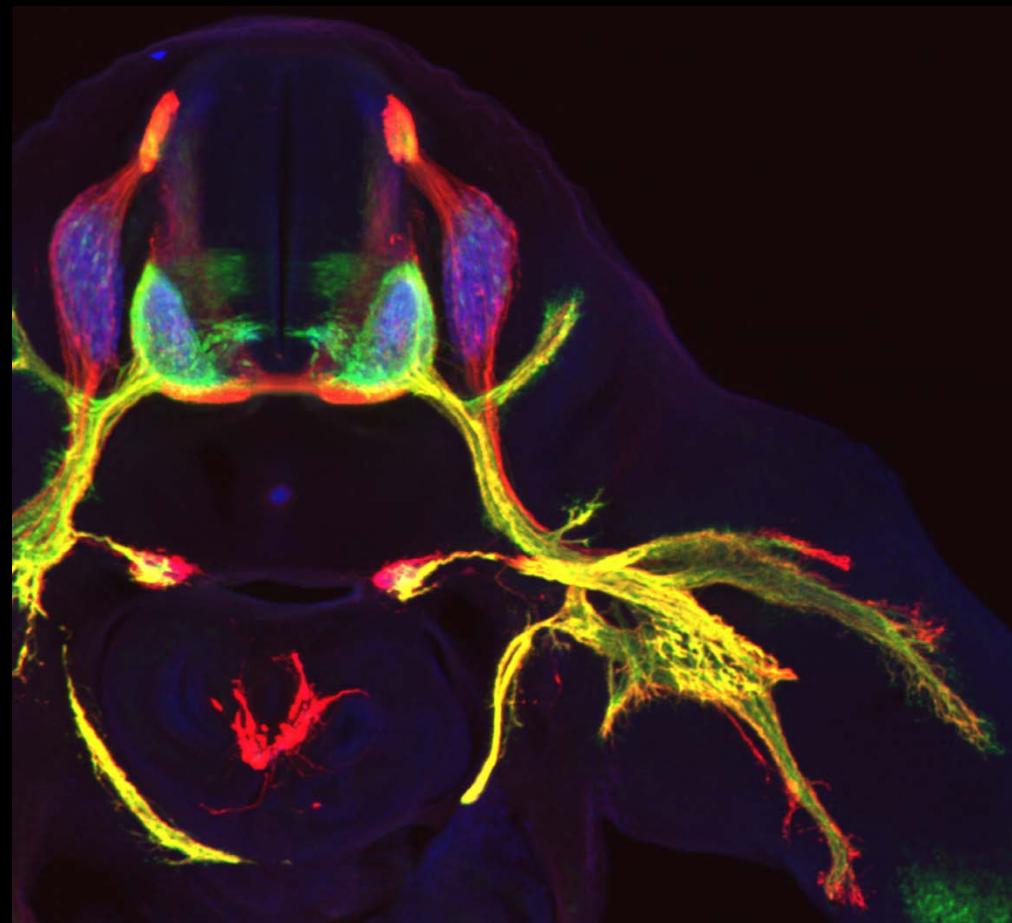
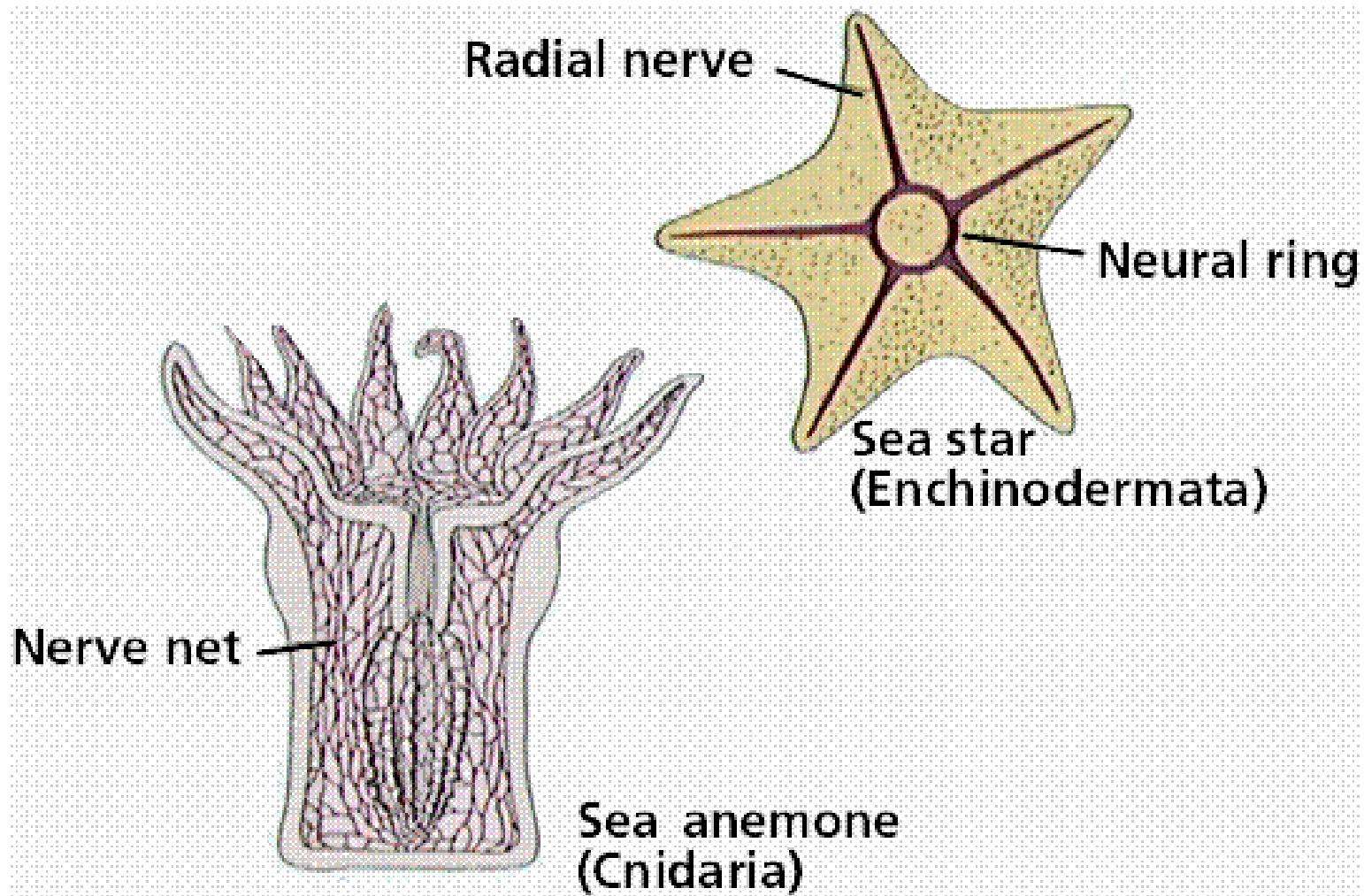


Evolution of Nervous Systems



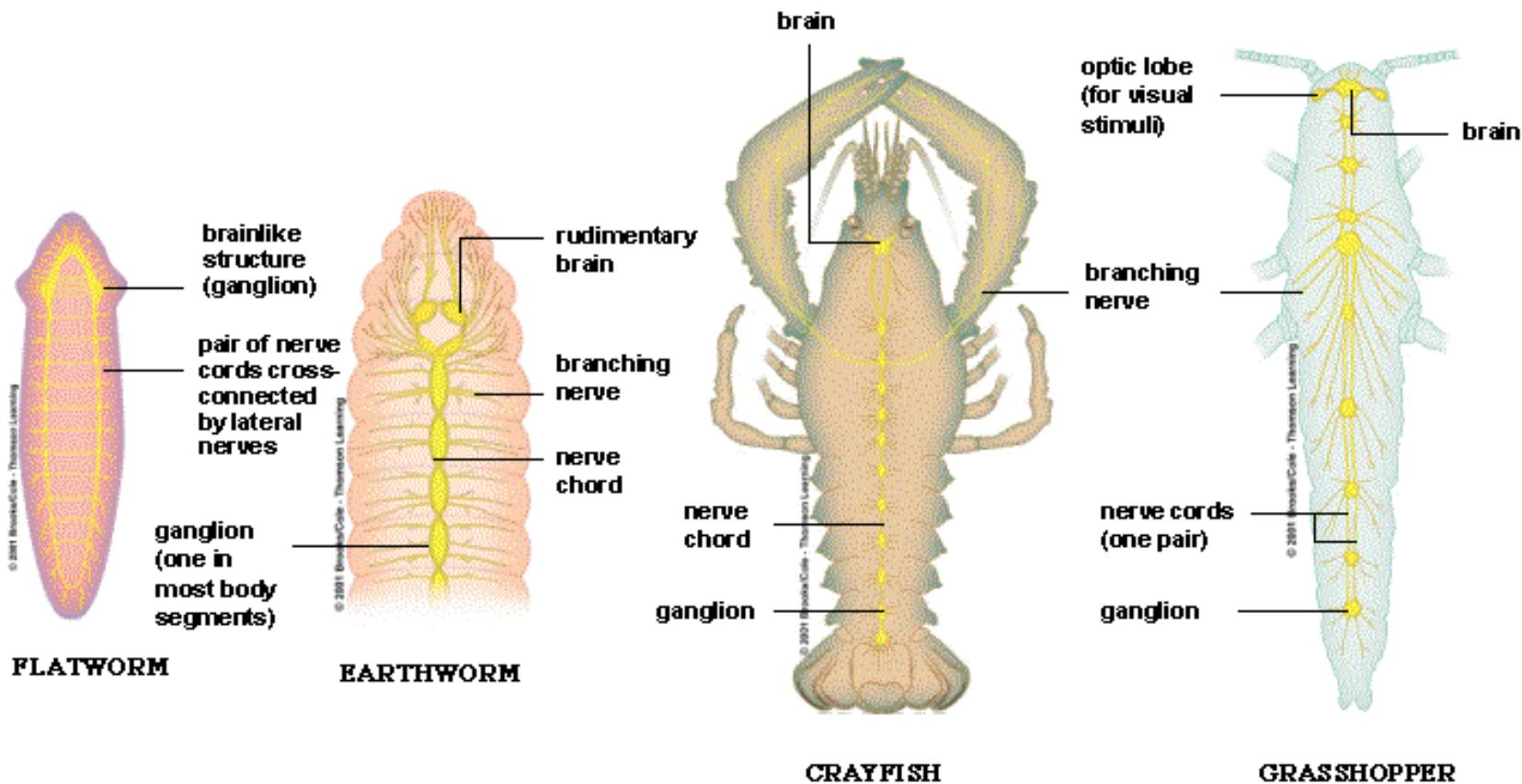
Hb9::GFP

Simplest nervous systems : the nerve net



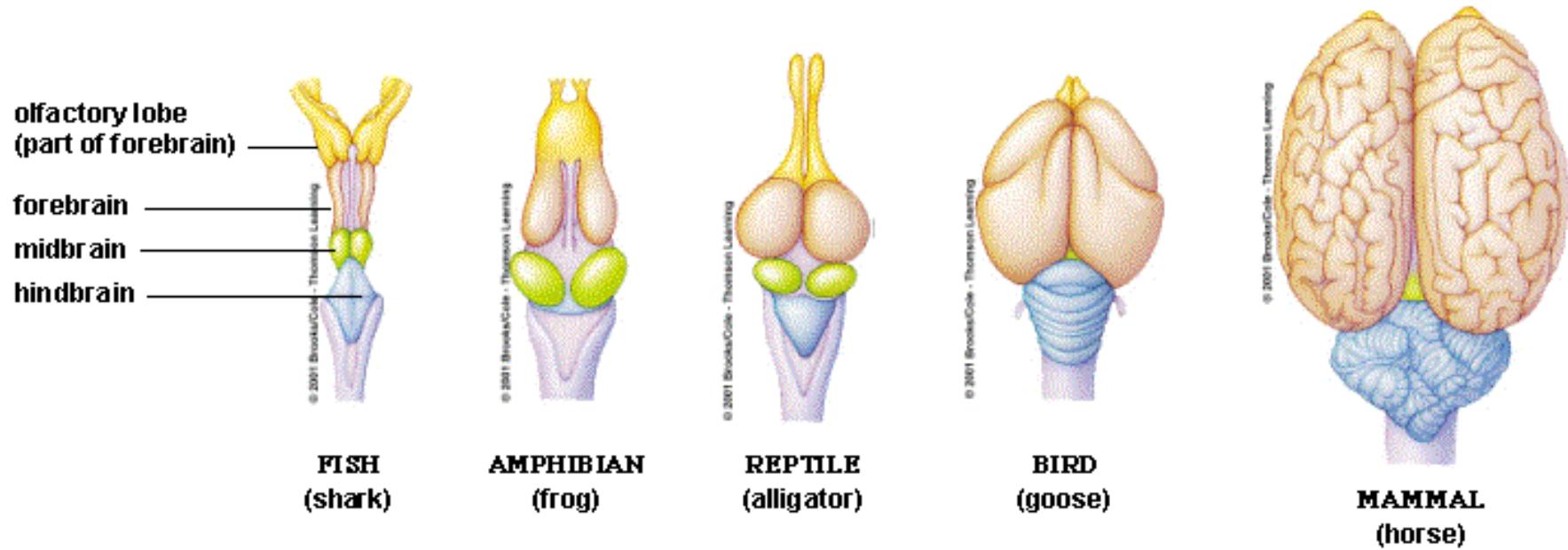
Allows animal to move in response to stimuli

Bilateral Nervous Systems



**“Brain” – Associated with development of anterior structures:
Feeding, sensory organs.**

Vertebrate nervous systems and brain growth

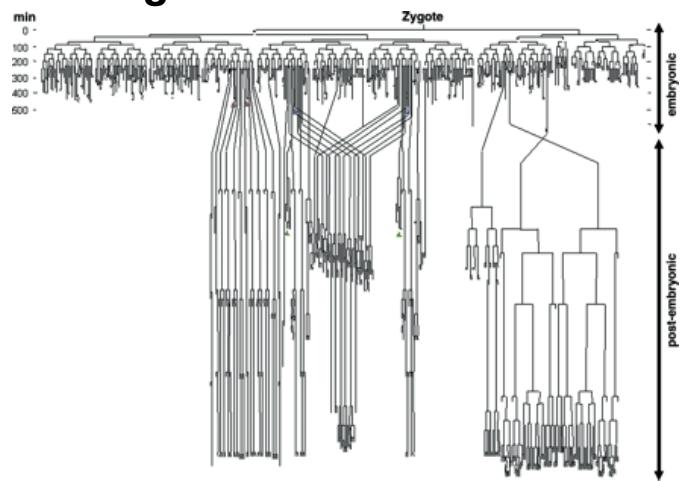


Growth of forebrain
Appearance of convolutions
Switch from nuclear to layered organization in cortex

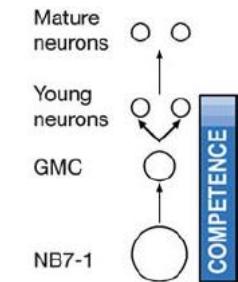
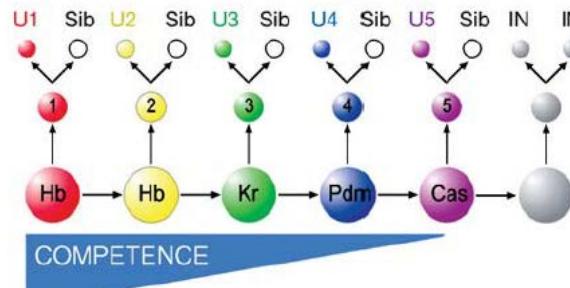
Diverse Strategies of Neurogenesis

