Mouse Lung Tumor Workshop
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Of Mice and Humans – The Lung

Gross Anatomy

• **Mouse** –
  – Right Lung – Four Lobes
  – Left – One Lobe

• **Human**
  – Right Lung – Three Lobes (upper, middle, lower)
  – Left Lung – Two Lobes (upper, lower)

Intrapulmonary Airways

• **Mouse** –
  – Monopodial Branching 13 – 17 Generations
  – Intrapulmonary Bronchi Lack Cartilage
  – None or one Respiratory Bronchiole

• **Human**
  – Dichotomous Branching 17 – 21 Generations
  – Intrapulmonary Bronchi Have Cartilage
  – Several Orders of Respiratory Bronchioles

Intrapulmonary Airways

Asymmetrical branching in Mouse

Bronchus

Bronchus in Mouse connects to terminal bronchiole
<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Mouse</th>
<th>Humans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciliated</td>
<td>28-36</td>
<td>37</td>
</tr>
<tr>
<td>Clara</td>
<td>59-61</td>
<td>-</td>
</tr>
<tr>
<td>Mucus Globlet</td>
<td>&lt;1</td>
<td>10</td>
</tr>
<tr>
<td>Basal</td>
<td>&lt;1</td>
<td>32</td>
</tr>
</tbody>
</table>

Suarez, 2012; Fox, 2007; Plopper and Hyde, 2008
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<th>Cell Type</th>
<th>Mouse</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Ciliated</td>
<td>20-40</td>
<td>52</td>
</tr>
<tr>
<td>Clara</td>
<td>60-80</td>
<td>-</td>
</tr>
<tr>
<td>Serous</td>
<td>0</td>
<td>35</td>
</tr>
<tr>
<td>Basal</td>
<td>&lt;1</td>
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</tr>
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Suarez, 2012; Fox, 2007; Plopper and Hyde, 2008
Lung Hyperplasia in Mice

Arises in periphery of lung; alveolar structures are visible
Bronchioloalveolar Adenomas

Peripheral and Solid

Cells have Type II Appearance
Bronchioloalveolar Adenoma

More Tubular Pattern
May be Clara Cells
Bronchioloalveolar Carcinoma

Carcinomas Show Local Invasion, Extension Throughout the Lung and Distant Metastases
## B/A Lung Tumor Incidences (%)

<table>
<thead>
<tr>
<th>Mouse/Sex</th>
<th>Adenoma</th>
<th>Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>B6C3F1/Male</td>
<td>16.7 (8 – 36)</td>
<td>7.6 (0 – 16)</td>
</tr>
<tr>
<td>B6C3F1/Female</td>
<td>6.4 (0 – 14)</td>
<td>3.3 (0 – 12)</td>
</tr>
<tr>
<td>CD1/Male</td>
<td>13.7 (8 – 38)</td>
<td>5.8 (2 – 16)</td>
</tr>
<tr>
<td>CD1/Female</td>
<td>5.8 (2 – 16)</td>
<td>3.3 (1 – 20)</td>
</tr>
<tr>
<td>rasH2/Male</td>
<td>10.1 (0 – 24)</td>
<td>0.6 (0 – 8)</td>
</tr>
<tr>
<td>rasH2/Female</td>
<td>5.8 (0 – 24)</td>
<td>1.1 (0 – 4)</td>
</tr>
</tbody>
</table>

Maronpot et al., 1999; Charles River, 2014; Paranjpe et al., 2013
Bronchioloalveolar Tumors Mice

• Tumors arise in Periphery of Lung
• Originate from Type 2 and Clara Cells
• Rates are highly variable (Adenoma)
  – 8% to 36%: male B6C3F1 at 104 weeks (gps/25)
  – 8% to 38%: male CD-1 at 78-104 weeks (gps/50)
  – 0% to 24%: male rasH2 at 26 weeks (gps/25)
• Carcinoma is less common
Lung Cancer in Humans

- Bronchogenic Carcinoma: 90 – 95%
  - Squamous Cell Carcinoma (25 – 40%)
  - Adenocarcinoma (25 – 40%)
  - Small Cell Carcinoma (20 – 25%)
  - Large Cell Carcinoma (10 – 15%)

- Bronchial Carcinoid: 5%

- Mesenchymal and Other: 2 – 5%

Lung Tumors in Mice and Humans

• Mouse Tumors Originate Peripherally
  – Usually at terminal acinus
  – Type II Cell or Clara Cell Origin
  – May be Spontaneous or Chemically Induced

• Human Tumors Originate Centrally in Bronchi
  – 80 – 85% associated with smoking
  – Basal or Bronchial Cell Origin
Conclusions

• Mouse and Human Lung Tumors Differ
  – Location
  – Site of Origin
  – Predominate Cell Type

• Mouse has Mixed Record as a Predictive Model
  – A strain Mouse NTP study was not Predictive
  – NTP studies Variable Results
Mouse Lung Tumor Models