Development and Characterization of a New BSL-2 Animal Model of Mycobacterial Lung Infection

Brandon S. Russell, Sasilada Sirirungruang, Nicola M. A. Parry, Megan E. McBee, James G. Fox, and Peter C. Dedon

Departments of Biological Engineering and Chemistry, Division of Comparative Medicine, and Center for Environmental Health Sciences - MIT, Cambridge, MA

Tuberculosis Health Burden

- Mycobacterium tuberculosis infects 33% of world population
- 10 million new cases, 2 million deaths per year
- Widespread drug resistance; need new therapies

Problems with Animal Models

- Many limitations with common animal models
- Easy-to-handle models poorly mimic human TB
- Cost, reagent availability hamper better models

New Model Details and Methods

- M. bovis BCG as a BSL-2 analogue of M. tb
- 34 outbred female Wistar CRL rats at 6 weeks old

Sustained Infection, Strong Immune Response, and Robust Pathology

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Dosed</th>
<th>CFU+</th>
<th>CFU-</th>
<th>Success</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>4</td>
<td>4</td>
<td>0</td>
<td>100%</td>
</tr>
<tr>
<td>Week 1</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>75%</td>
</tr>
<tr>
<td>Week 2</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>75%</td>
</tr>
<tr>
<td>Week 3</td>
<td>4</td>
<td>4*</td>
<td>0</td>
<td>100%</td>
</tr>
<tr>
<td>Week 4</td>
<td>4</td>
<td>4</td>
<td>0</td>
<td>100%</td>
</tr>
<tr>
<td>Week 8</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>75%</td>
</tr>
<tr>
<td>Total</td>
<td>24</td>
<td>21</td>
<td>3</td>
<td>87.5%</td>
</tr>
</tbody>
</table>

Important Pathological Features
1. Large regions of inflammation with increased cellularity
2. Coalescing granulomas of lymphocytes, macrophages, & MNCs
3. Frequent peribronchiolar localization of granulomas
4. Attenuation of bronchiolar epithelium by impinging granulomas

Summary of Contributions

We have developed a new BSL-2 rat model of mycobacterial lung infection. This model is affordable, easy to use, and features persistent infection, heavy immune infiltration, and robust pathology with granuloma formation. We are now characterizing the granulomas with MPO, CD3, and iNOS stains before publication.

This new model will be useful for future drug delivery, biomarker, and metabolomic studies, and it will help accelerate the development of new tuberculosis diagnostics and therapeutics.