Lineage

C. elegans

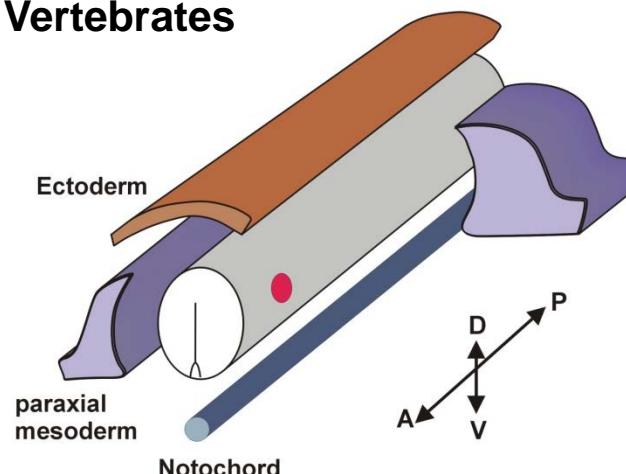


Drosophila

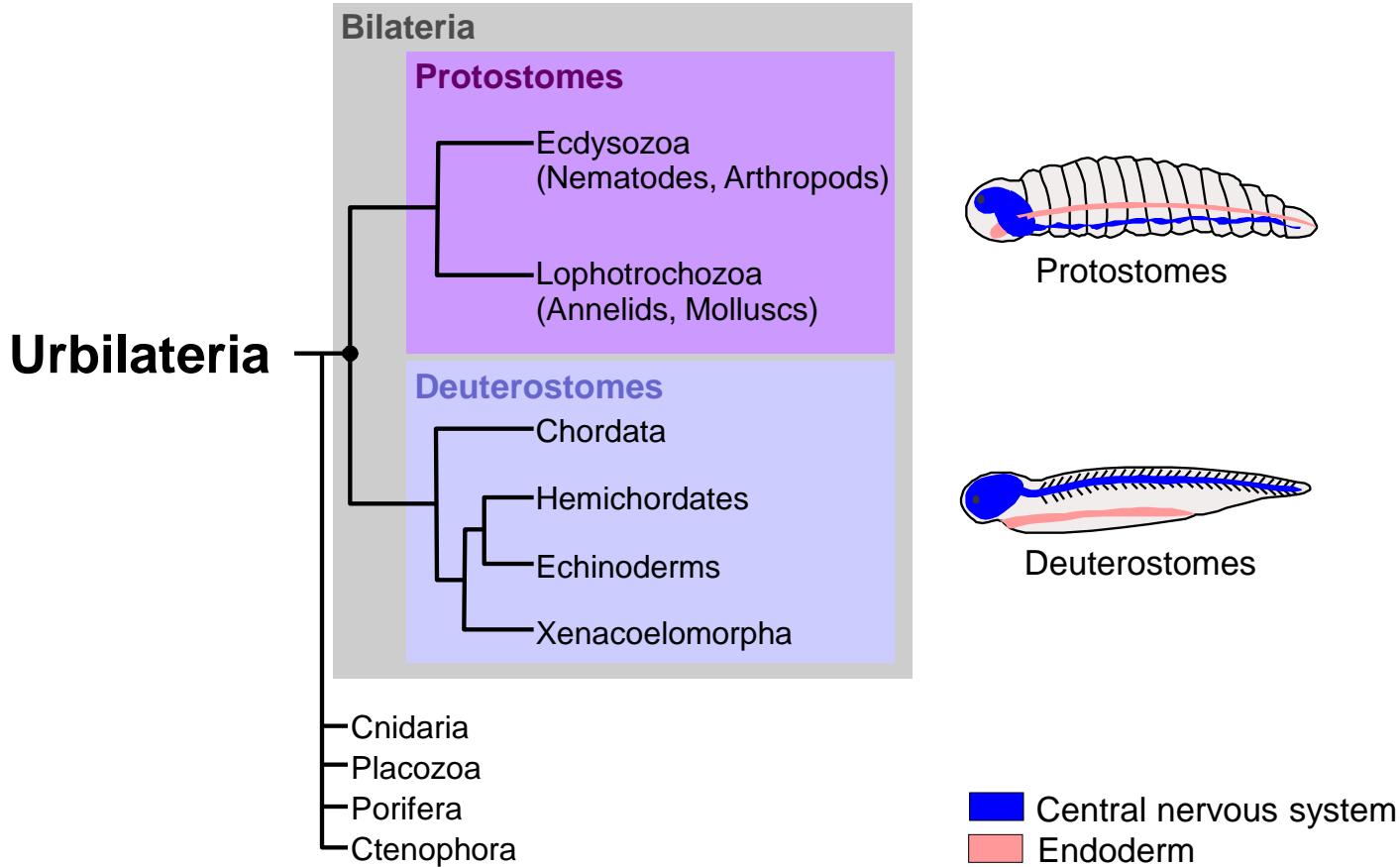


Positional identity

Vertebrates

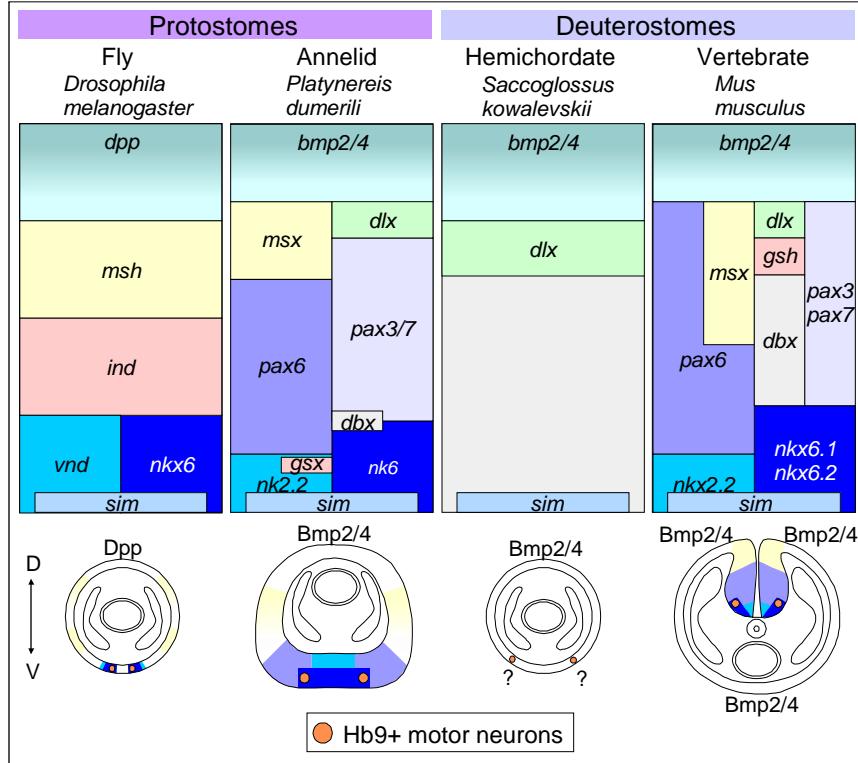


Urbilaterian Hypothesis

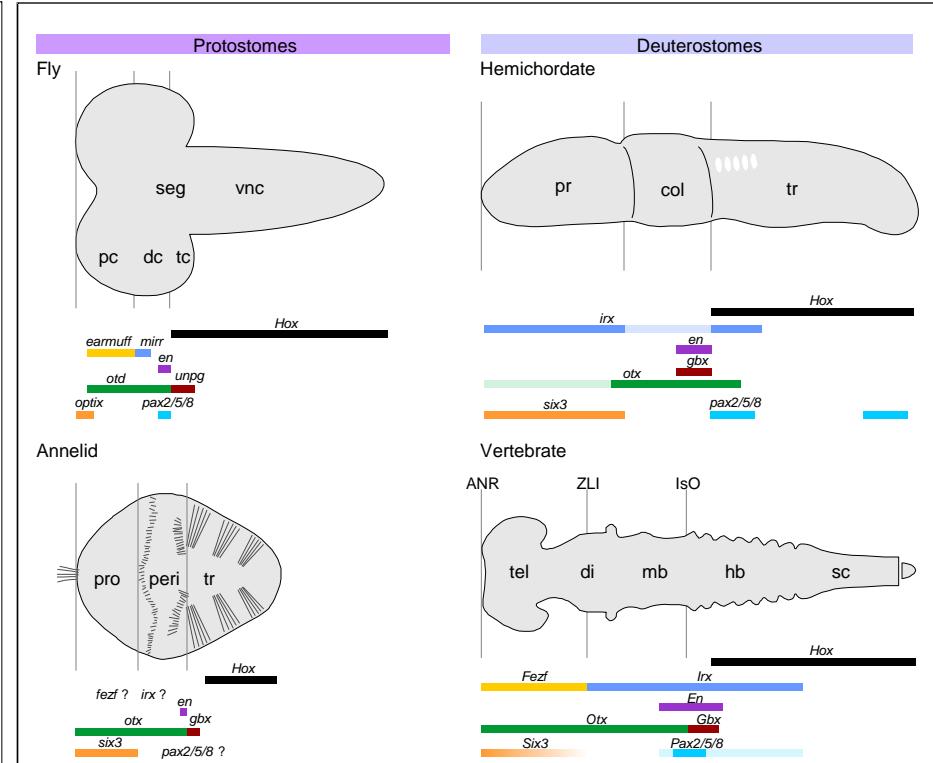


Conserved Patterning Systems in Bilateria

Dorsoventral axis



Rostrocaudal axis



Diversity of locomotor behaviors

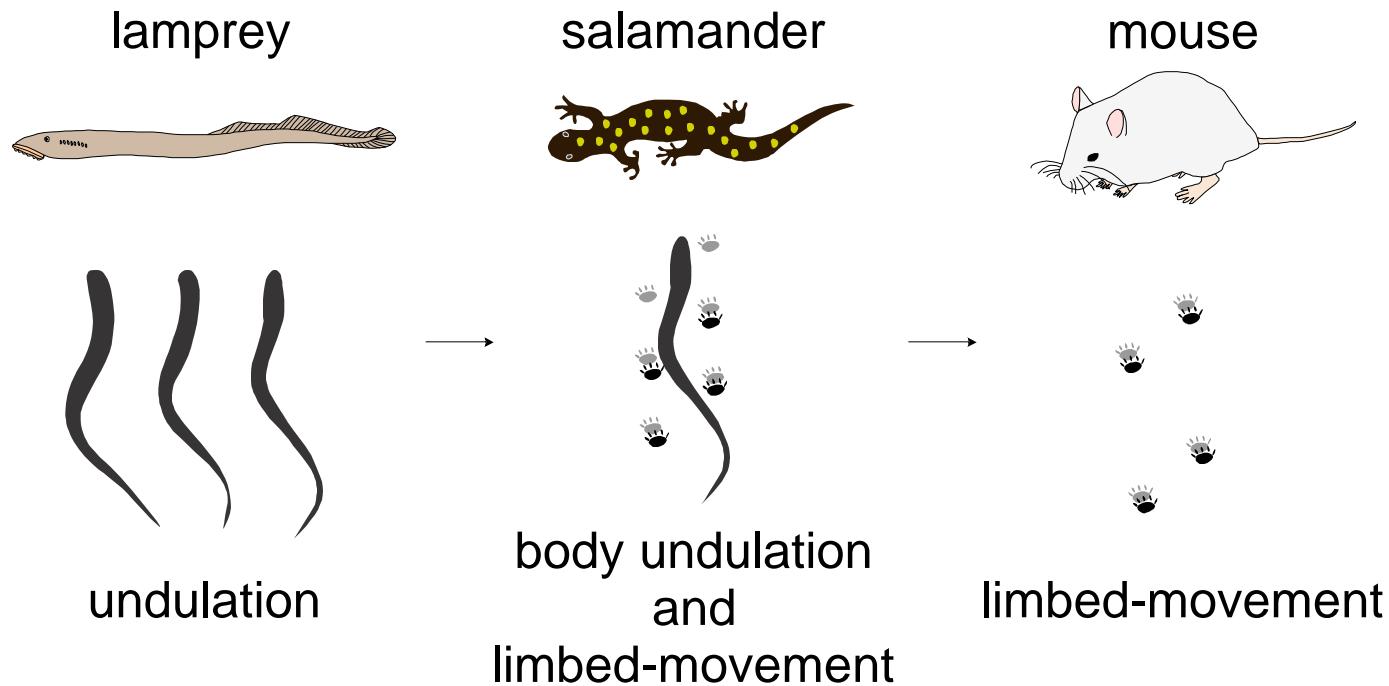
undulatory



ambulatory



Traditional View of Evolution of Locomotor Behaviors

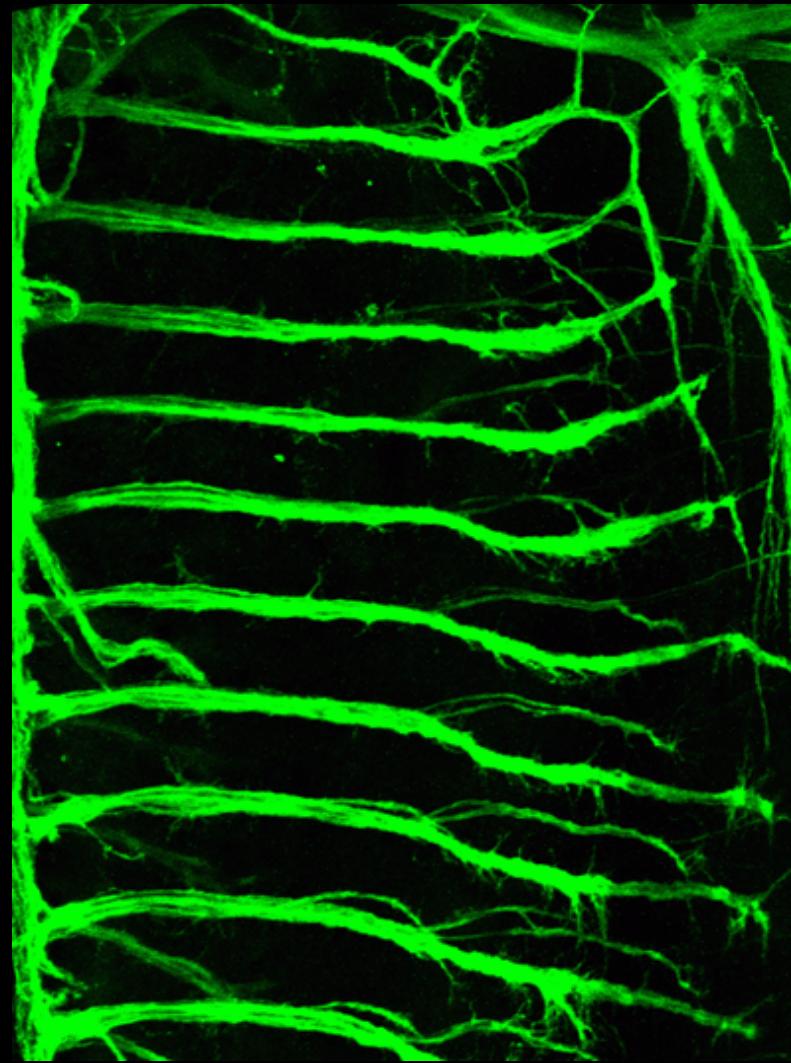


Regional diversity of tetrapod motor innervation patterns

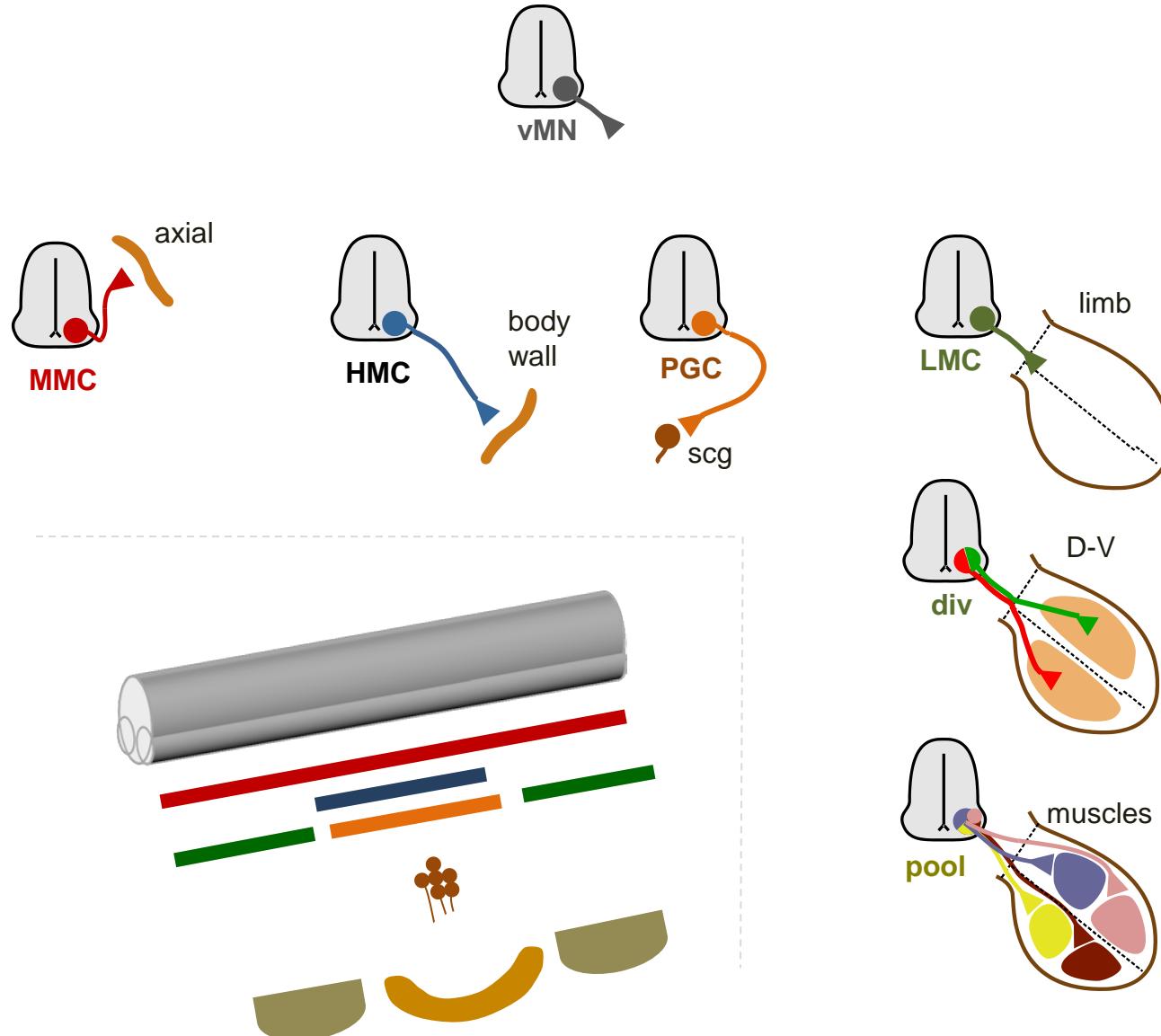


e12.5

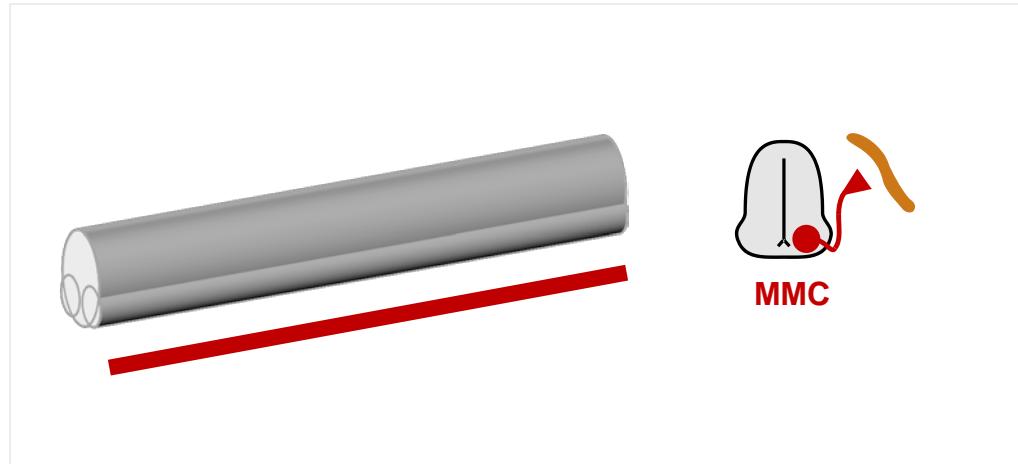
e13.5



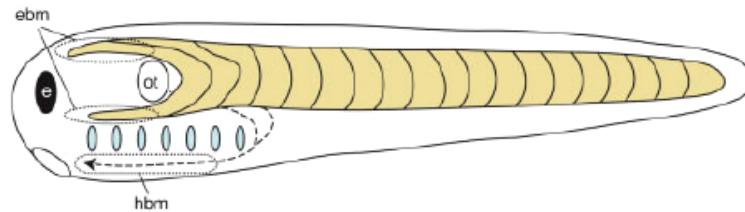
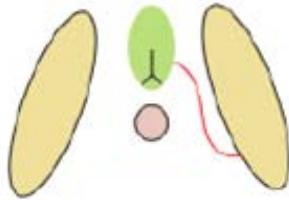
Organization and projections of mammalian MNs



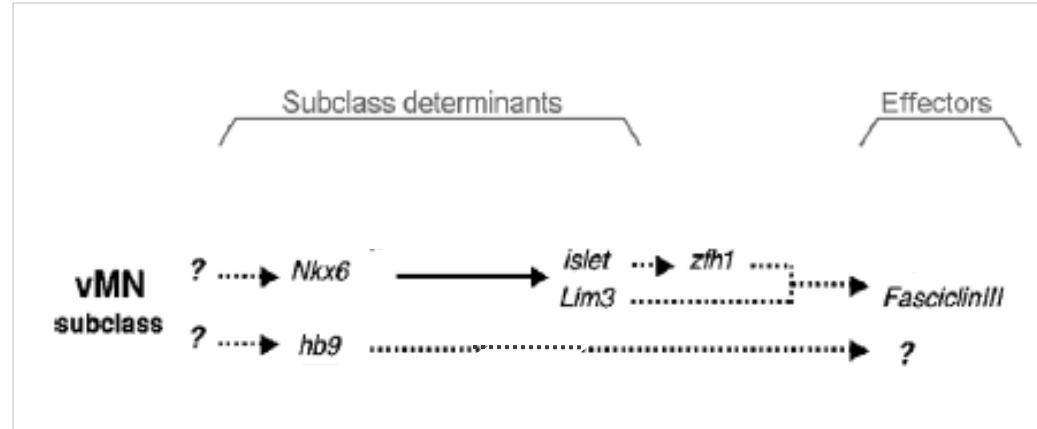
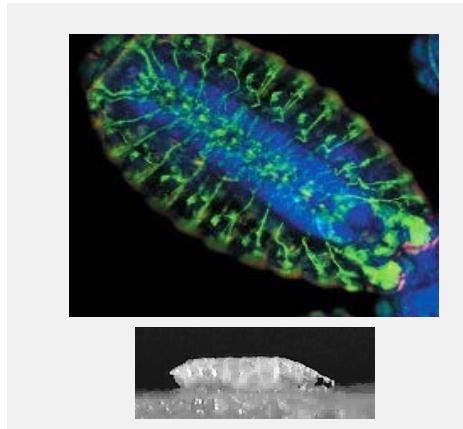
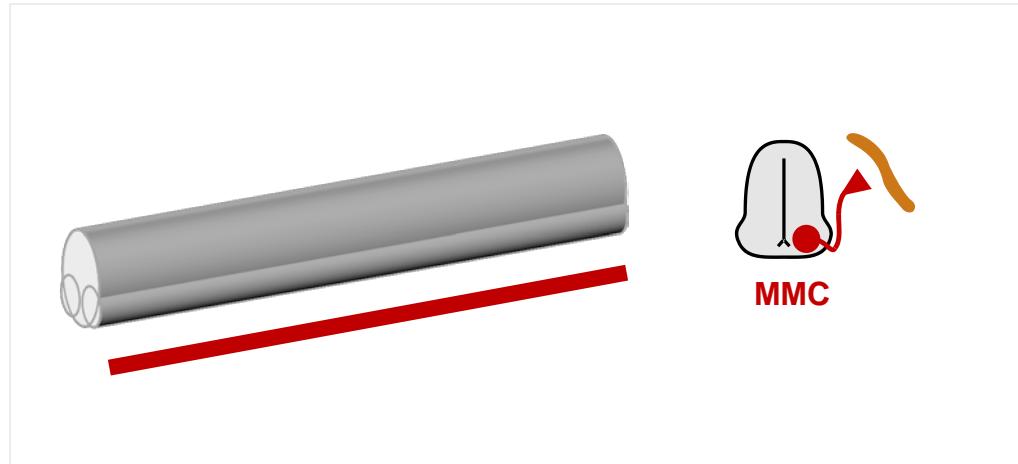
motor neuron diversification : an ancestral motor neuron class



