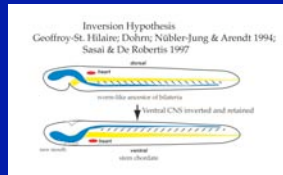


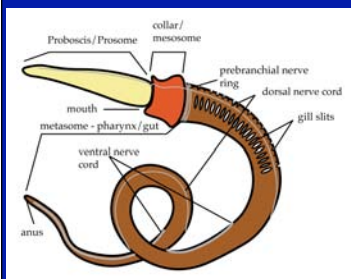
## Part 2. Telling the back from the front or what the chordates invented

Marc Kirschner  
Dept. of Systems Biology  
Harvard Medical School  
Boston Massachusetts

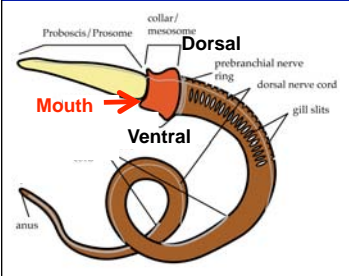
The position of the CNS has been used to define the body plan of organisms



But what does that say for an organism that has a clear D/V axis but no centralized nervous system?



Using the standard convention call the mouth, ventral



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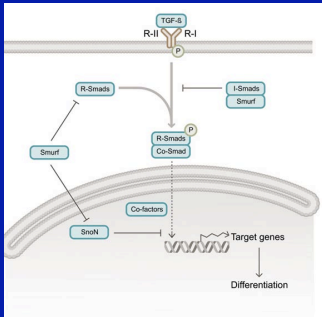
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BMP, a form of TGF- $\beta$ , is involved in D/V patterning



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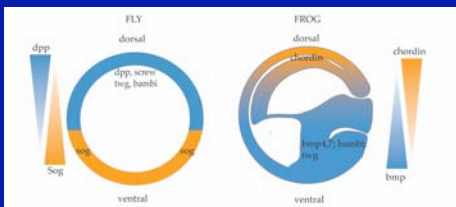
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BMP and anti-BMP (chordin, sog) are conserved in neural specification in flies and frogs



What role do they have in hemichordates which have no CNS?

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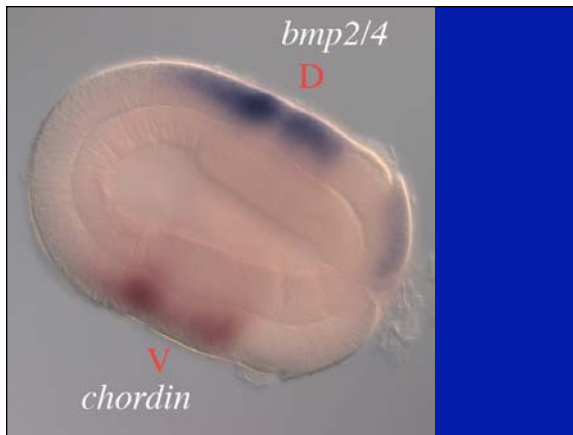
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The genes that are patterned by BMP in the vertebrate neural tube are *not* conserved in Saccoglossus

Shh responsive

bmp responsive

A diagram of a vertebrate neural tube shows the expression of various genes: *eng2*, *shh*, *sox1*, *sox2*, *sox3*, *sox4*, *sox5*, *sox6*, *sox7*, *sox8*, *sox9*, *sox10*, *sox11*, *sox12*, *sox13*, *sox14*, *sox15*, *sox16*, *sox17*, *sox18*, *sox19*, *sox20*, *sox21*, *sox22*, *sox23*, *sox24*, *sox25*, *sox26*, *sox27*, *sox28*, *sox29*, *sox30*, *sox31*, *sox32*, *sox33*, *sox34*, *sox35*, *sox36*, *sox37*, *sox38*, *sox39*, *sox40*, *sox41*, *sox42*, *sox43*, *sox44*, *sox45*, *sox46*, *sox47*, *sox48*, *sox49*, *sox50*, *sox51*, *sox52*, *sox53*, *sox54*, *sox55*, *sox56*, *sox57*, *sox58*, *sox59*, *sox60*, *sox61*, *sox62*, *sox63*, *sox64*, *sox65*, *sox66*, *sox67*, *sox68*, *sox69*, *sox70*, *sox71*, *sox72*, *sox73*, *sox74*, *sox75*, *sox76*, *sox77*, *sox78*, *sox79*, *sox80*, *sox81*, *sox82*, *sox83*, *sox84*, *sox85*, *sox86*, *sox87*, *sox88*, *sox89*, *sox90*, *sox91*, *sox92*, *sox93*, *sox94*, *sox95*, *sox96*, *sox97*, *sox98*, *sox99*, *sox100*.

