Clinically relevant humanized FcRn mouse models demonstrate therapeutic half life concordant with human and non-human primates.

- Generate cost-effective *in vivo* half-life data that drive decisions.
- Rapidly discriminate between multiple therapeutic candidates.
- Rely on JAX’s vast experience in developing and executing *in vivo* studies with FcRn mouse models.

**JAX In Vivo** Pharmacology Services can evaluate therapeutics for validation, optimization, and pre-clinical testing phases.
THE JAX hFcRn PLATFORM OFFERS A NUMBER OF CRITICAL SOLUTIONS

Half-life results for monoclonal antibodies tested in conventional mice do not correlate with the pharmacokinetics in humans, because human IgG binds mouse FcRn too tightly.

**SOLUTION:** Two different FcRn transgenic mice were created. Tg32 carries the endogenous human promoter and all known regulatory sequences and is commonly used to model human PK behavior of therapeutic antibodies, giving the highest half-lives. Tg276 carries ubiquitously expressed human FcRn cDNA transgene and is best suited for more subtle discriminations among antibody therapeutics.

**RELATIVE BINDING OF IgG TO FcRn**

<table>
<thead>
<tr>
<th></th>
<th>Human FcRn</th>
<th>Mouse FcRn</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human IgG</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Mouse IgG</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

**CLINICAL RELEVANCY OF PRECLINICAL MODELS FOR PHARMACOKINETICS**

<table>
<thead>
<tr>
<th>Model</th>
<th>Cost</th>
<th>Correlation with human data</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>In vitro</em></td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Standard mice</td>
<td>Moderate</td>
<td>Low</td>
</tr>
<tr>
<td>Humanized FcRn mice</td>
<td>Moderate</td>
<td>Very good</td>
</tr>
<tr>
<td>Non-human primates</td>
<td>High</td>
<td>Very good</td>
</tr>
</tbody>
</table>

*Figure 1. Comparison of clearance of monoclonal antibodies (mAb) in hFcRn transgenic mice hemizygous for the Tg32 or Tg276 transgenes (data courtesy of Dr. Derry Roopenian).*

A) Tg32: Both antibodies administered to Tg32 hemi mice yielded similar, long half-life data.

B) Tg276: Tg276 hemi mice readily distinguished mAb2 as having a longer half-life than mAb1.
Albumin-based therapies are rapidly cleared from conventional humanized FcRn mice because murine albumin out-competes human albumin.

**SOLUTION:** Mouse albumin was knocked out in the humanized FcRn mice.

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**Table:**

<table>
<thead>
<tr>
<th>Model</th>
<th>Endogenous promoter</th>
<th>Longest half-life</th>
<th>Can see subtle differences in PK values</th>
<th>Immunodeficient</th>
<th>Albumin PK</th>
</tr>
</thead>
<tbody>
<tr>
<td>FcRn Tg32 (014565)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td>FcRn Tg276 (004919)</td>
<td>✗</td>
<td>✗</td>
<td>✓</td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td>Tg32 Scid (018441)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✗</td>
<td>✓</td>
</tr>
<tr>
<td>Tg276 Scid* (021146)</td>
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<td>✗</td>
<td>✓</td>
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<td>✗</td>
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<tr>
<td>Tg276 Rag1 (016919)</td>
<td>✗</td>
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<td>✓</td>
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<tr>
<td>Tg32 Alb KO (025201)</td>
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<td>✓</td>
<td>✗</td>
<td>✗</td>
<td>✓</td>
</tr>
</tbody>
</table>

*Only available via cryorecovery*
**Example Pharmacokinetic Study:**

**Humanized FcRn Model:**
B6.Cg-Fcgrttm1Dcr Tg(CAG-FCGRT)276Dcr/DcrJ (004919)

**# of mice:** 6 per group

**Groups:**
- Vehicle Control
- Compound A
- Compound B
- Compound C

**Data Collection:** Blood samples are collected 1, 2, 6, 10, 14, 18, 22 and 26 days after intravenous compound administration.

**Data Analysis:** The concentration of the test compounds are quantified by ELISA and PK Solutions software is used to calculate the pharmacokinetic data.

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**Example Pharmacodynamic Study:**

**Humanized FcRn Model:**
B6.Cg-Fcgrttm1Dcr Tg(FCGRT)32Dcr/DcrJ (014565)

**Human IgG is administered via IV injection and blood collected 24 hours later. Test articles and a vehicle control are administered via IV 1 hour after the blood collection.**

**# of mice:** 6 per group

**Groups:**
- Vehicle Control
- Compound A
- Compound B
- Compound C

**Data Collection:** Blood samples are collected 32, 48, 56, 72, 96, 120, and 144 hours after intravenous compound administration.

**Data Analysis:** The concentration of the human IgG or albumin can be quantified by ELISA and PK Solutions software is used to calculate the pharmacodynamic data.

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**ABOUT OUR TEAM**

We evaluate the pharmacokinetics, bioavailability, and efficacy of therapeutic monoclonal antibodies and albumin-conjugates in vivo with our unique Humanized FcRn Mouse Models. These mice were developed by Prof. Derry Roopenian at JAX. Our In Vivo Pharmacology Team has performed over 35 external, multiphase studies as well as numerous compound validations within the last two years. The team combines expertise in the FcRn field, including developing and maintaining the mouse models, and vast experience running clinically relevant in vivo studies using state-of-the-art mouse models.

**EXTENSIVE VALIDATION**


3. Tam SH; McCarthy SG; Brosnan K; Goldberg KM; Scallon BJ. 2013. Correlations between pharmacokinetics of IgG antibodies in primates vs. FcRn-transgenic mice reveal a rodent model with predictive capabilities. MAbs. 5(3):397-405. PMID: 23549129 https://www.ncbi.nlm.nih.gov/pubmed/23549129


See jax.org/fcrn for a full list of references.