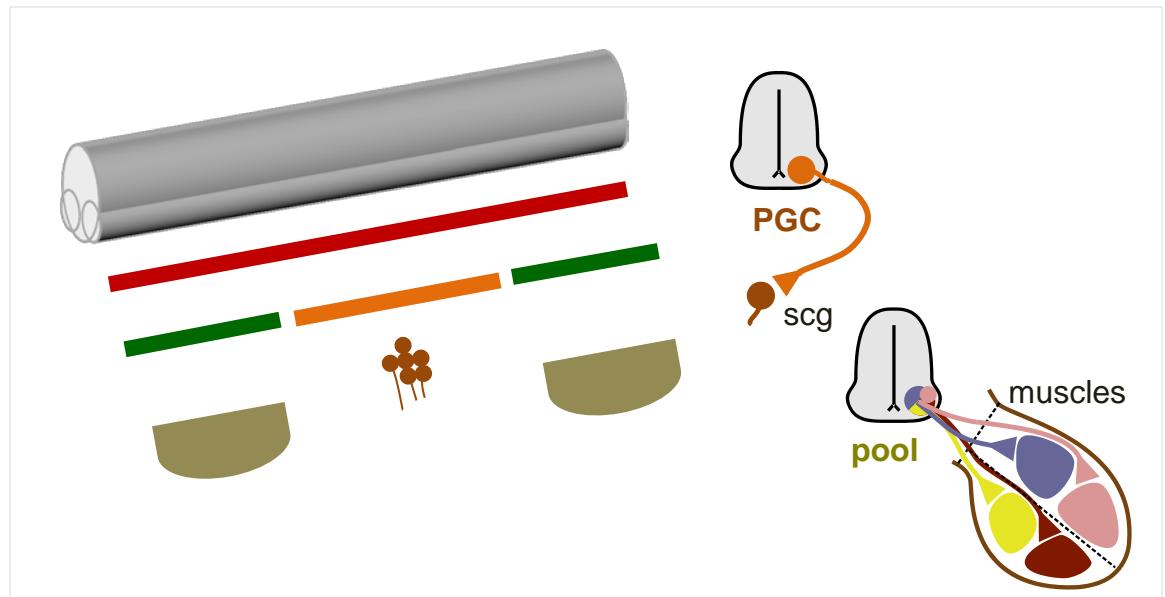
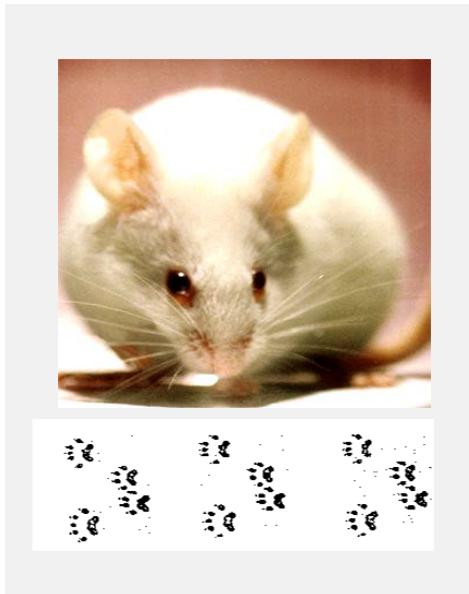
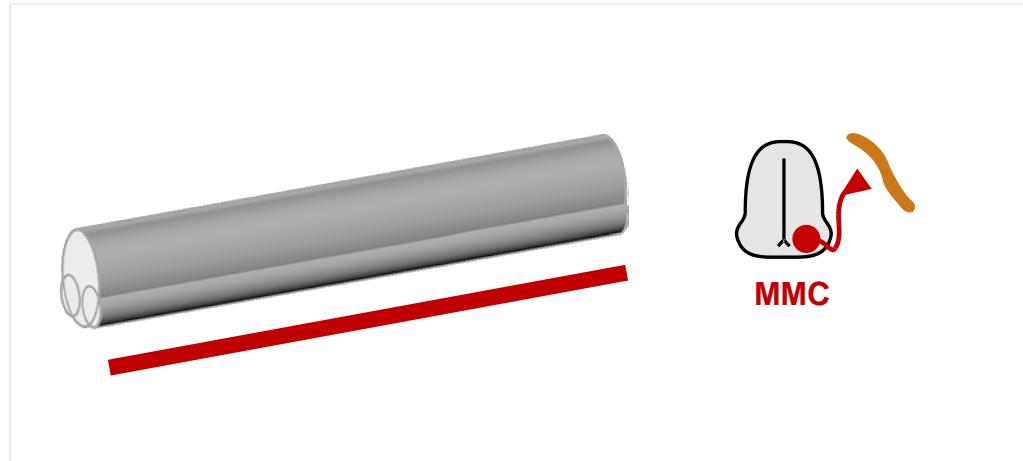
jawless fish
[hagfish / lamprey]



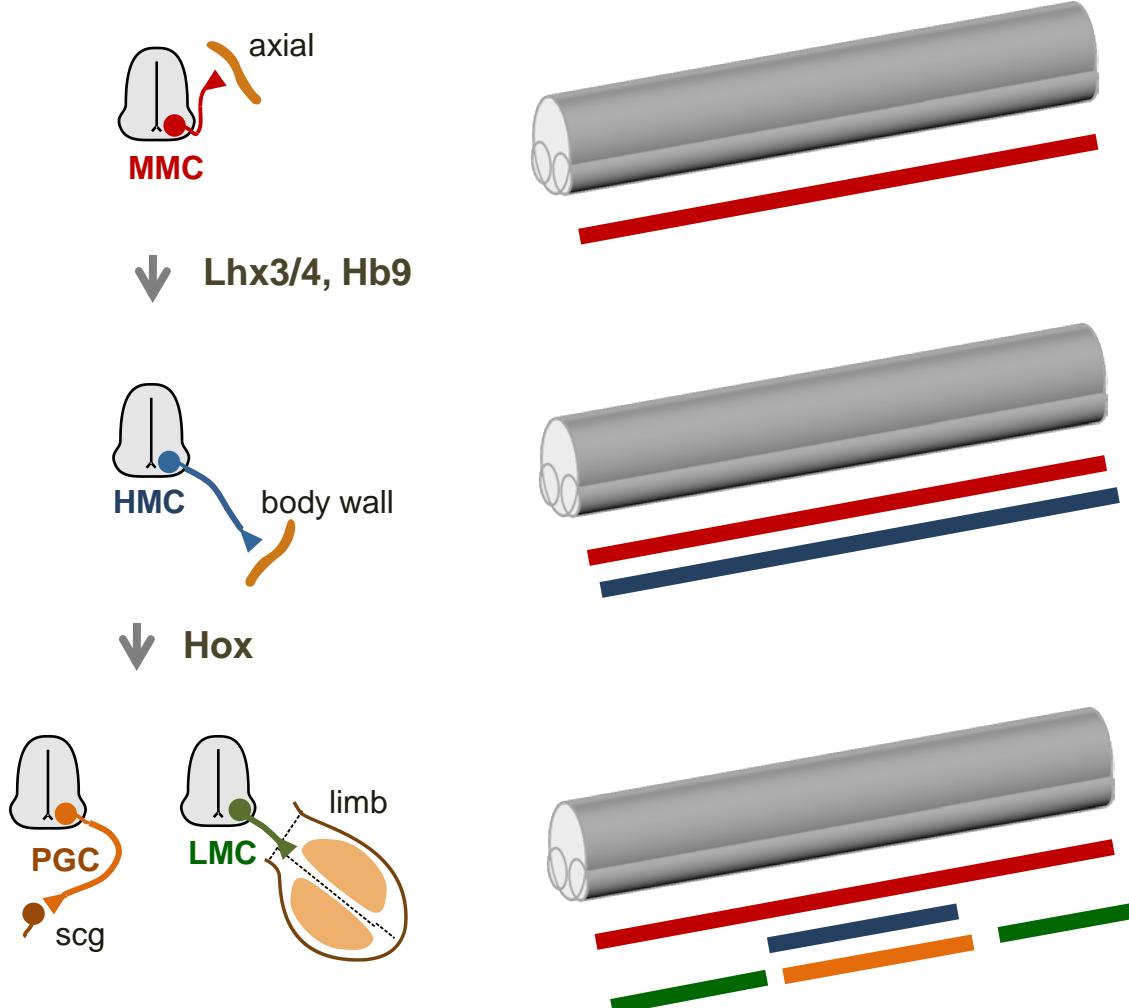
motor neuron diversification : an ancestral motor neuron class



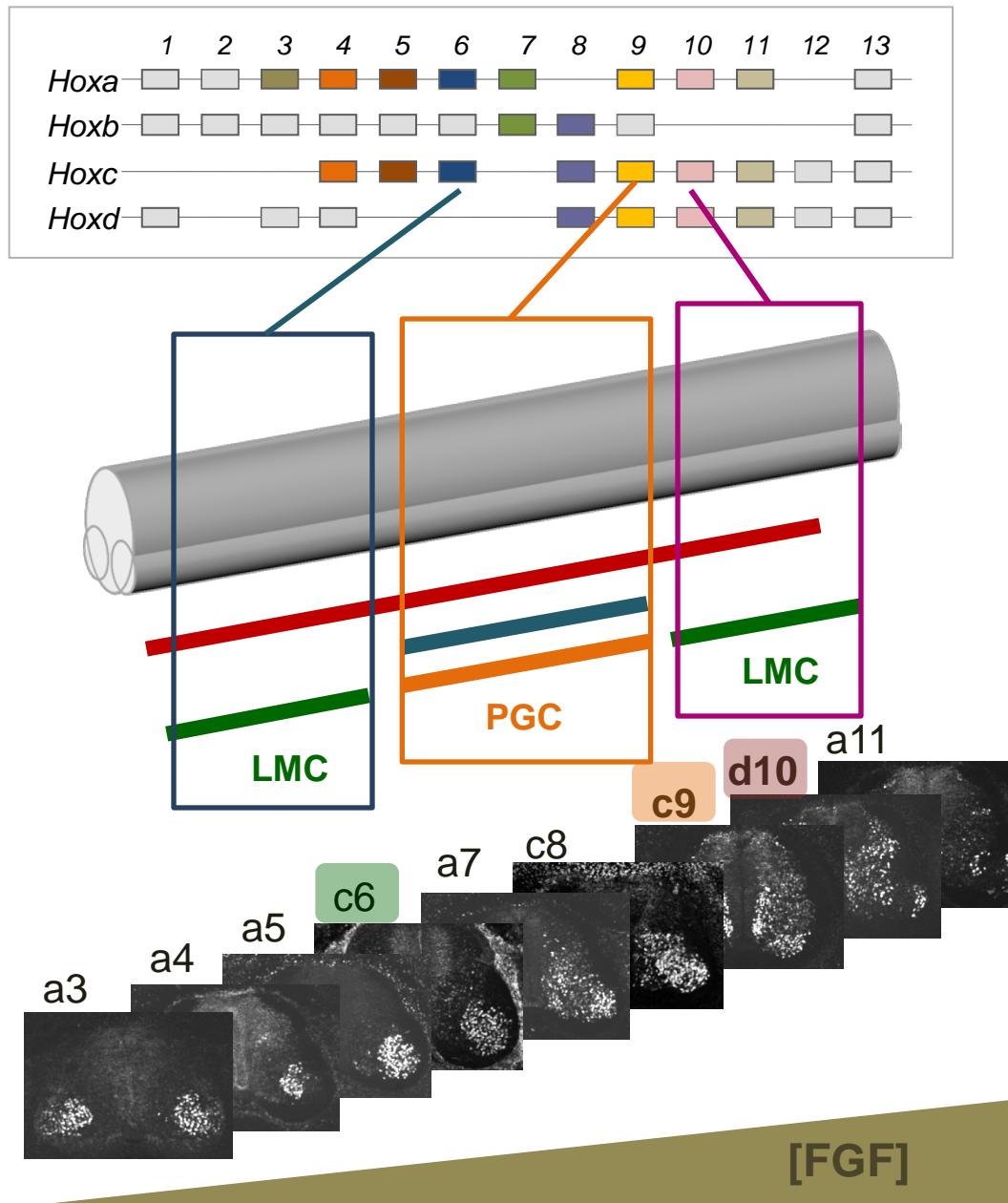
motor neuron diversification : an ancestral motor neuron class



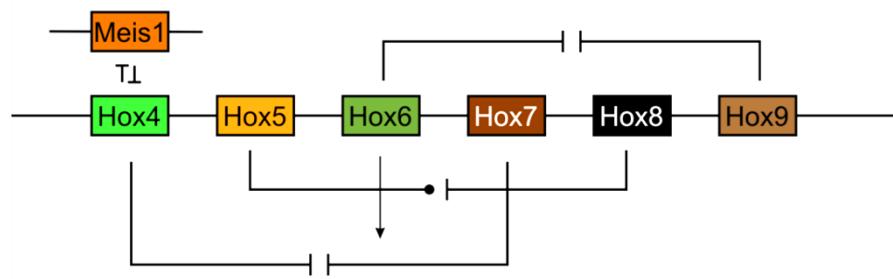
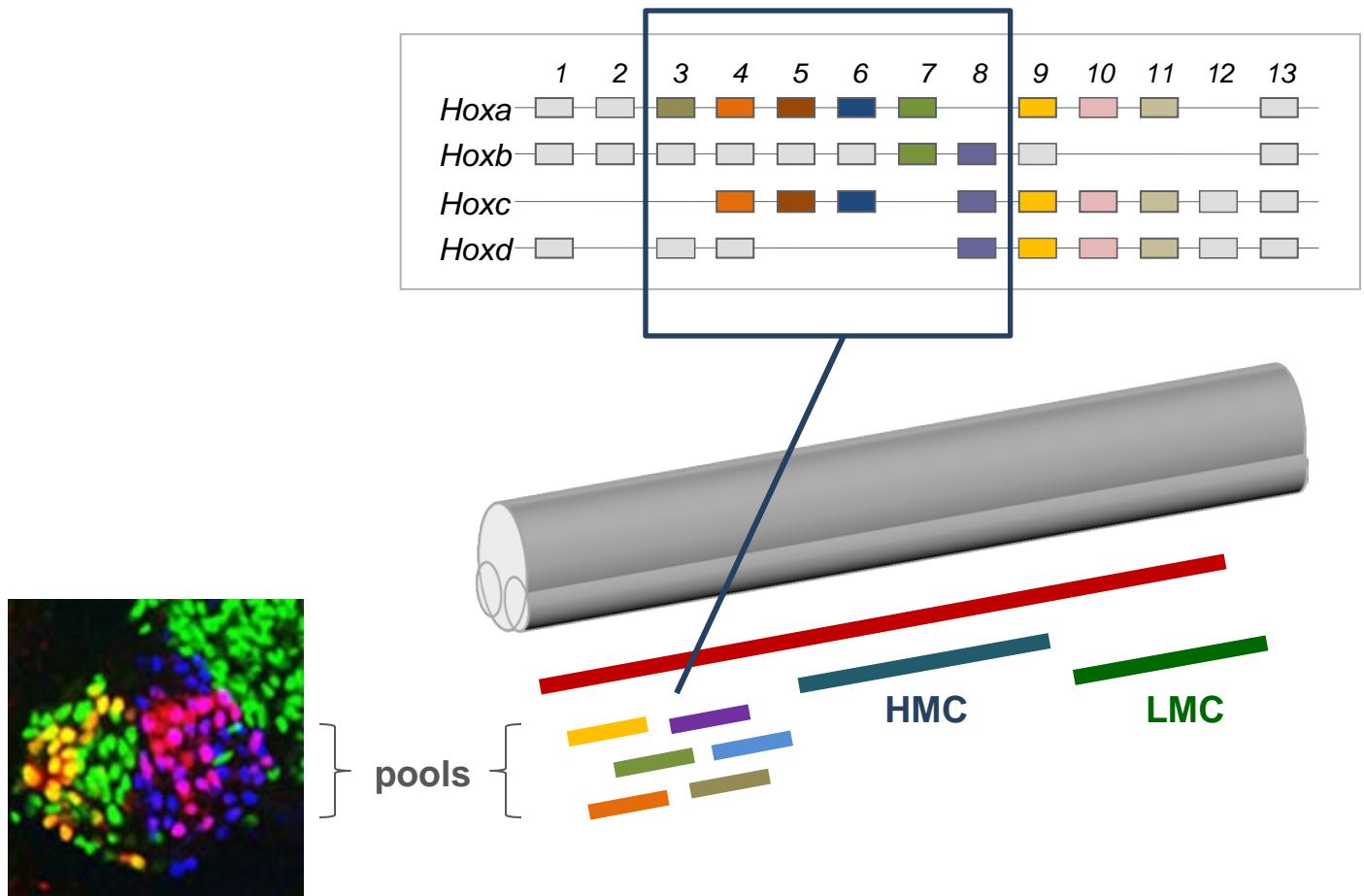
transcriptional logic of LMC and PGC specification



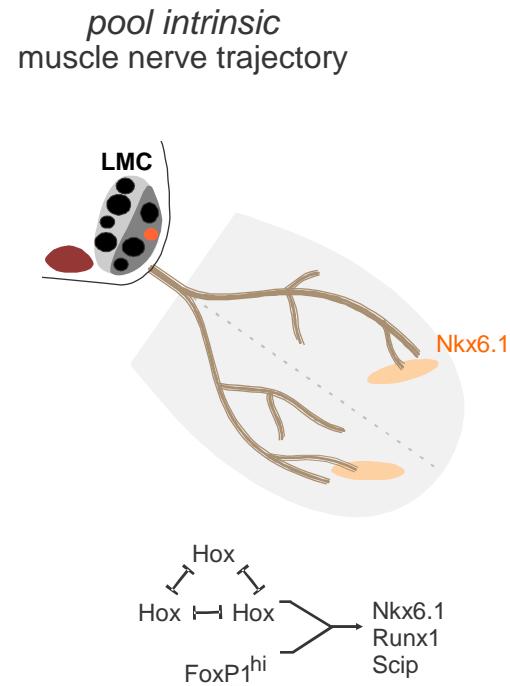
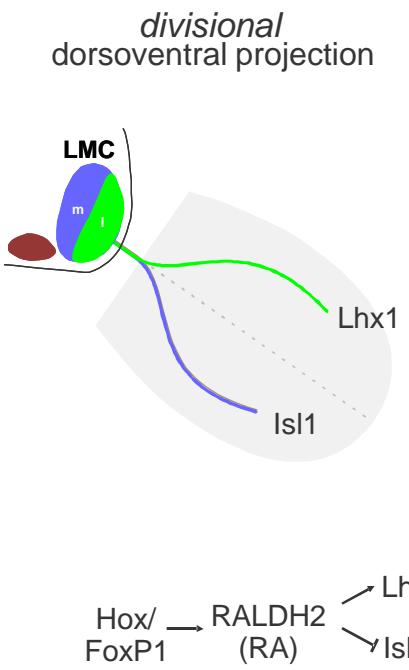
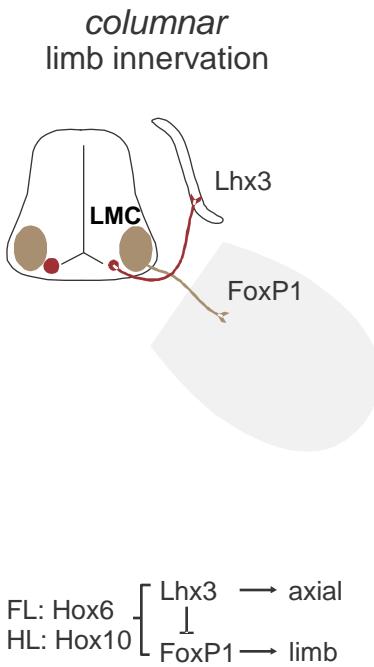
Hox genes assign LMC identity



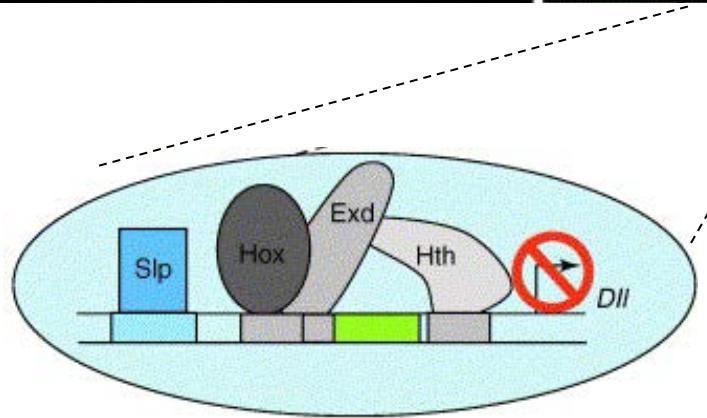
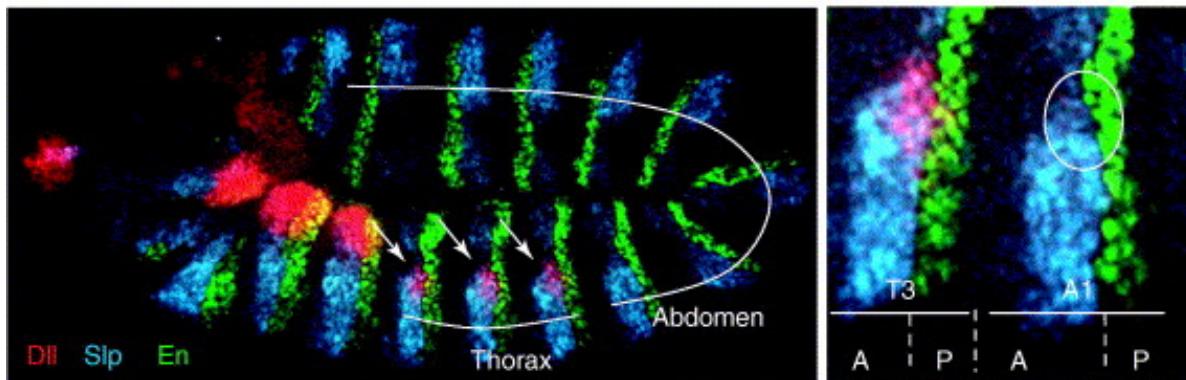
Hox repressor circuitry directs motor pool diversity



