

Developing a mouse model for chordoma.

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Reasons for creating an animal model

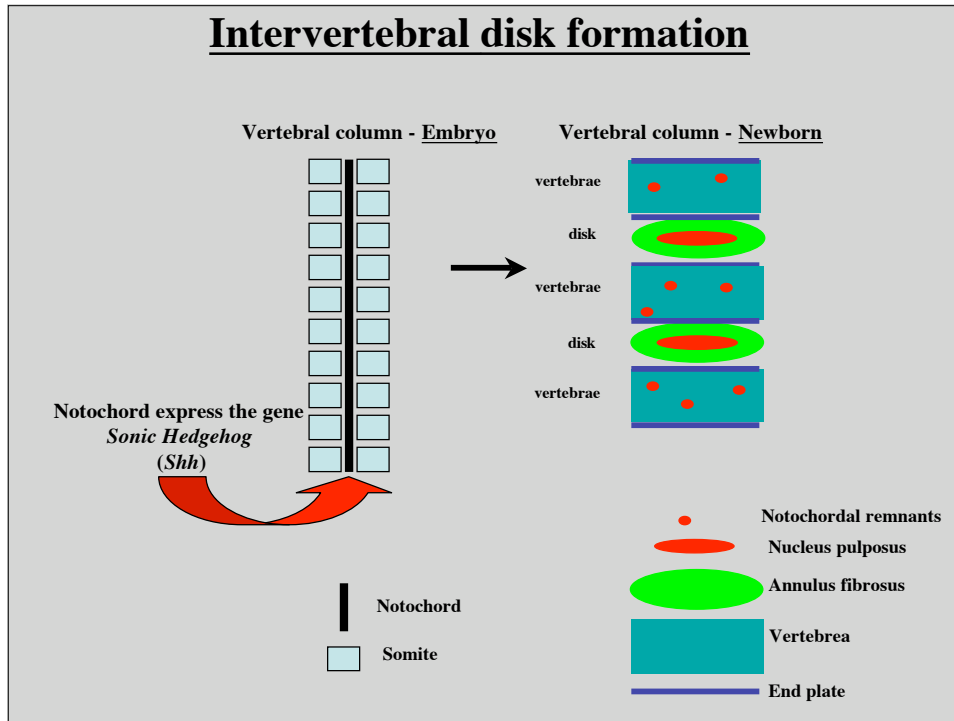
1. Screen drugs - 2007 Chordoma Action Plan: Need animal model.

Why use mice?

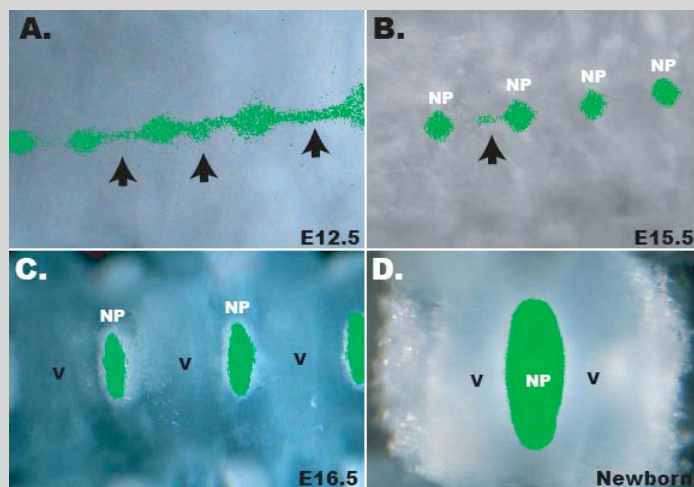
1. Can alter the DNA of the mice (mark cells).
2. Breed large numbers easily.
3. Similar to humans.

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.

