Developing a mouse model for chordoma.

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Reasons for creating an animal model


Why use mice?

1. Can alter the DNA of the mice (mark cells).
2. Breed large numbers easily.
3. Similar to humans.

UF animals has been continuously accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care International (AAALAC) since 1966 and is registered with the United States Department of Agriculture as a research site.
**Vertebral column - Newborn**

- vertebrae
- disk

**Vertebral column - Embryo**

- vertebrae
- disk

**Intervertebral disk formation**

Notochord express the gene Sonic Hedgehog ($Shh$)

Notochord forms the entire nucleus pulposus.

- Notochordal remnants
- Nucleus pulposus
- Annulus fibrosus
- Vertebrae
- End plate

Mouse notochordal remnants - Adult

- In every animal.
- Distribution: random, along entire length of spine, appear ventral biased, located in “middle” of each vertebra.

Hypothesis: Very rare mutation in notochordal remnants activates Shh (or hedgehog signaling) and causes chordomas.
Hedgehog Signaling pathway and disease.

Am J Hum Genet. 2000 November; 67(5);1047-1054

SHH and PTCH Expression in Chordal Tissues and Skull Base Chondrosarcoma

<table>
<thead>
<tr>
<th>Type of Tumor</th>
<th>SHH+</th>
<th>PTCH+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional chordoma</td>
<td>27</td>
<td>26</td>
</tr>
<tr>
<td>Chondroid chordoma</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Dedifferentiated chordoma</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Benign notochordal cell tumor</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Chondrosarcoma</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Nucleus pulposus of IVD</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Notochord</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

Shh signaling and chordoma

Justin Cates, Vanderbilt University Medical Center

<table>
<thead>
<tr>
<th>BNCT</th>
<th>Chordoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTC</td>
<td>PTC</td>
</tr>
</tbody>
</table>
Mouse notochordal remnants and chordoma

**Idea:** Activate the Shh signaling pathway in notochordal remnants.

- activate Shh signaling pathway in notochord (NP, remnants)
- Do you get chordoma?

**Idea:** Remove genes that have been shown to be absent in chordomas.
- Tsc1 and Pten (Dr. Vijaya Ramesh, MGH)

**Status:** Experimental animals are being born (as of last week).
- Shh activated in notochordal remnants or Tsc1 or Pten have been removed.

**Potential Problems:**
1. Mice have never been reported to have chordomas
2. Mice may die before chordomas form.
3. Mice may have to be “aged” to see chordomas - old mice = 2 years.

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**Summary**

1. All cells in the mouse nucleus pulposus are derived from the notochord.
2. Notochordal remnants are present in mice.

**Ideas/thoughts:**
1. Express genes (Shh) in remnants to model chordoma.
2. Remove Tsc1 or Pten to model chordoma.
3. Make a mouse model and then give it to everyone to screen drugs.
Thanks to: Cohn Lab (Maden Lab, Ormerod Lab, Sarkisian Lab)

Chordoma: Justin Cates (Vanderbilt) and Vijaya Ramesh (MGH)

Harfe Lab (bharfe@mgm.ufl.edu)

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