Genetic pathways controlling limb innervation

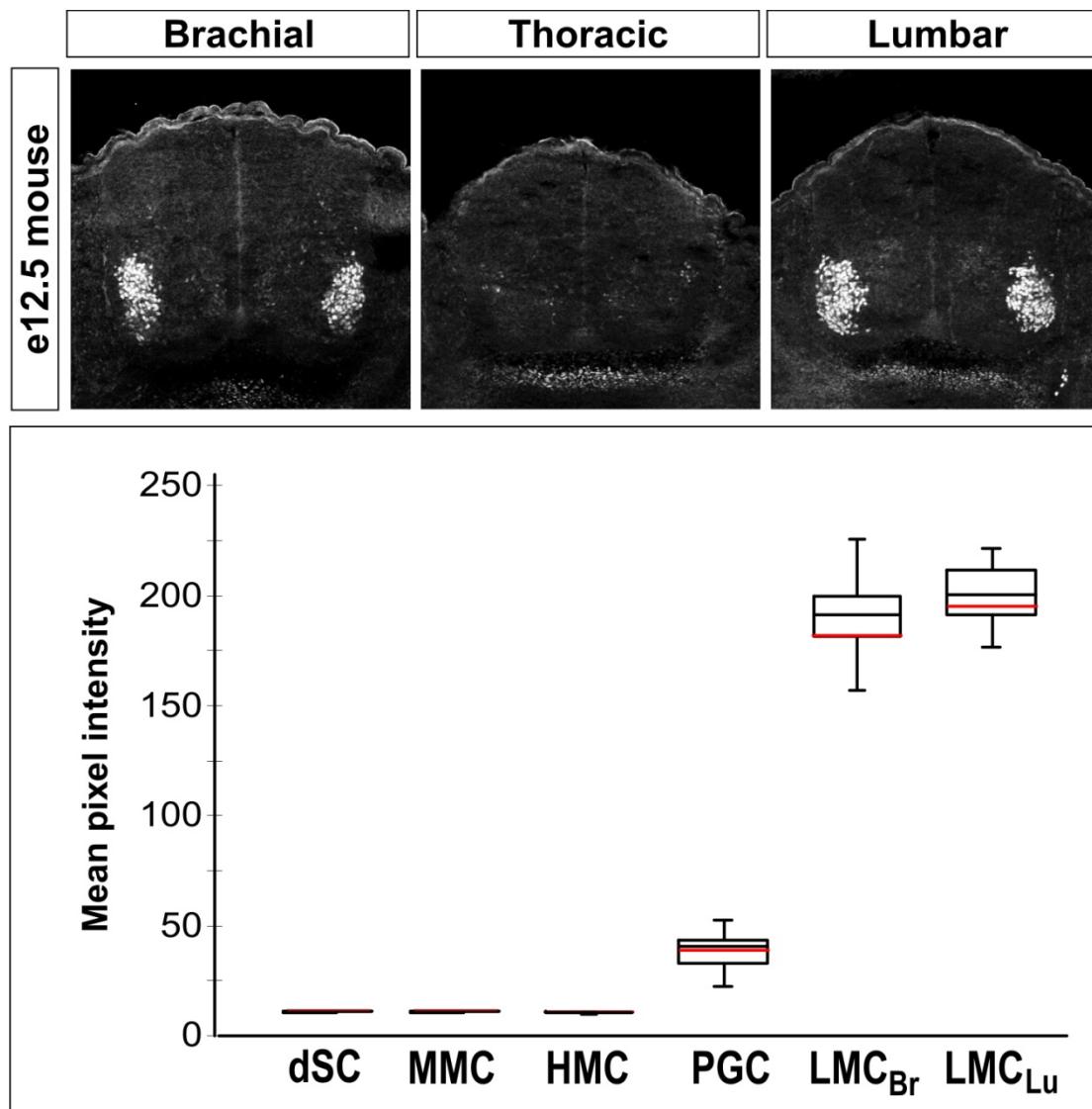


Hox activities in fly depend on transcriptional co-factors



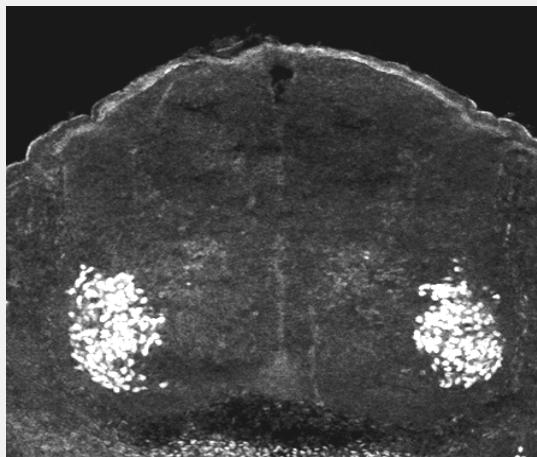
fly Slp vertebrate FoxP

Differences in FoxP1 protein levels in MNs along the rostrocaudal axis

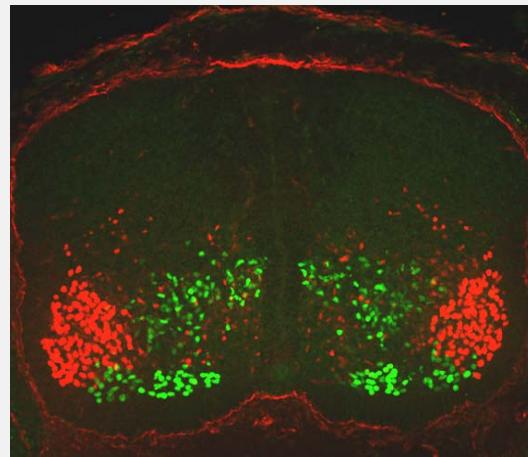


FoxP1 expression defines LMC neurons

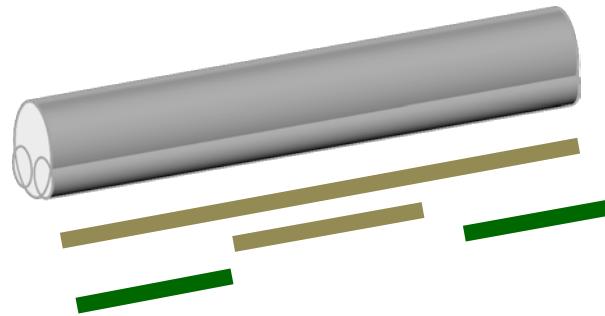
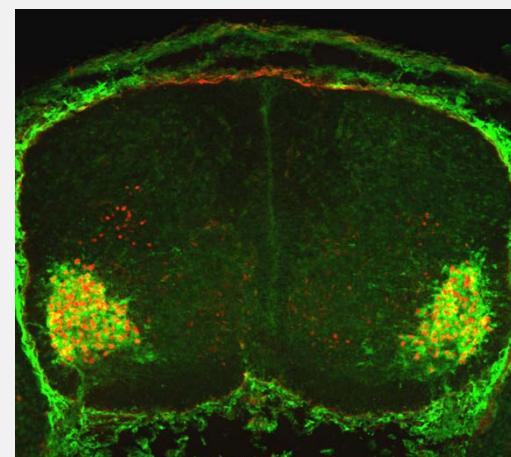
FoxP1



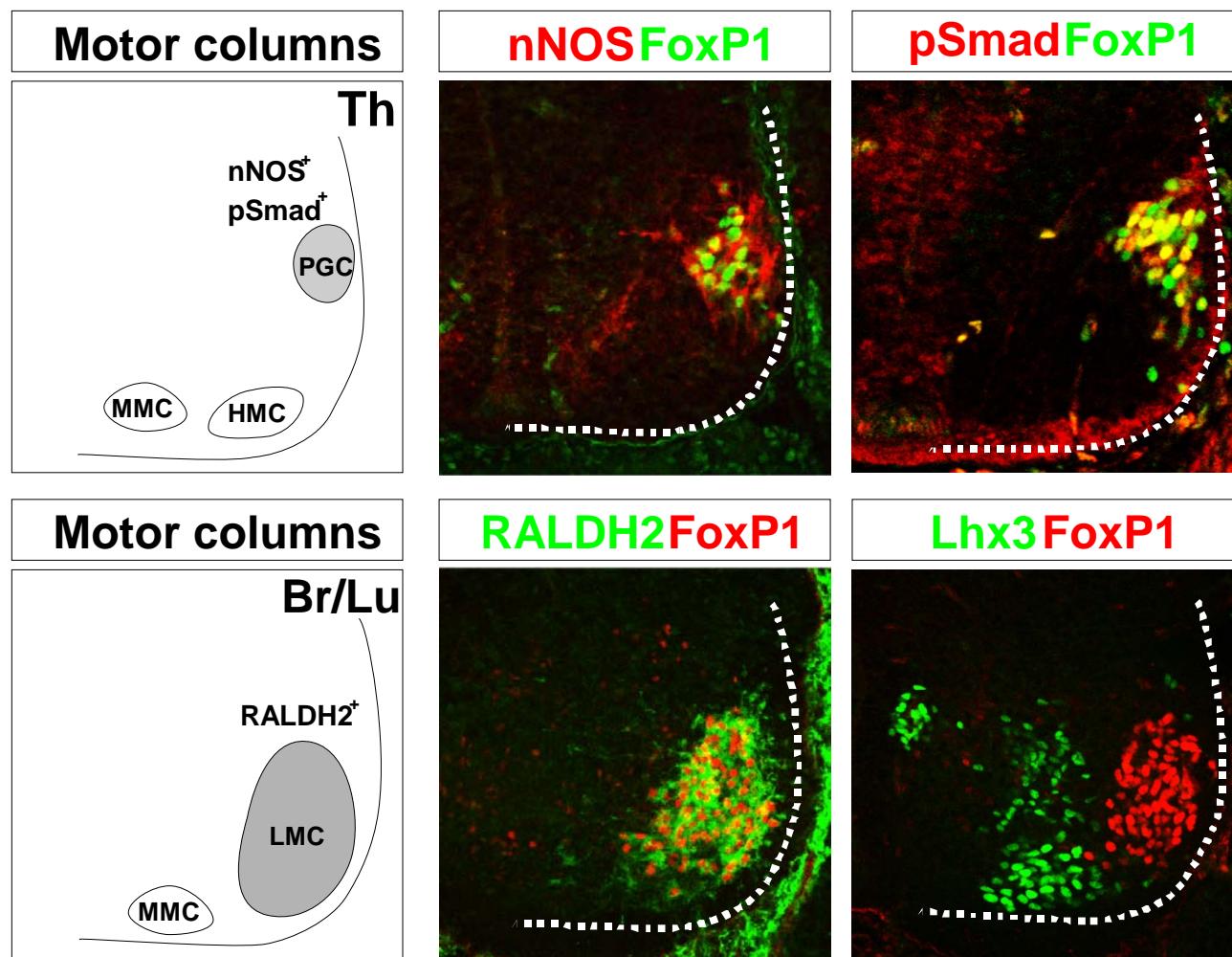
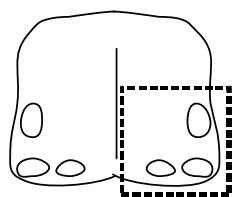
FoxP1 Lhx3



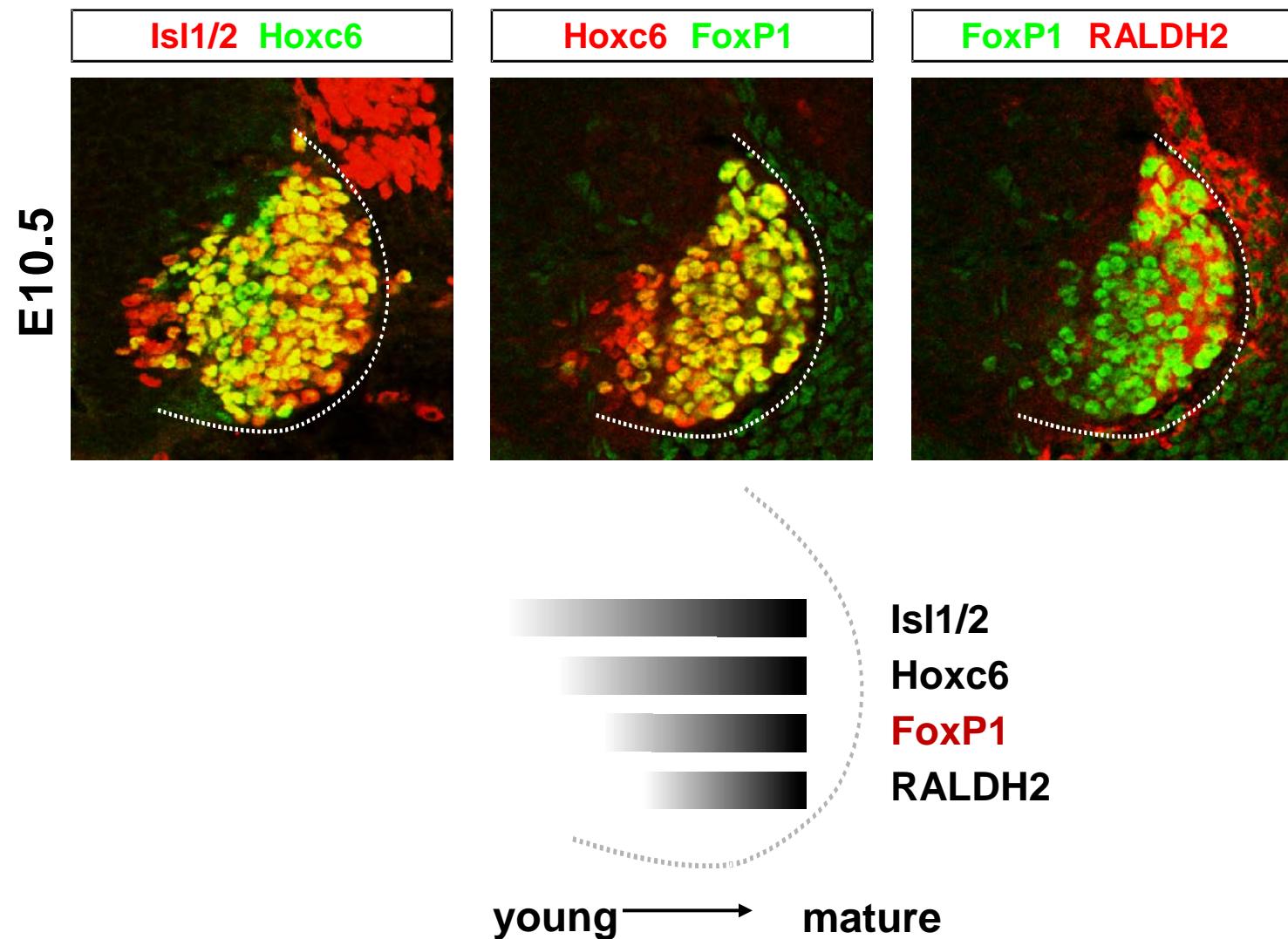
FoxP1 RALDH2



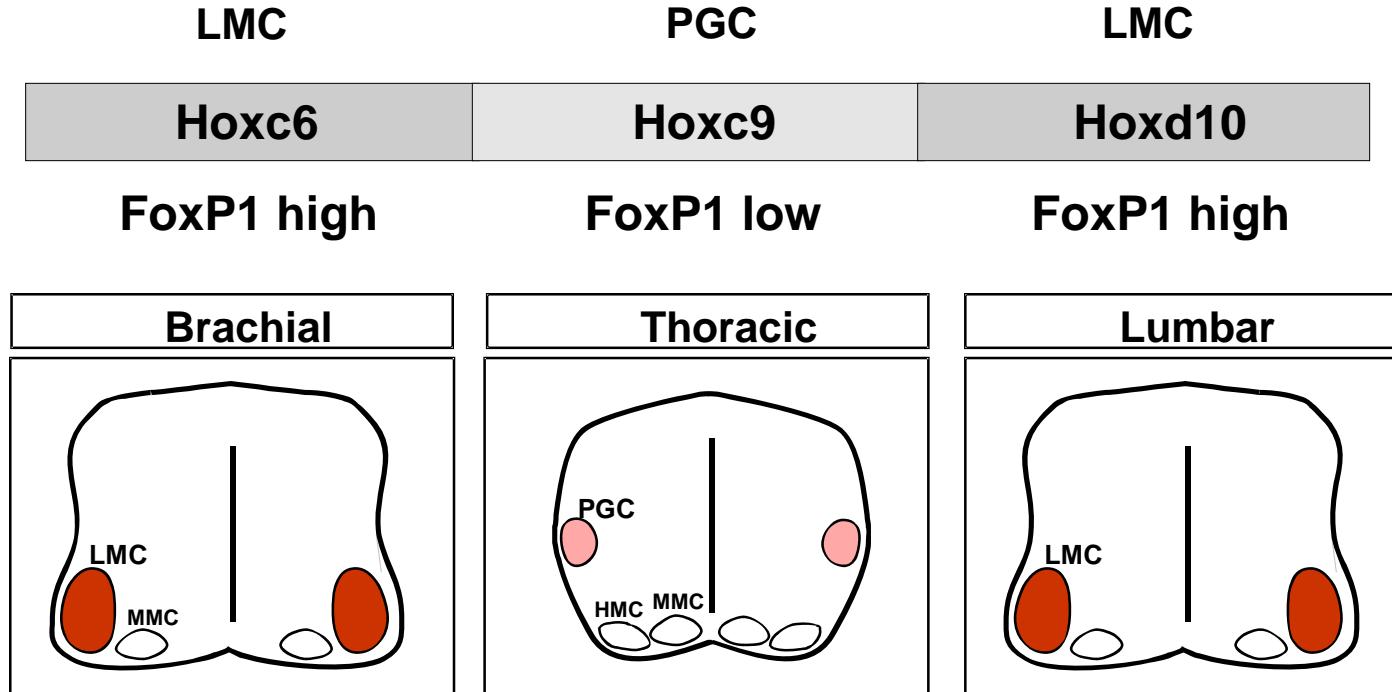
Expression of FoxP1 in two Hox-sensitive motor columns



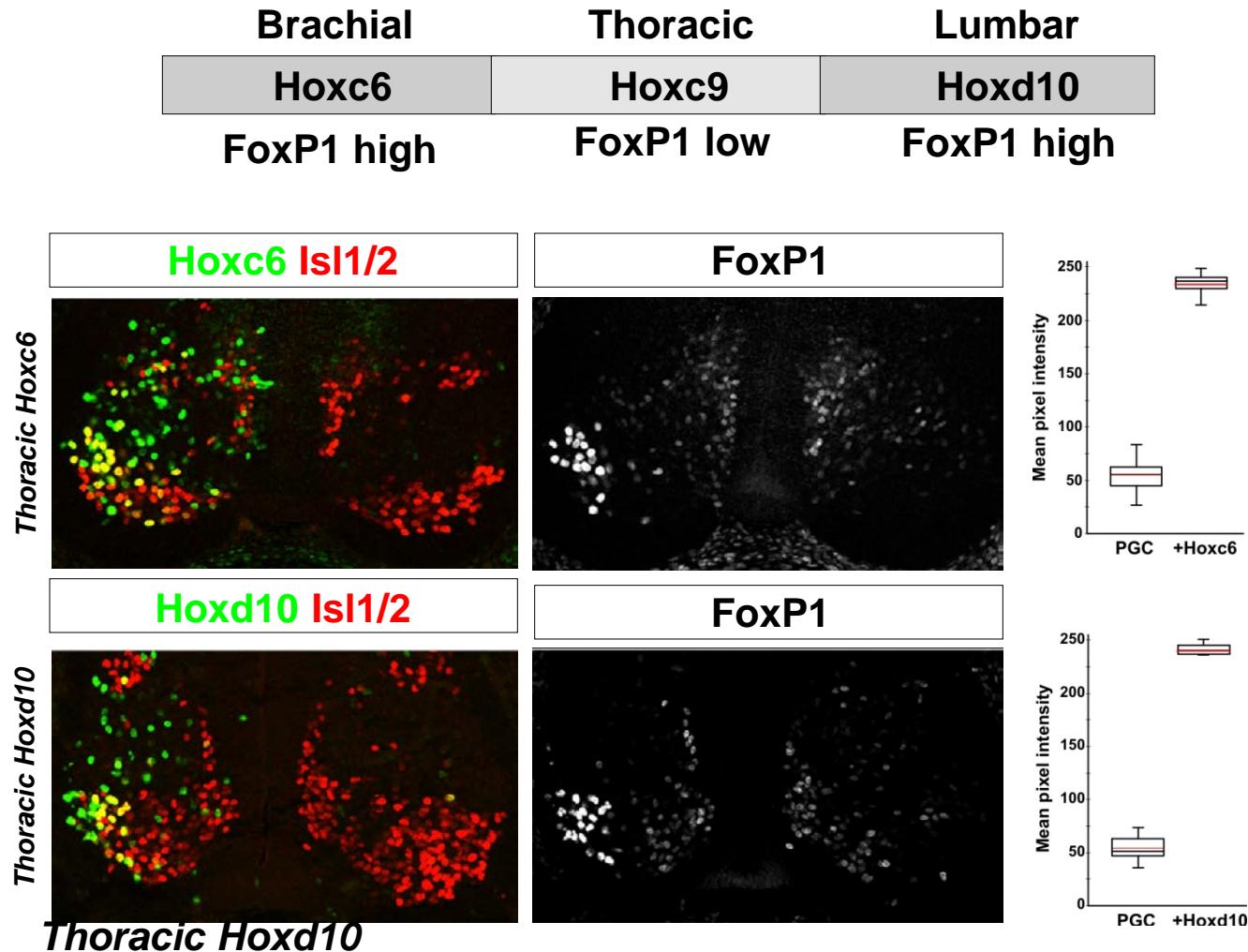
Temporal profile of FoxP1 expression in early post-mitotic LMC neurons



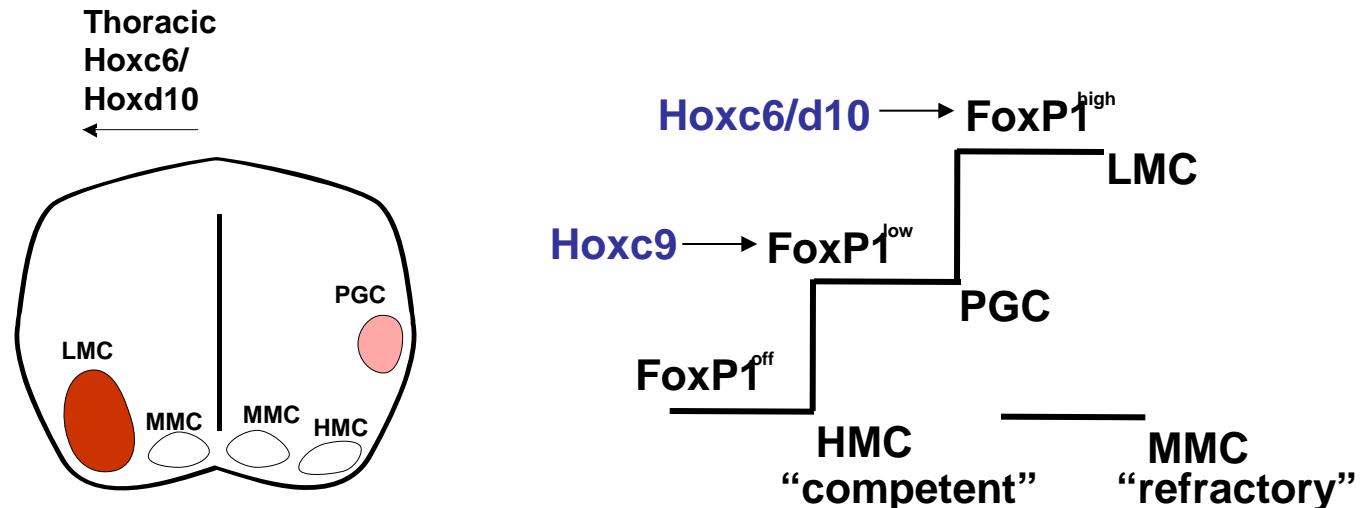
Are the levels FoxP1 expression in MNs set by Hox protein activities?