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Yet, every detail of the BMP gradient seems fundamental to D/V patterning

Two micrographs of Saccoglossus embryos. The left one shows dorsal (D) and ventral (V) expression of a gene. The right one shows dorsal (D) and ventral (V) expression of *bmp2/4* and *u/bmp*.

What is the BMP pathway being used for?

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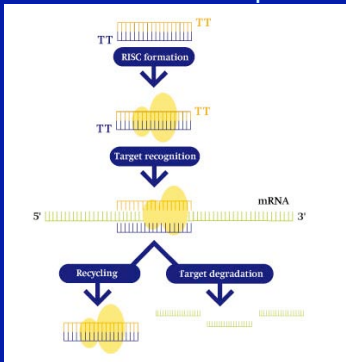
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siRNA is a powerful tool in for answering such questions




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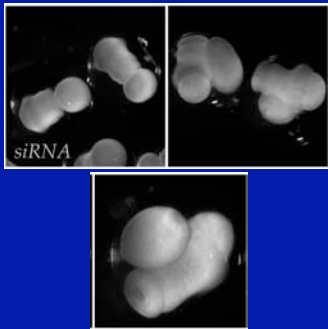
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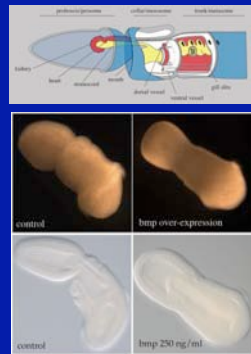
Knockdown of BMP causes ventral radialized embryos



So radialized the dorsal structure that holds the proboscis to the collar doesn't form and the proboscis falls off.

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Increased BMP dorsalizes




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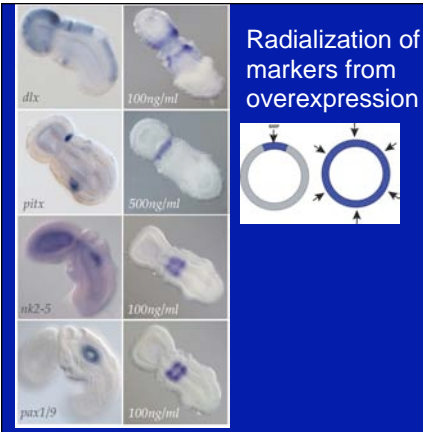
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Radialization of *dorsal* markers from overexpression



dx1 100ng/ml  
pitx 500ng/ml  
jnk2-5 100ng/ml  
pax1/9 100ng/ml

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Wildtype Knockdown Knockdown of BMP radializes *ventral* markers



netrin  
dlx  
pitx

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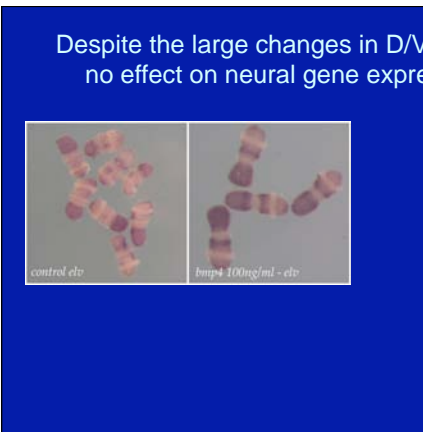
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Despite the large changes in D/V there is no effect on neural gene expression



control elv      bmp4 100ng/ml - elv

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### D/V conclusions

- Bmp/ chordin is not exclusively associated with centralization of CNS
- It has an overall role in patterning anatomy
- It operates independently of the anterior-posterior dimension

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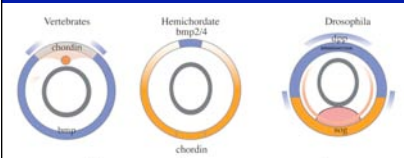
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Bmp plays a conserved role in dorso-ventral patterning in all phyla examined




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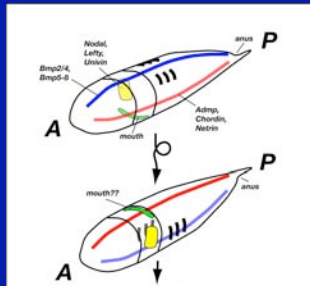
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### How to get a chordate from a hemichordate

First flip the chordate on its back




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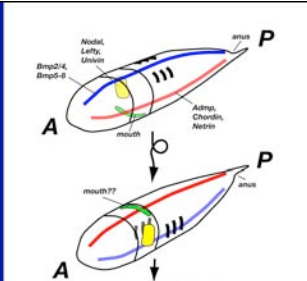
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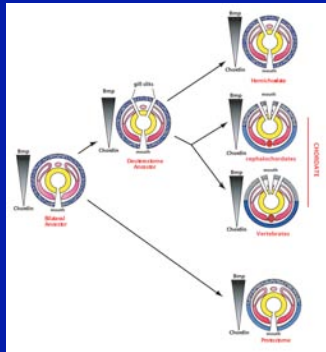
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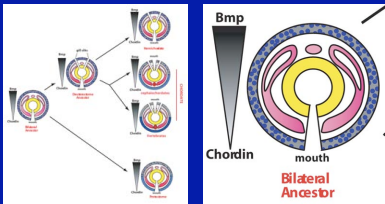
First flip the chordate on its back