Intervertebral disk formation

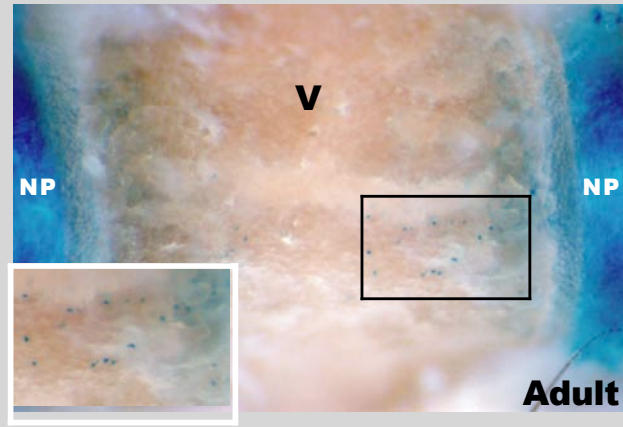


Notochord forms the entire nucleus pulposus.



Choi KS, Cohn MJ, Harfe BD. *Dev Dyn.* 2008 3953-8.

Mouse notochordal remnants - Adult



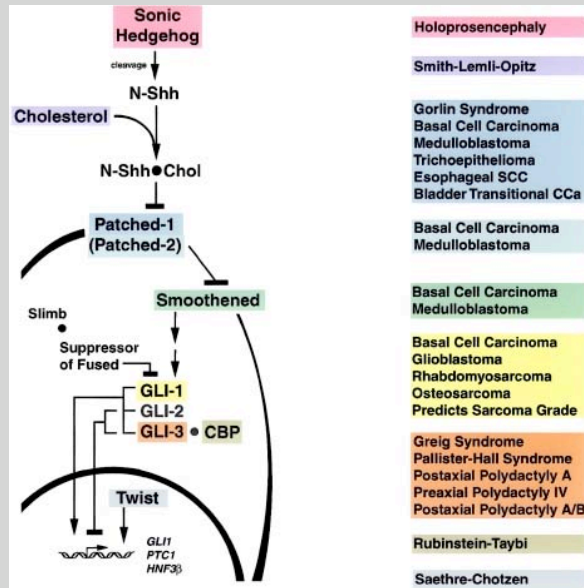
- In every animal.
- Distribution: random, along entire length of spine, appear ventral biased, located in “middle” of each vertebra.

Hypothesis: Very rare mutation in notochordal remnants activates *Shh* (or hedgehog signaling) and causes chordomas.



Second International Chordoma Research Workshop - 2008

Hedgehog Signaling pathway and disease.

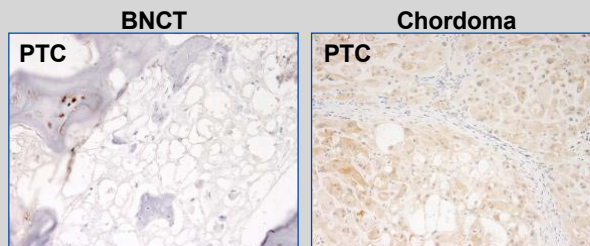


Am J Hum Genet. 2000 November; 67(5):1047-1054

Shh signaling and chordoma

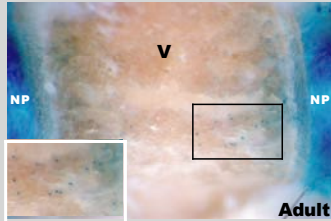
Justin Cates, Vanderbilt University Medical Center

SHH and PTCH Expression in Chordal Tissues and Skull Base Chondrosarcoma			
	n	SHH+	PTCH+
Conventional chordoma	27	26	21
Chondroid chordoma	5	5	4
Dedifferentiated chordoma	1	0	0
Benign notochordal cell tumor	2	0	0
Chondrosarcoma	6	1	1
Nucleus pulposus of IVD	7	1	0/3
Notochord	2	2	0



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.

Potenital 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.

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.

Harfe Lab (bharfe@mgm.ufl.edu)

Jen Maier (Chordoma)

Kyung-Suk Choi (Shh in disks)

Cort Bouldin (Limb development)

John Palsis (Limb development)

Bhavana Vangara (limb development)

Brad Bruggeman (Tmem16 family)

Daniela Iribarne (Tmem16 family)

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