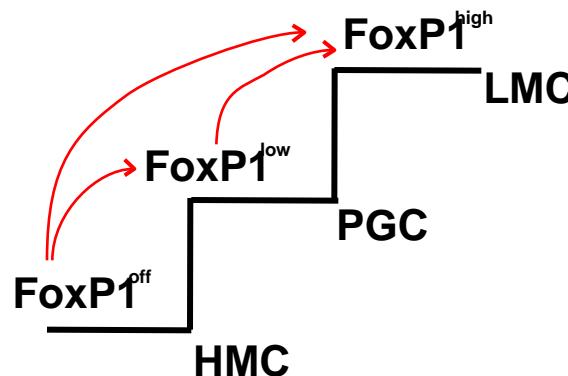
Expression of LMC Hox genes induces high levels of FoxP1 at thoracic levels



Models for FoxP1 function in specifying motor neuron subtype identities



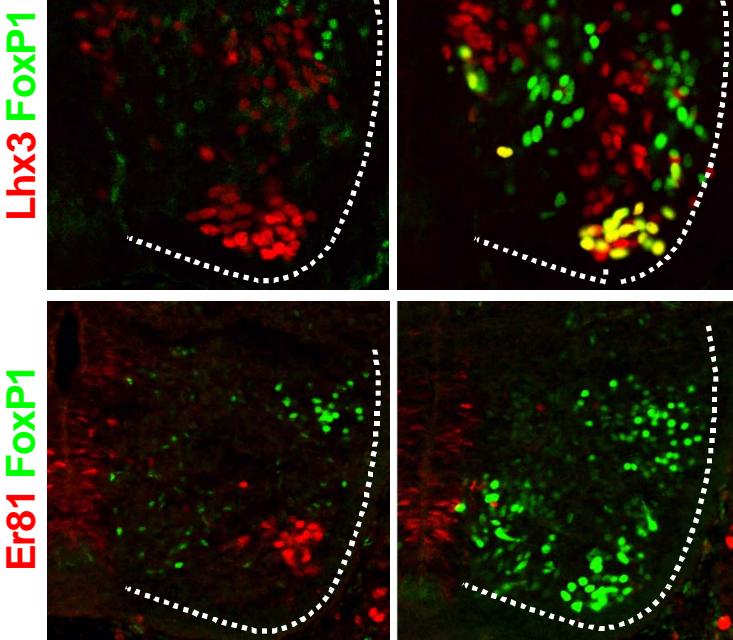
Graded FoxP1 in the Hox-dependent pathway of MN columnar fate?



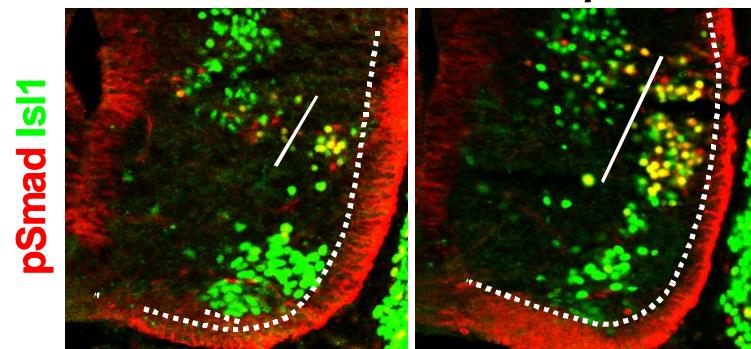
FoxP1 as a dose-dependent determinant of MN columnar subtypes



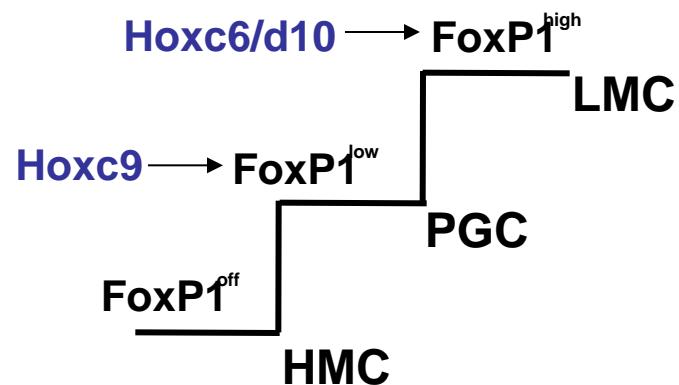
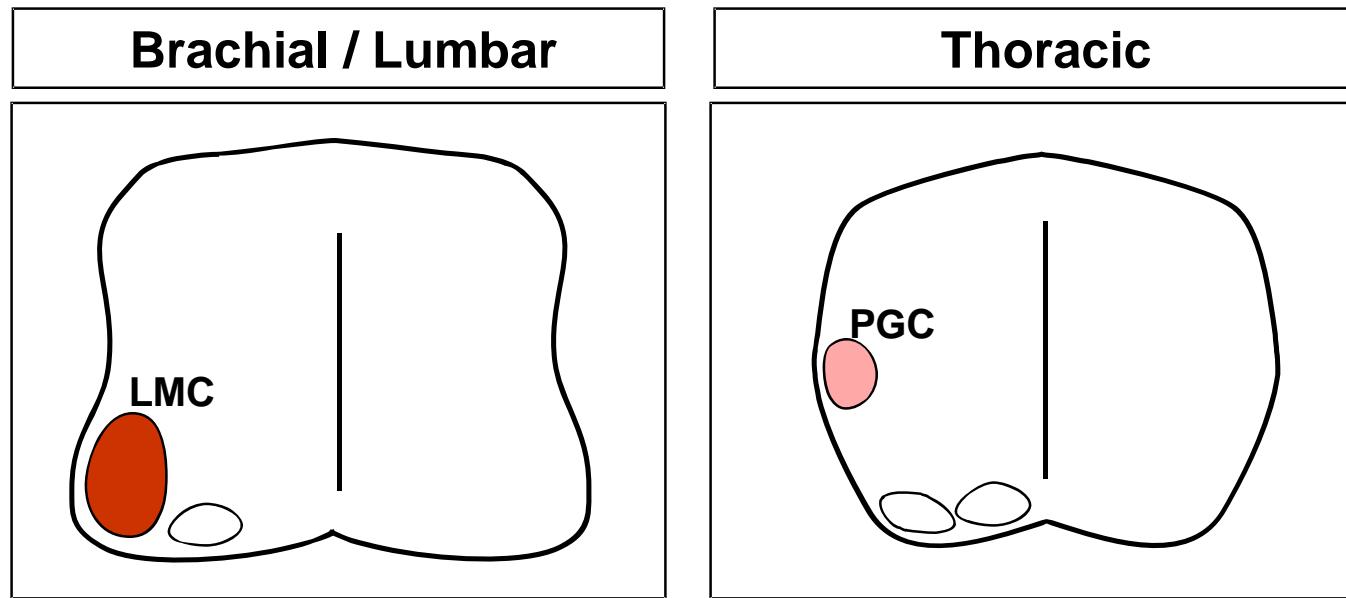
wt *Hb9::Foxp1iGFP*



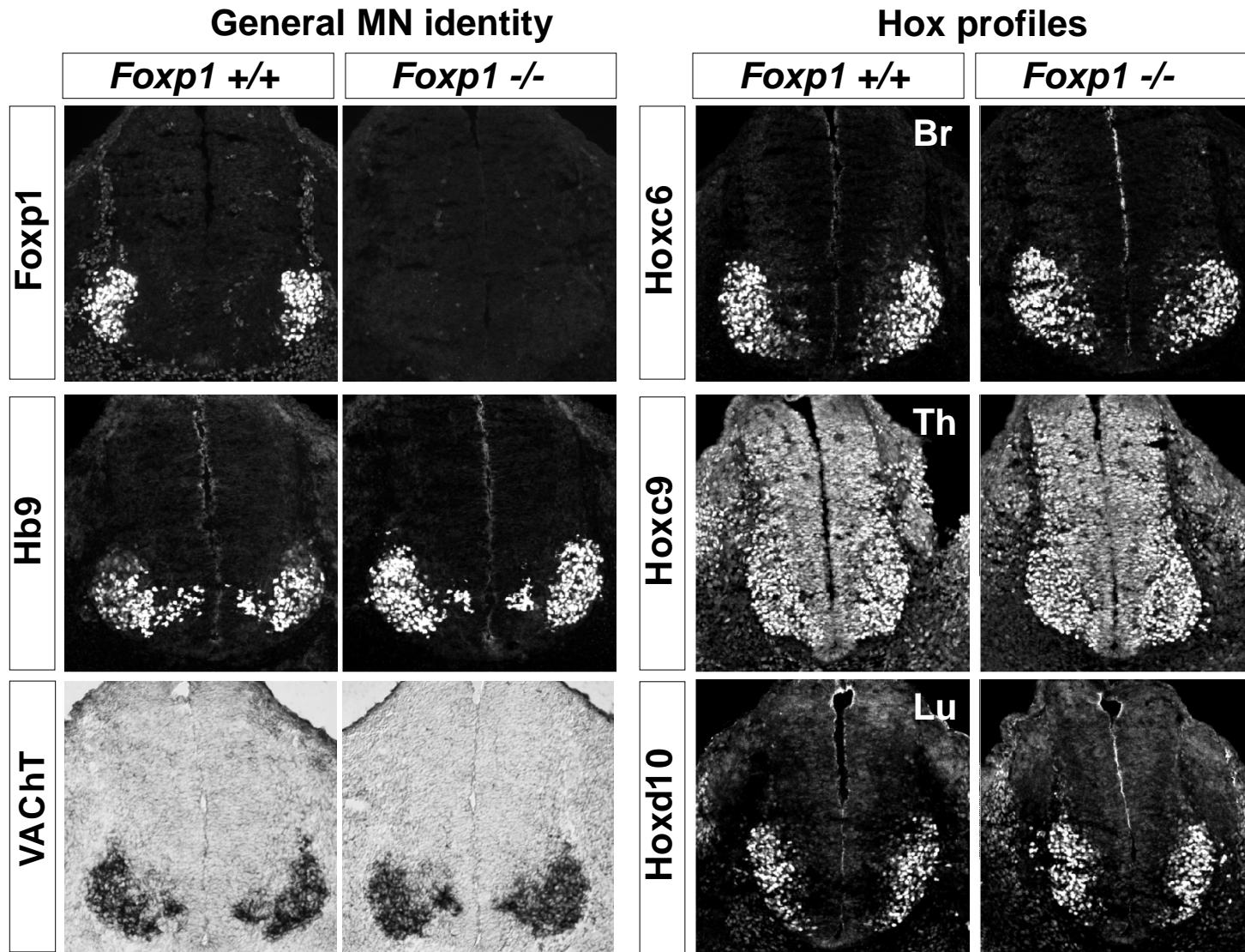
wt *Hb9::Foxp1iGFP*



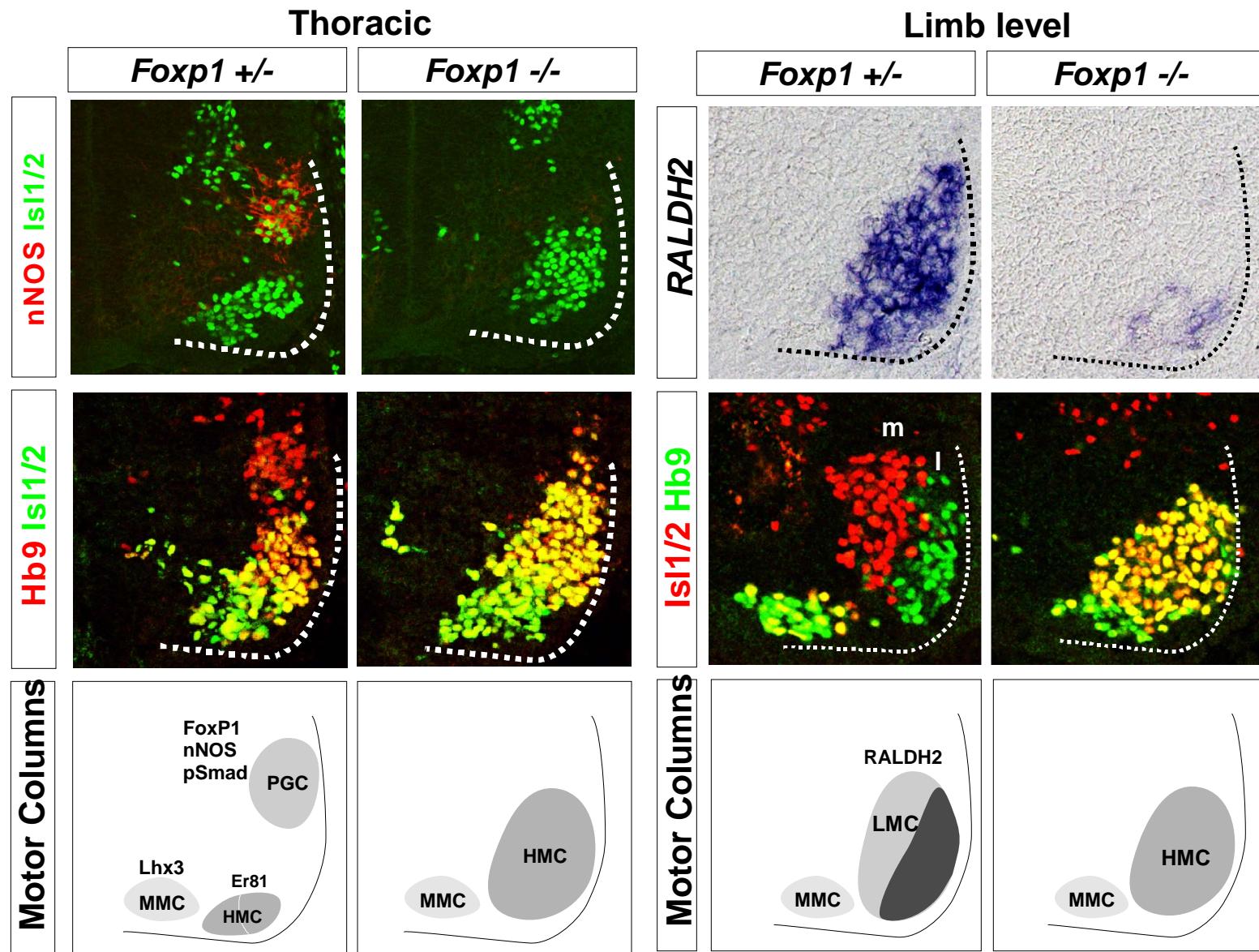
Is FoxP1 required for the generation of LMC and PGC motor neurons?



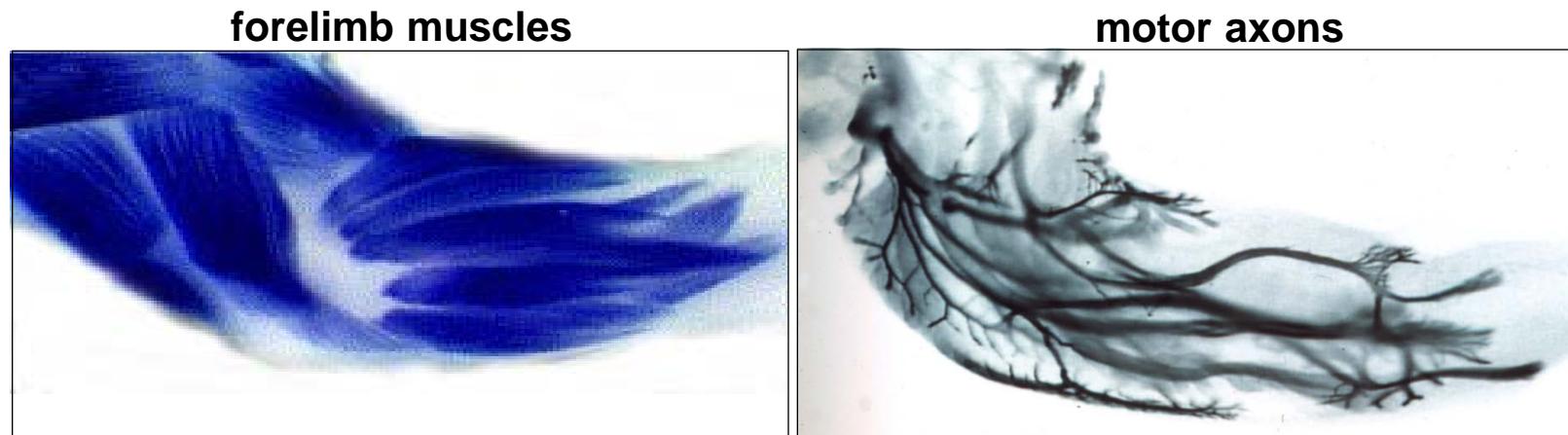
FoxP1 is dispensable for early aspects of MN identity



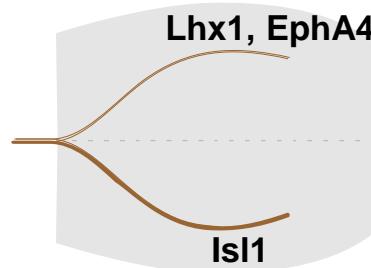
Switch in MN columnar identities in *Foxp1* mutants



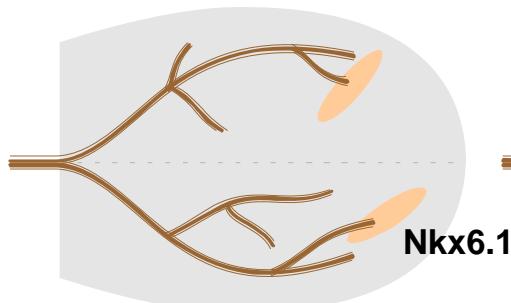
Hox-dependent programs for the innervation of limb musculature