1. Move the mouth to the BMP (ventral) side
2. Centralize the nervous system to the Chordin (dorsal) side
3. Centralize the mesoderm (notochord) to the Chordin (dorsal side)

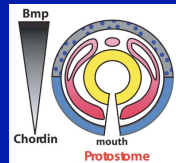
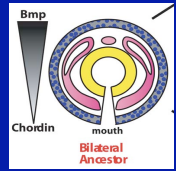
### A simple model for inversion



The basal bilateral ancestor is a nerve net and not a centralized NS



The protostomes centralized the nervous system on the chordin side



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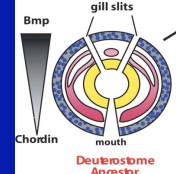
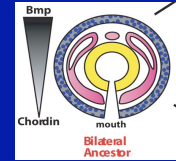
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The deuterostome ancestor added gill slits on the BMP side



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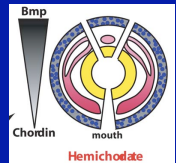
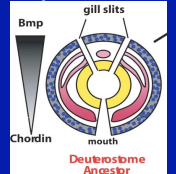
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The hemichordates retained the basic plan of the deuterostome ancestor



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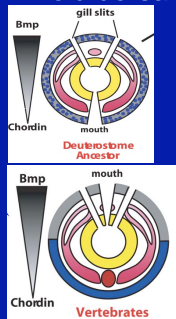
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The vertebrates centralized the NS on the BMP side and opened a new mouth on the old dorsal side - inverting the animal!



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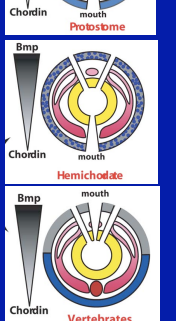
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There is no real axis inversion just different specification of the NS relative to the BMP-chordin gradient



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### Hemichordates and inversion

- The basal NS may not have been centralized
- The Bmp/chordin gradient controls D/V everywhere
- The BMP gradient does not affect the NS in hemichordates
- Simple inversion of the NS is not supported by the hemichordate data since there is little conservation of d/v expression

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Of course we really do not know what happened

But we can ask 3 confirmatory questions:

1. Are hemichordates ancient and related to early deuterostomes?

2. To what extent can we confirm fossils with evidence from gene expression?

3. If the vertebrates flipped, left should be right and right should be left.

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3. If the vertebrates flipped, left should be right and right should be left.  
RIGHT?

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Hemichordates are very old and modern ones may be closely related to stem deuterostomes

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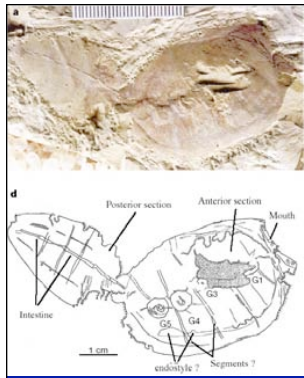
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Chengjiang fauna in China. Lower cambrian deposits (Shu et al., Nature, 2001)

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But are these holes really vertebrate-like gill slits?

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**Chordate gill slit markers: orthologs are expressed in the hemichordate gill slits**



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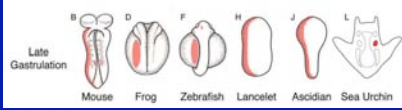
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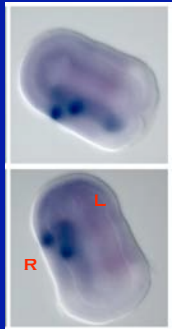
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### Final proof for the model of axis inversion in hemichordates?



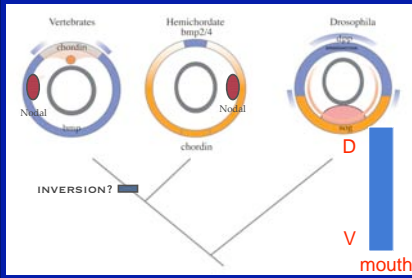
Nodal gene expression on the LEFT side when the mouth is defined as ventral in vertebrates (from Chea et al., 2005)

BUT nodal is on the RIGHT SIDE in when the mouth is ventral in Hemichordates



- If the mouth has been flipped relative to the Bmp/Chordin axis
- And if Nodal has kept its conserved relationship with Bmp/Chordin
- Then Nodal should flip from the RIGHT side in Hemichordates to the LEFT side in vertebrates

Expression of nodal supports a conserved mechanism of L/R patterning relative to BMP/chordin axis but an inversion of the relative to the vertebrate CNS and mouth



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