Med 2013; 19: 488–493</td>
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* Active Clinical Trials