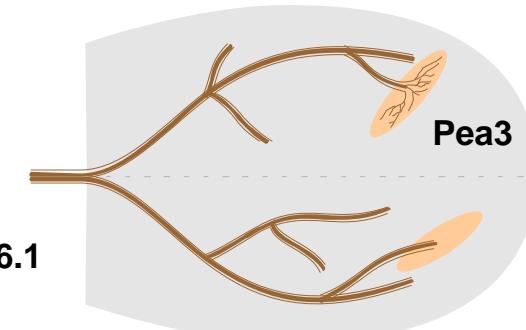
d-v projection



muscle nerve trajectory



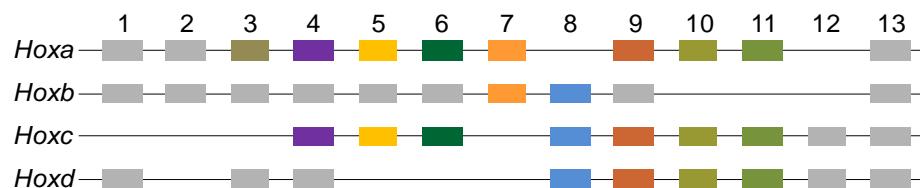
axonal arborization



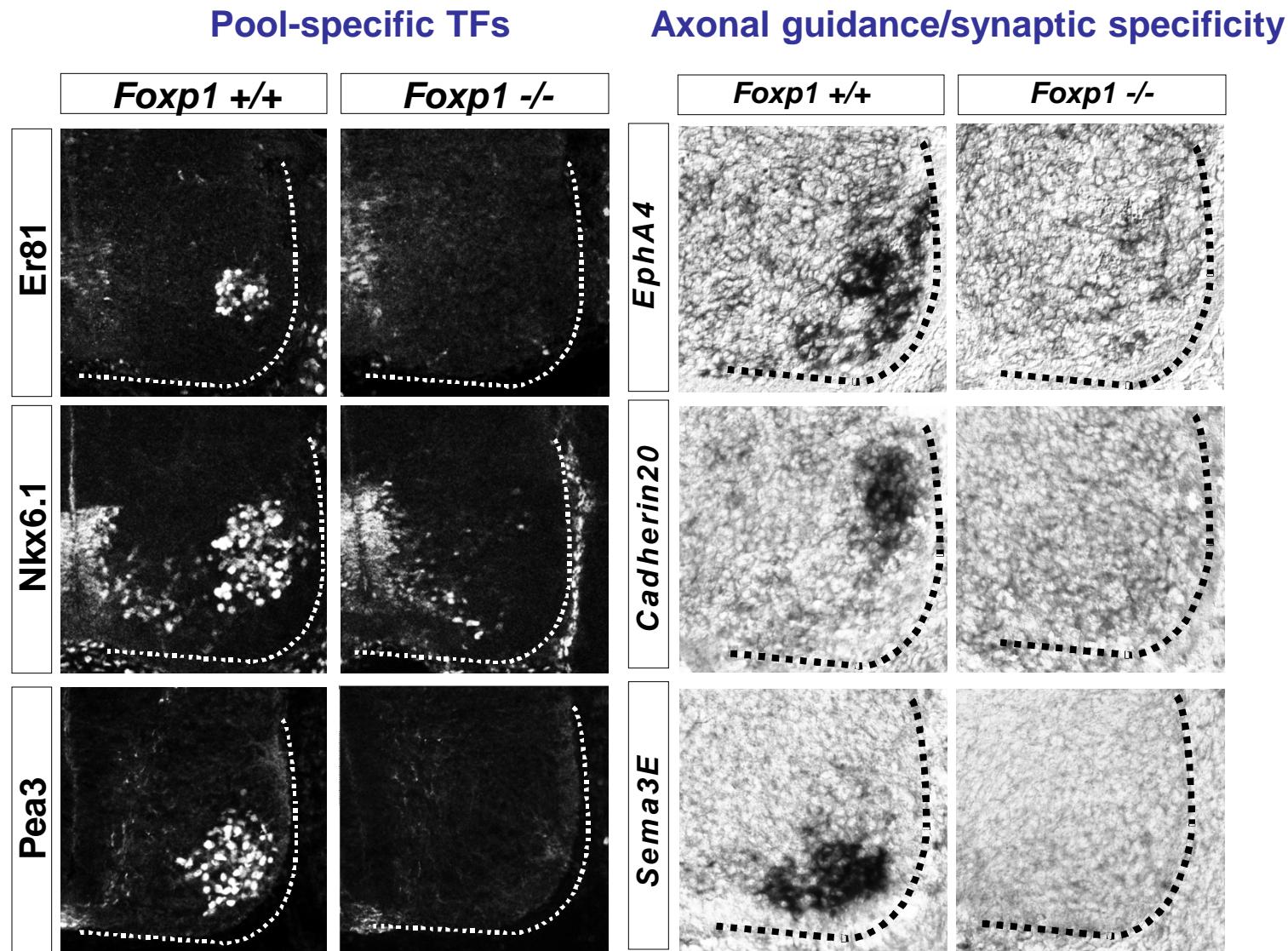
Hox6
Hox10

Hox10
Hox11
Hox12

Hox4
Hox6
Hox8



Loss of LMC-specific MN connectivity determinants in *Foxp1* mutants

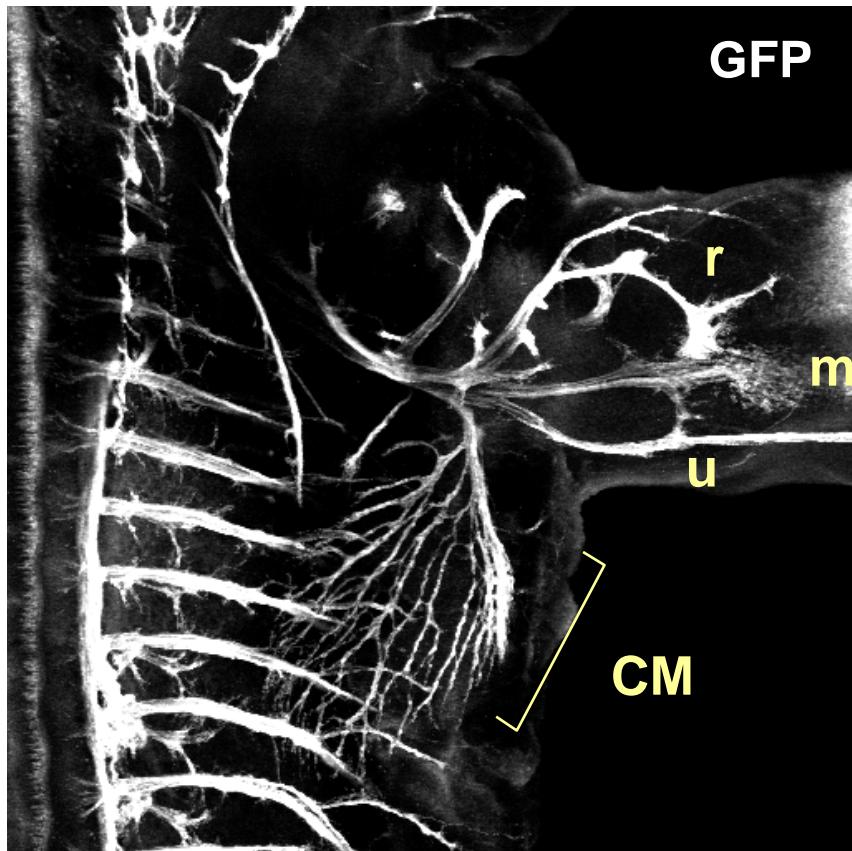


Loss of muscle-specific arborization programs in *Foxp1* mutants

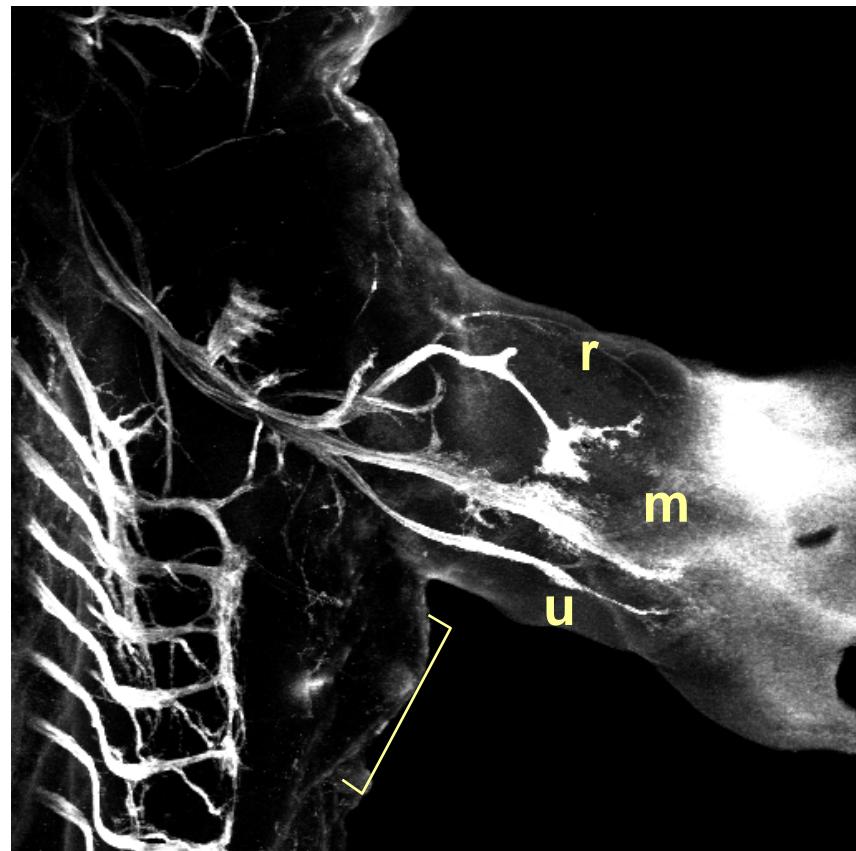
Hoxc8/c6/c4 → **Pea3** → **CM Innervation Pattern**

FoxP1

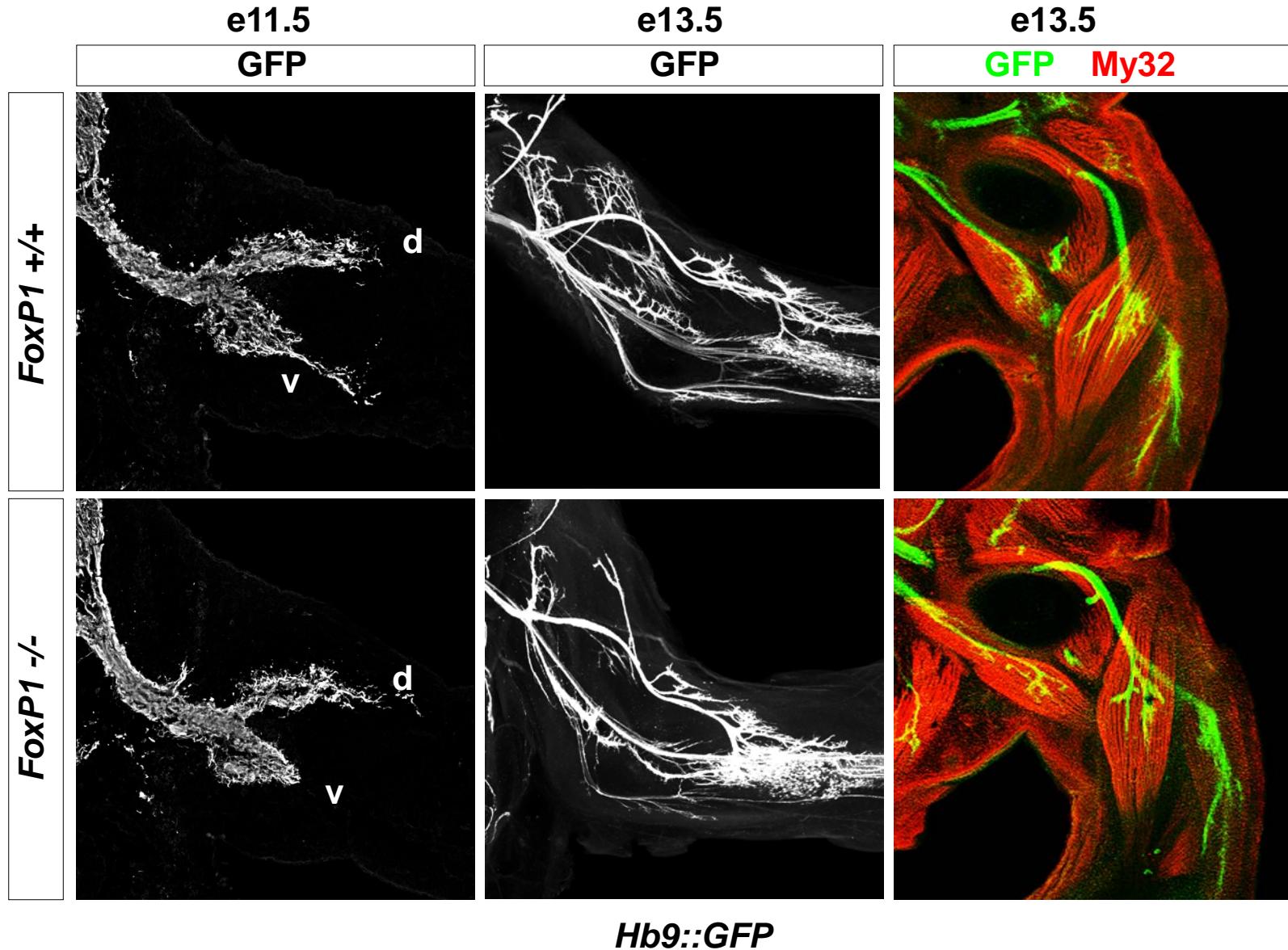
Foxp1* +/+ ; *Hb9::GFP



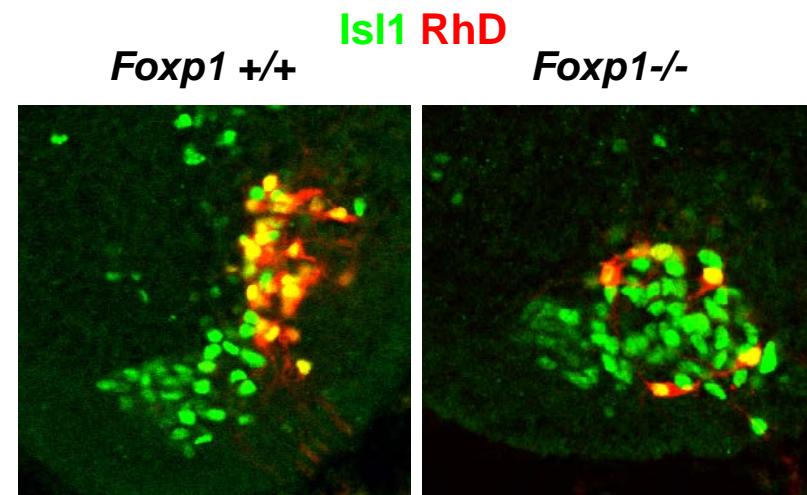
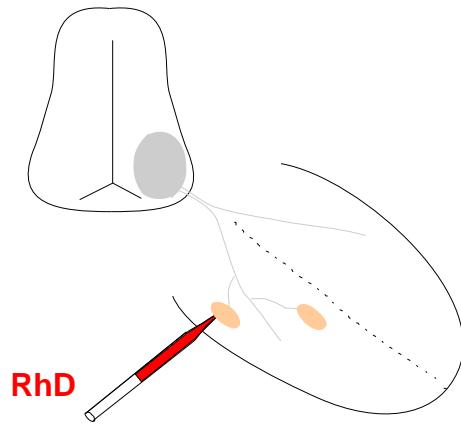
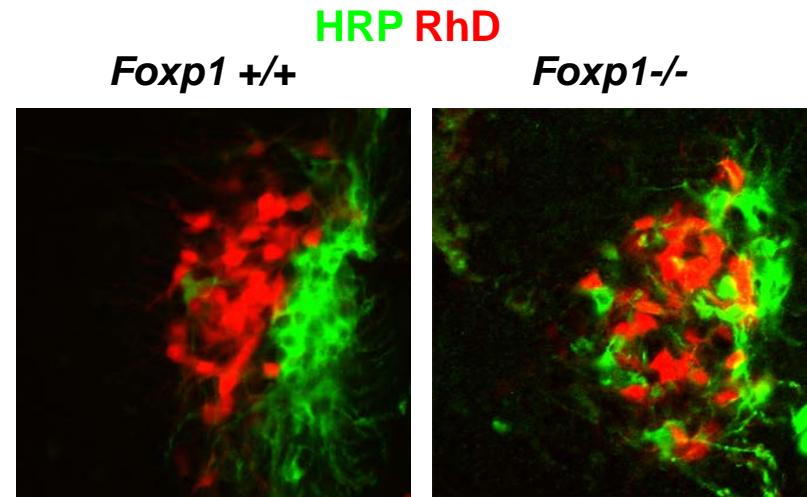
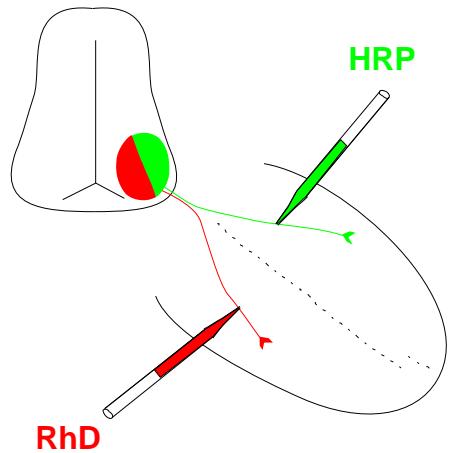
Foxp1* -/- ; *Hb9::GFP



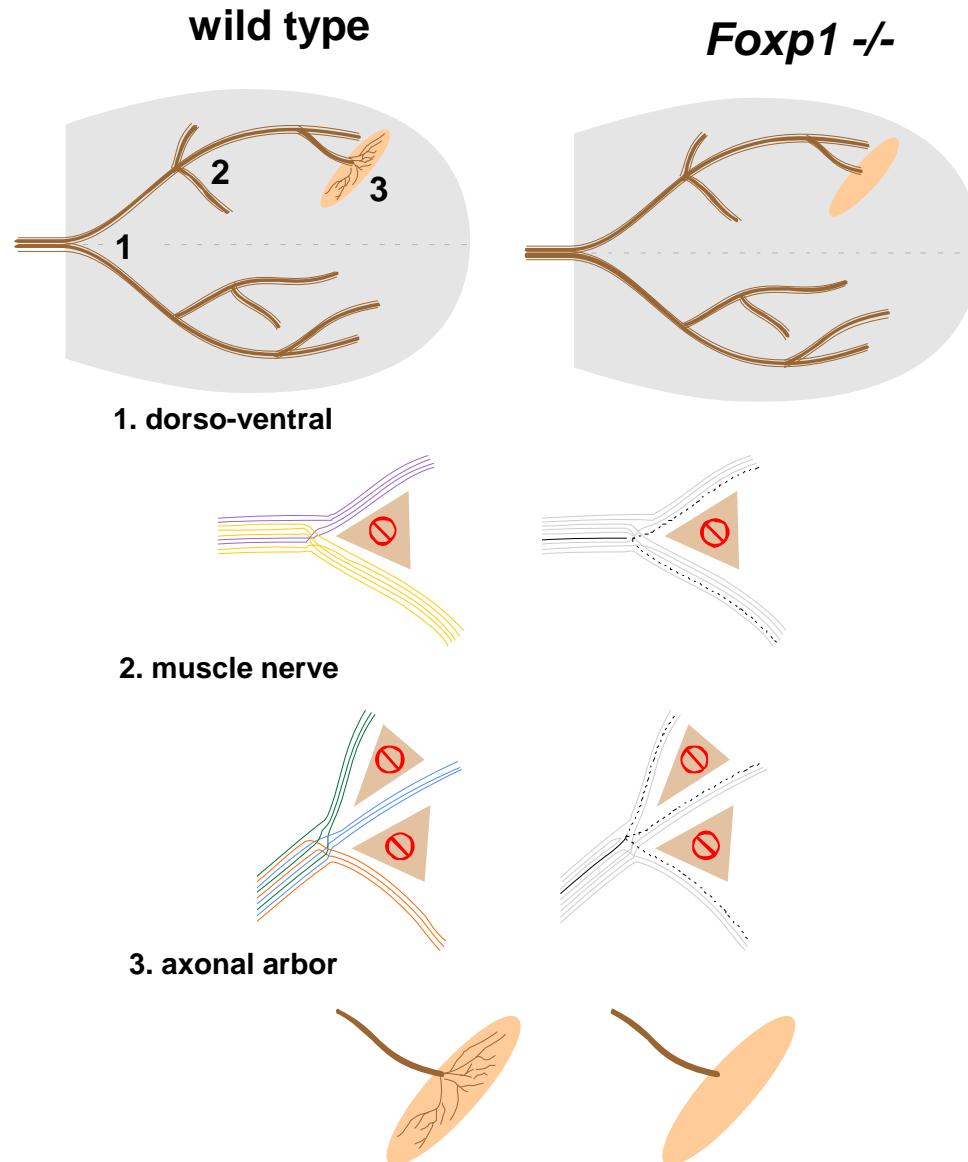
Motor axon projection patterns in *Foxp1* mutants



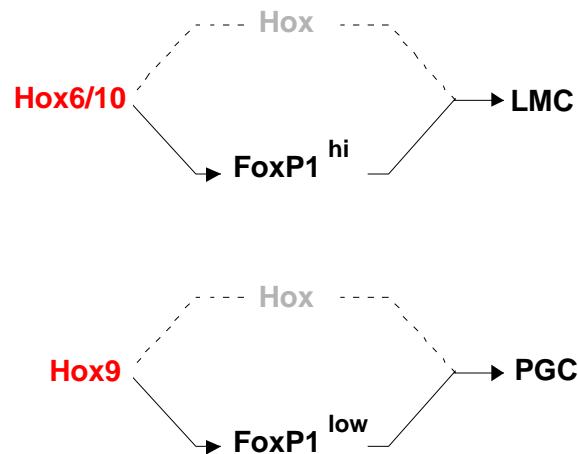
Evidence for randomization of target selection by MNs in *Foxp1* mutants



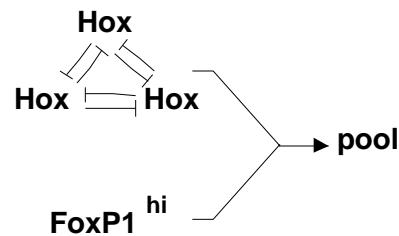
FoxP1 as an accessory factor in the Hox-dependent programs of MN identity and connection



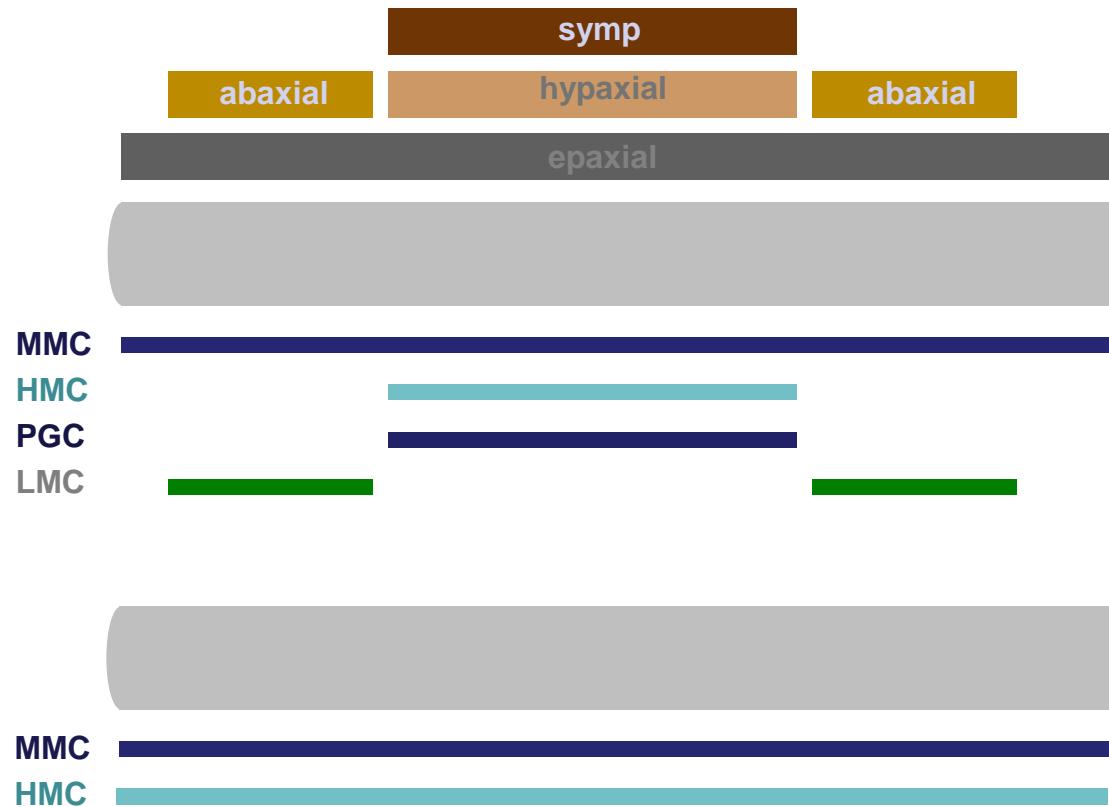
columnar specification



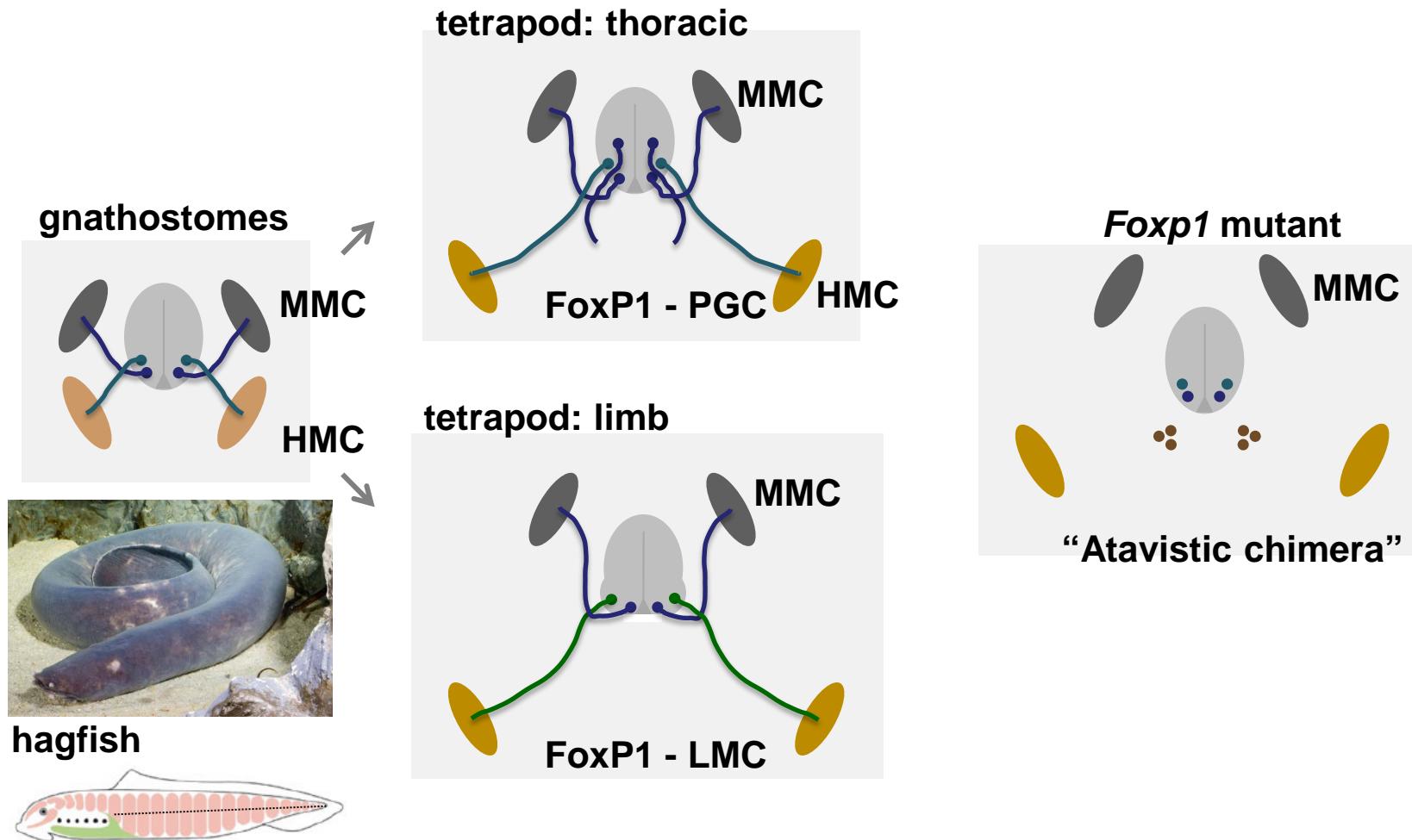
pool specification



Motor neurons revert to an HMC identity in the absence of *Foxp1*

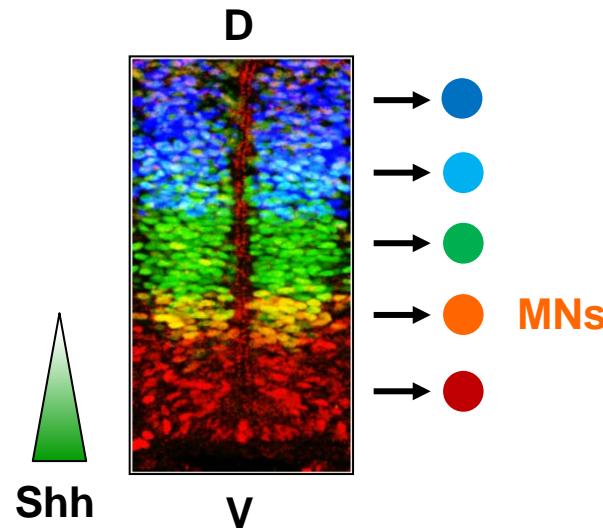


Reversion of MNs to an ancestral state in *Foxp1* mutants?

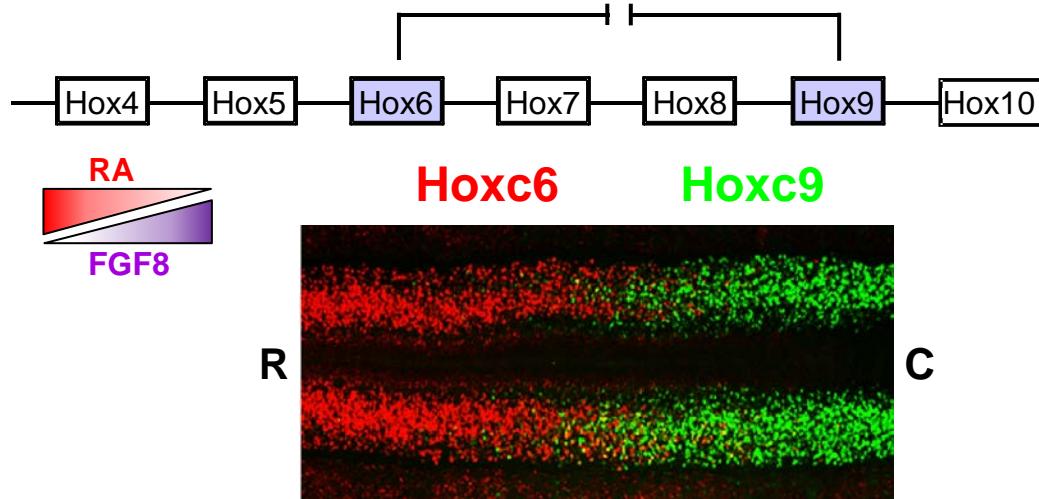


Generation of neuronal identity and diversity in the spinal cord

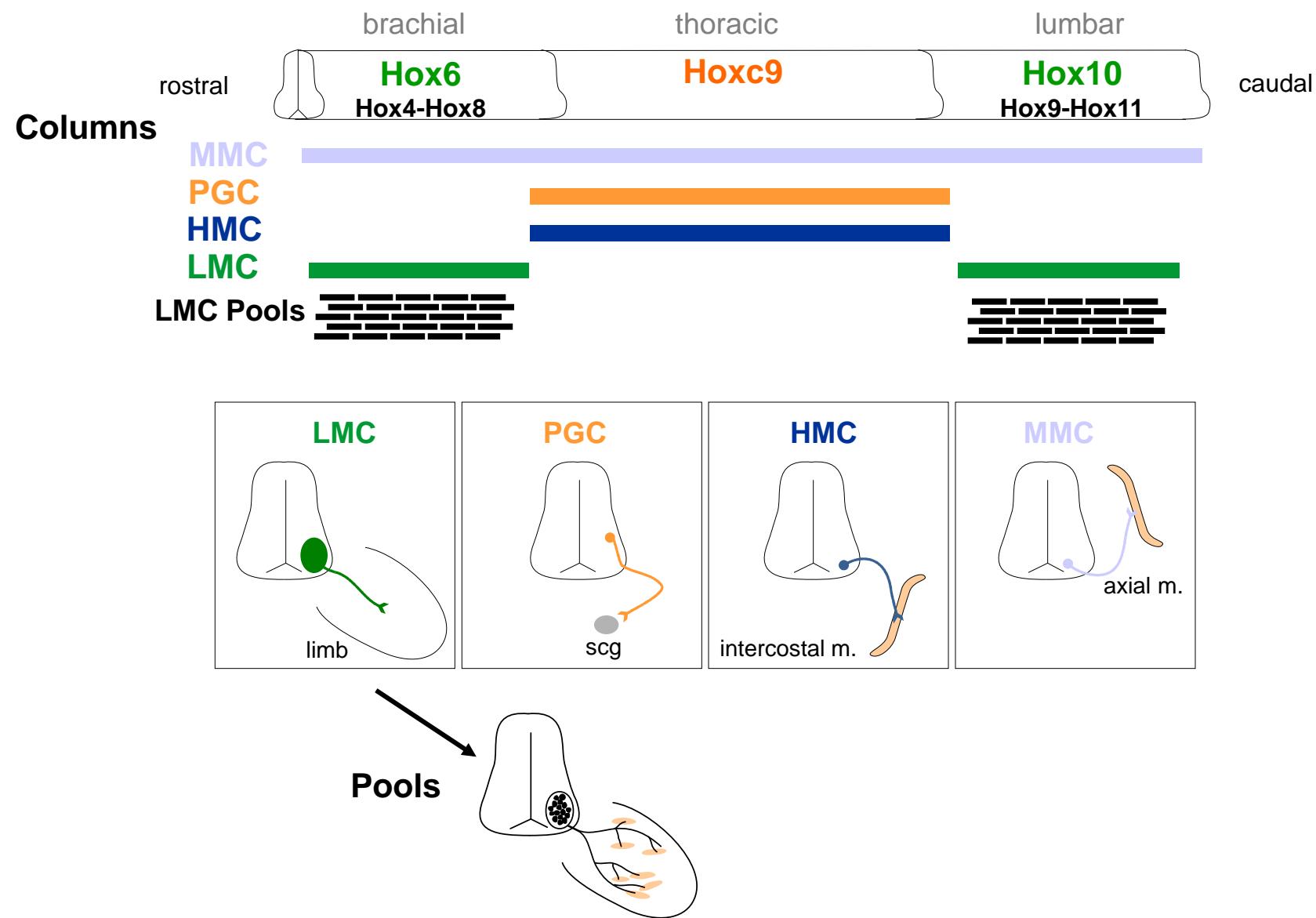
Dorsoventral axis



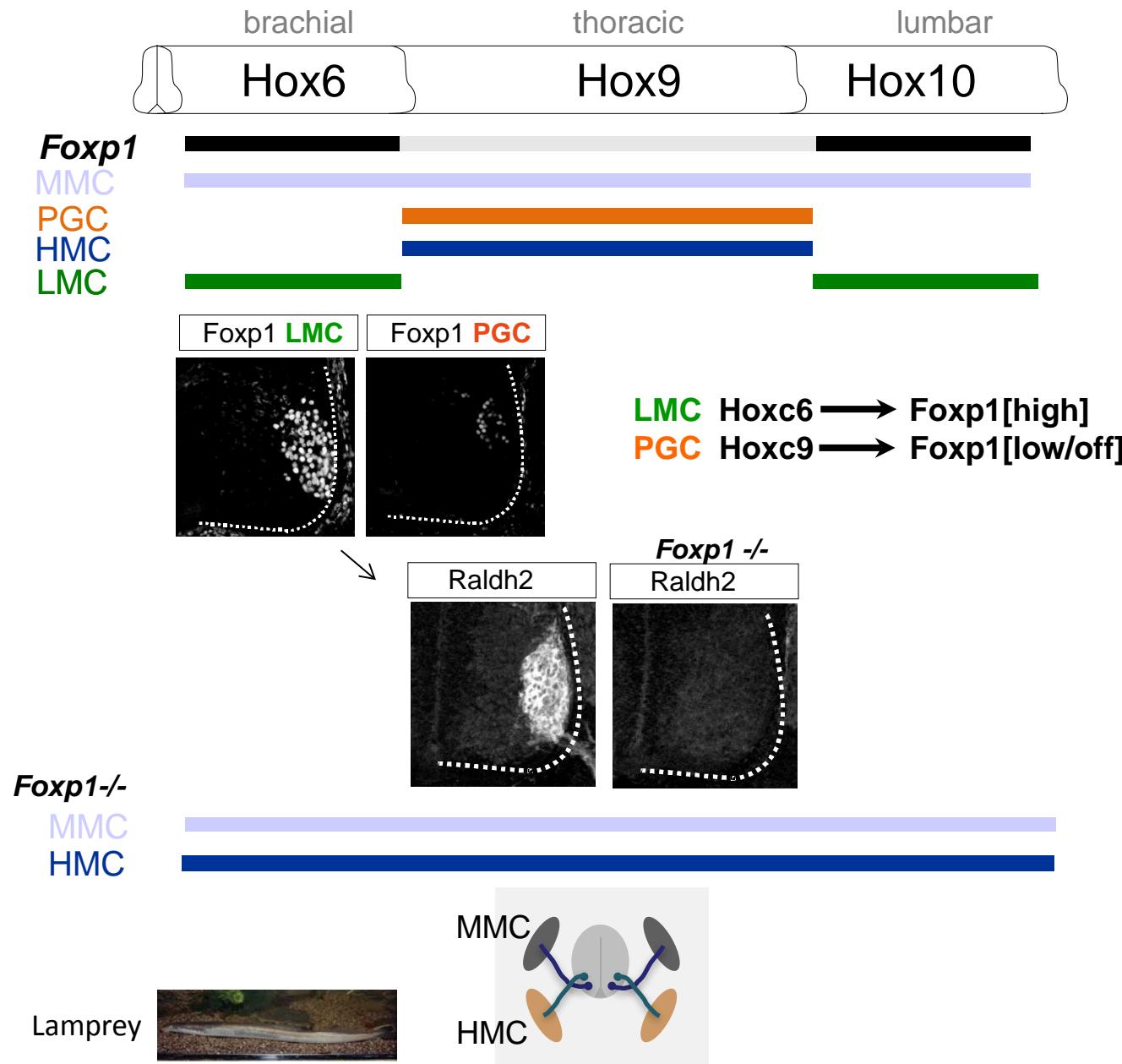
Rostrocaudal axis



Hox genes and MN organization along the rostrocaudal axis

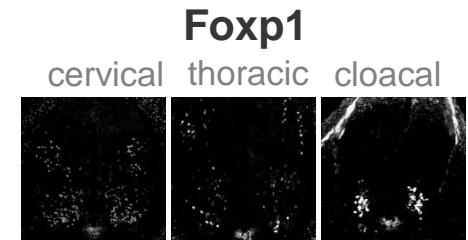
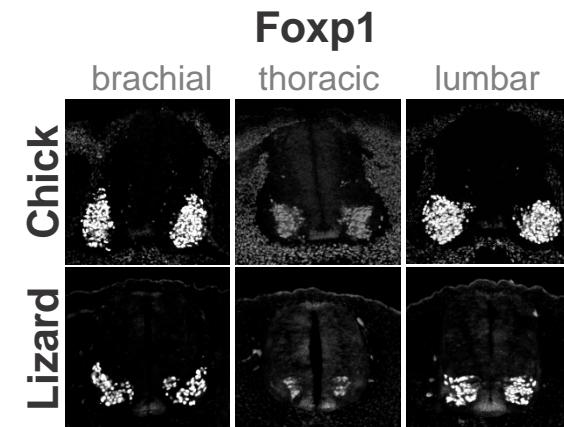
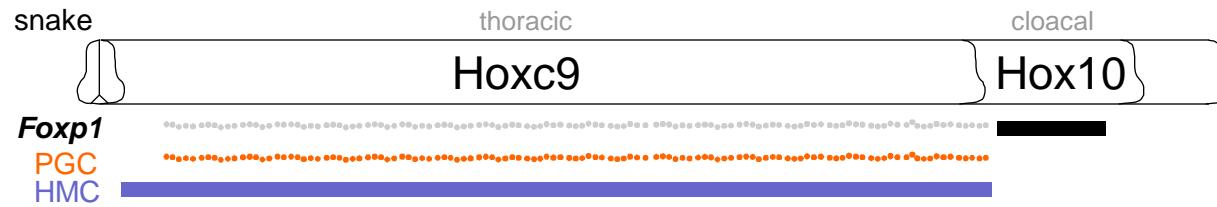
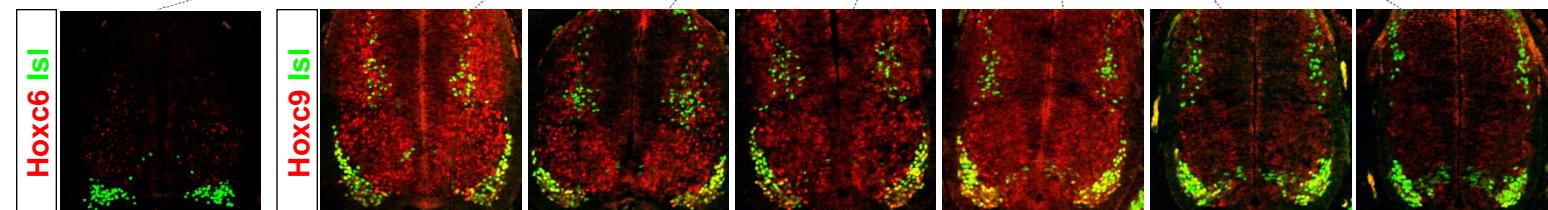
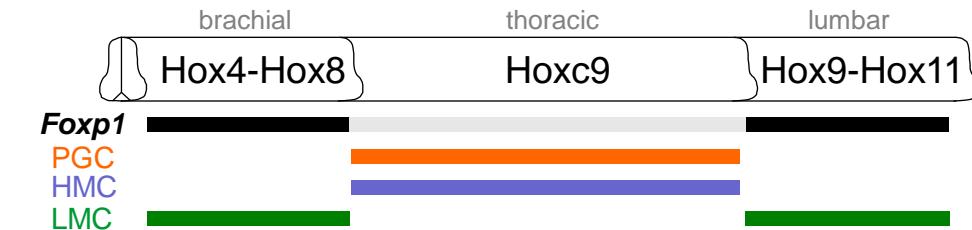


Foxp1 mediates Hox-dependent steps in MN specification

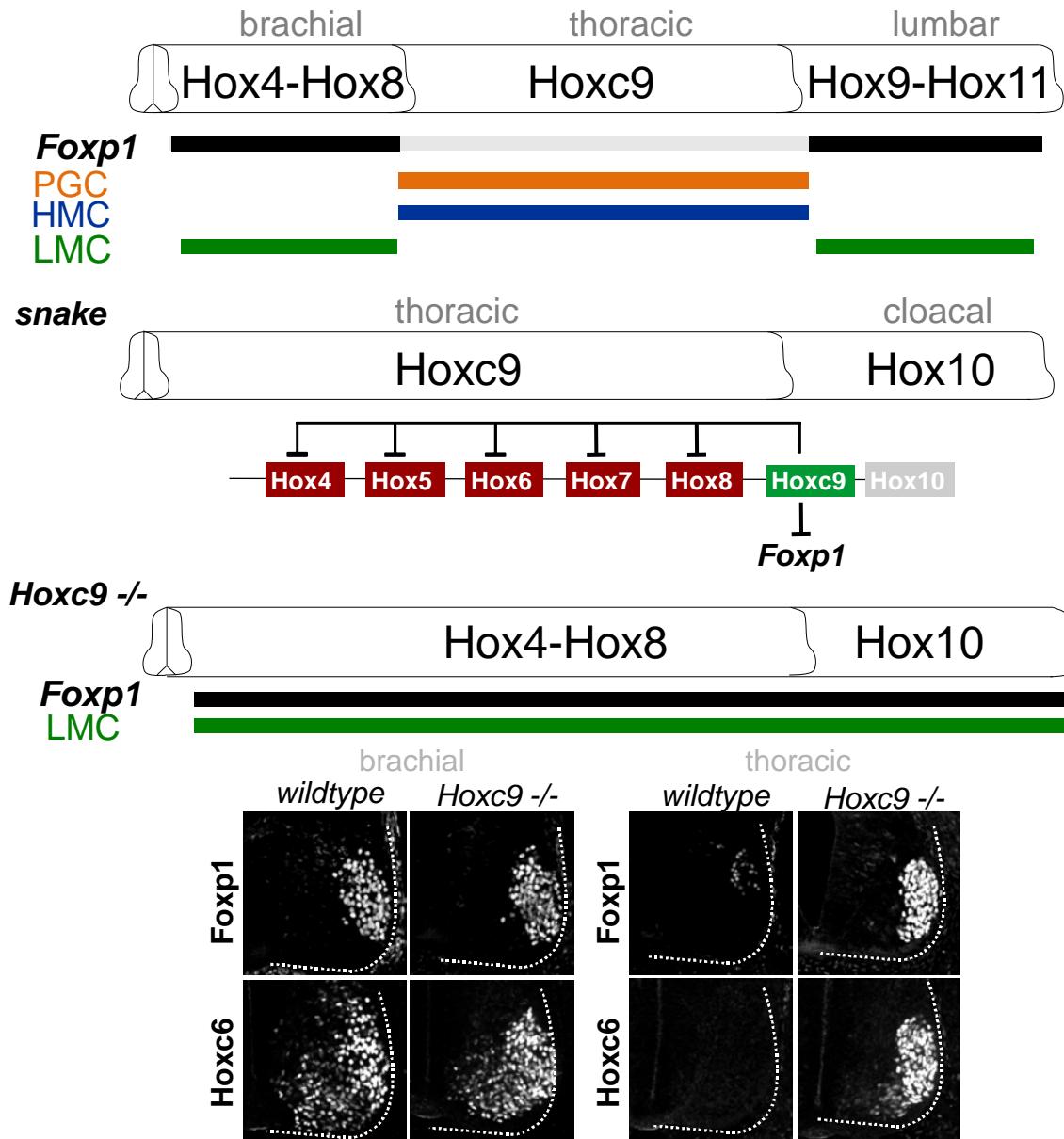


Columnar organization of limbed and limbless vertebrates

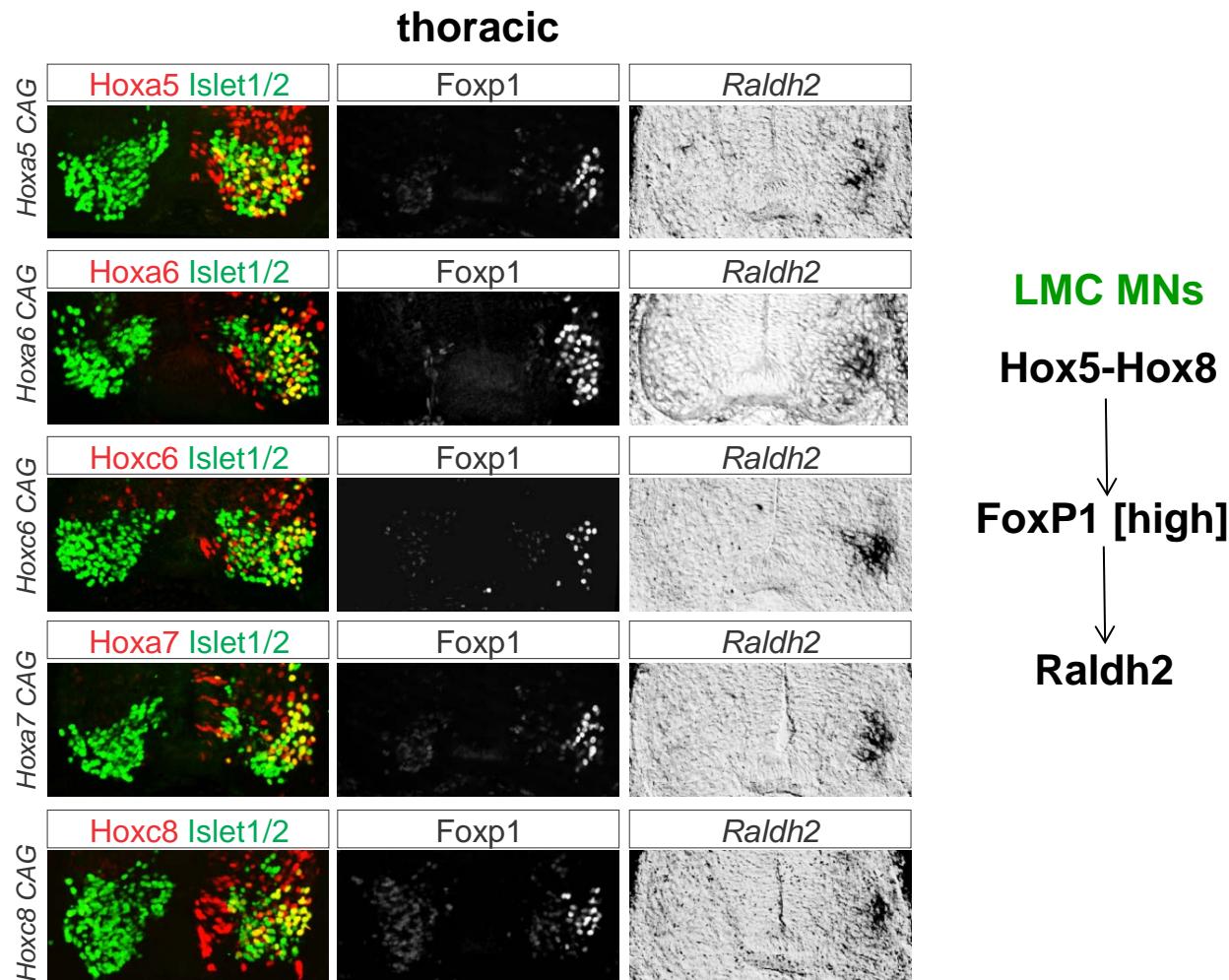
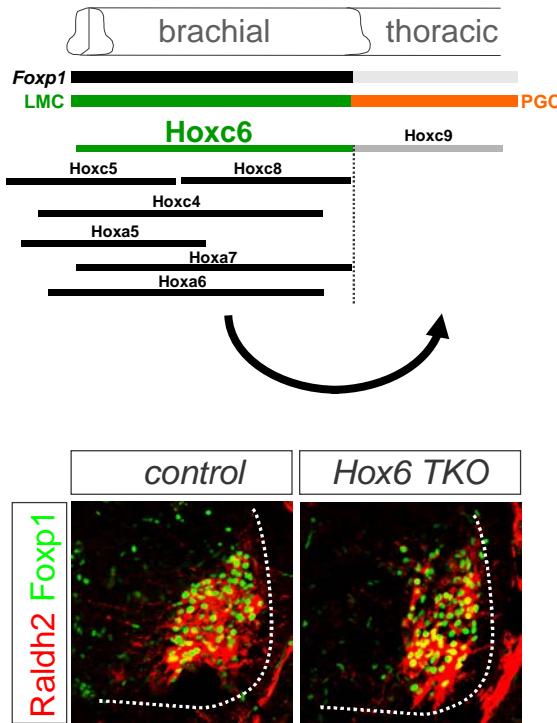
tetrapods : mammals, birds, reptiles, amphibians
mouse, chick, lizard, frog



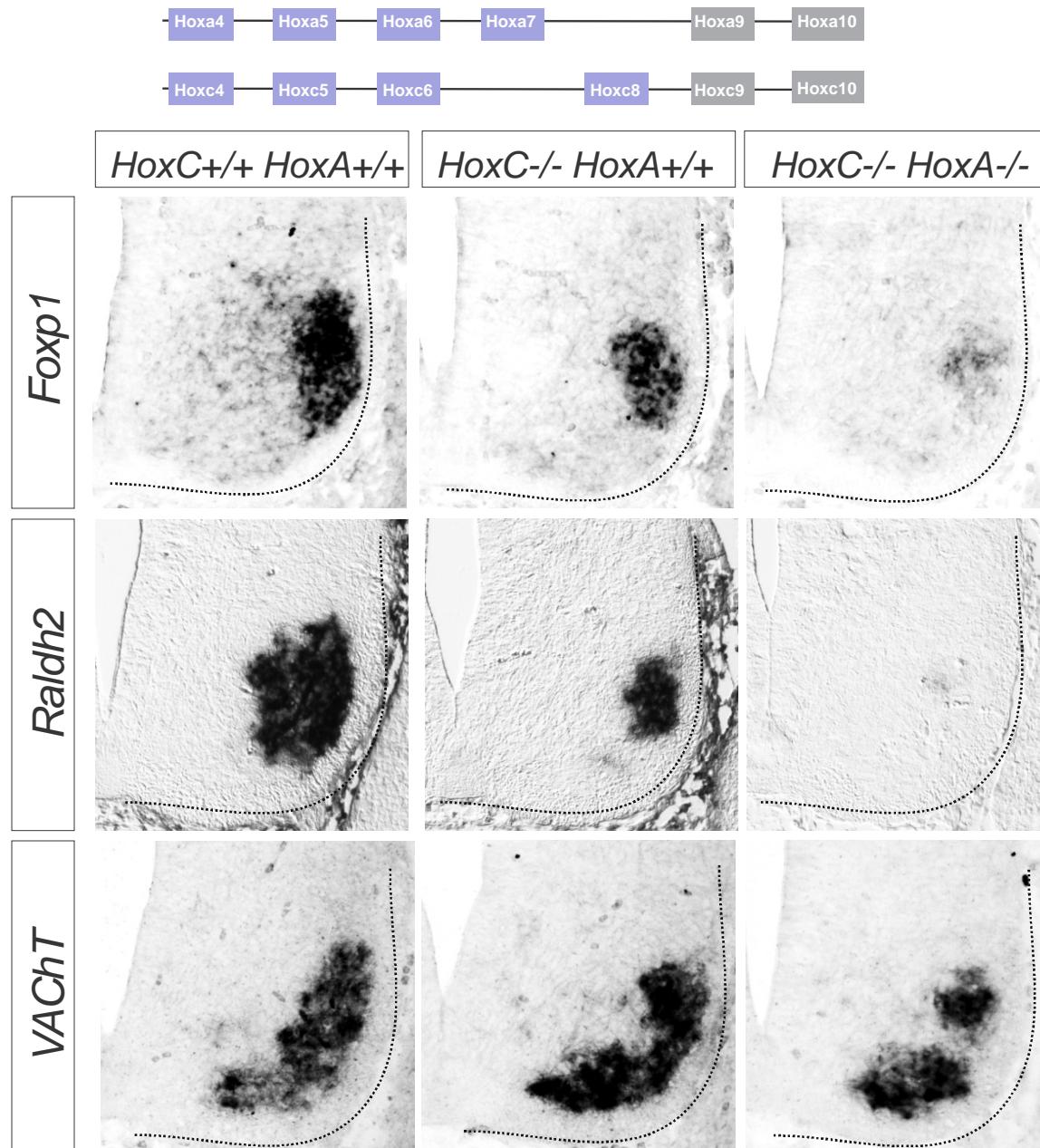
Hoxc9 is a central determinant of MN organization



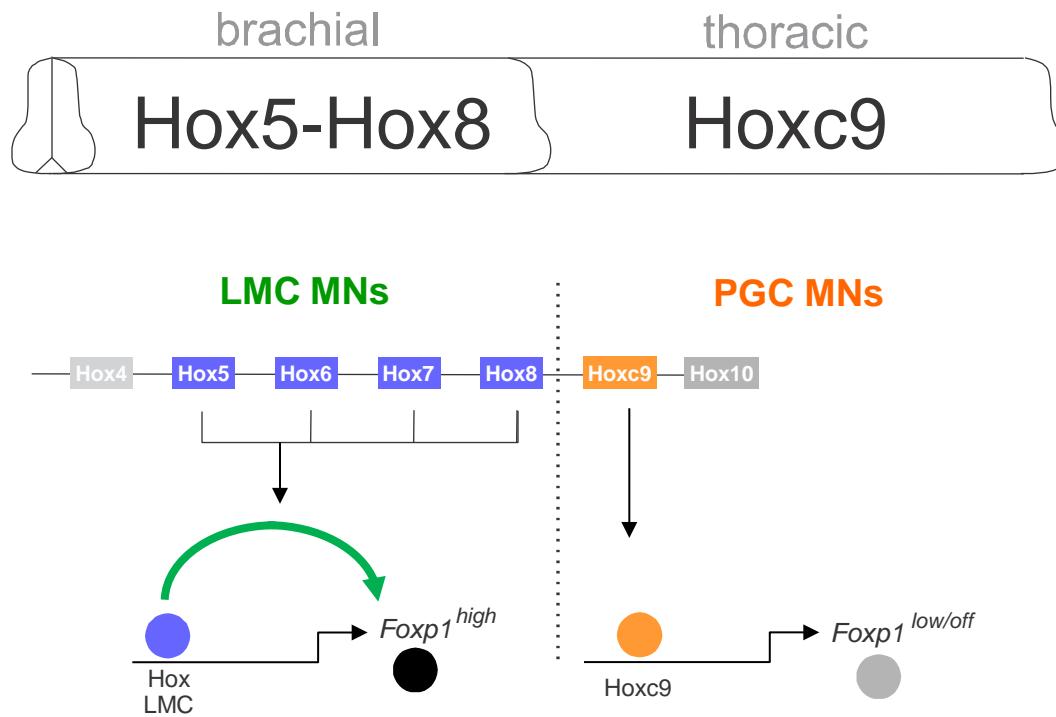
Multiple *Hox* paralogs can program thoracic MNs to an LMC fate



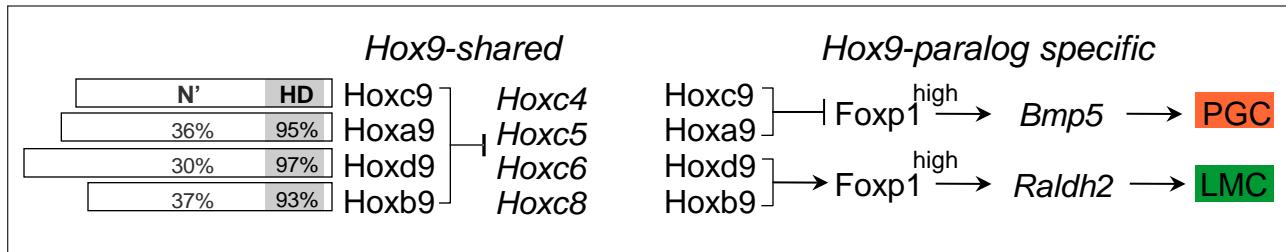
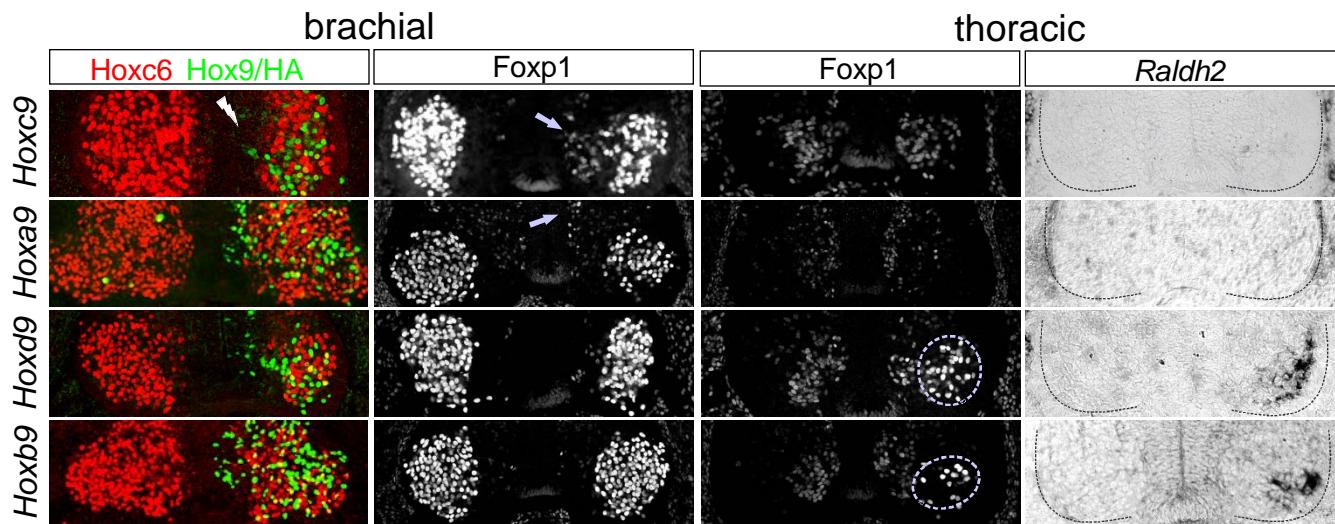
Combined *HoxA/HoxC* cluster deletion leads to LMC loss



Model for MN columnar specification through *Foxp1* regulation

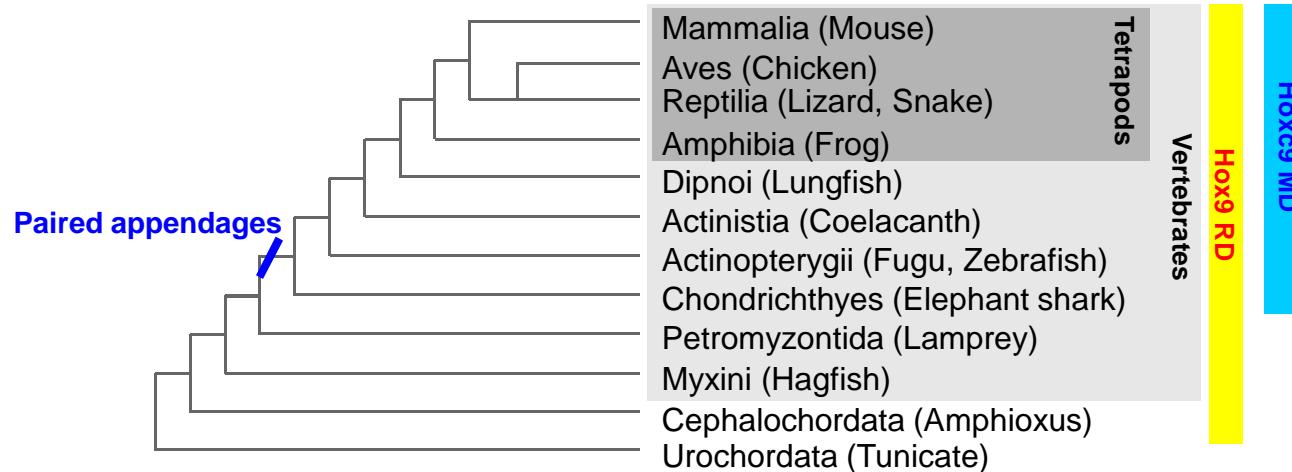


Divergence amongst Hox9 paralogs

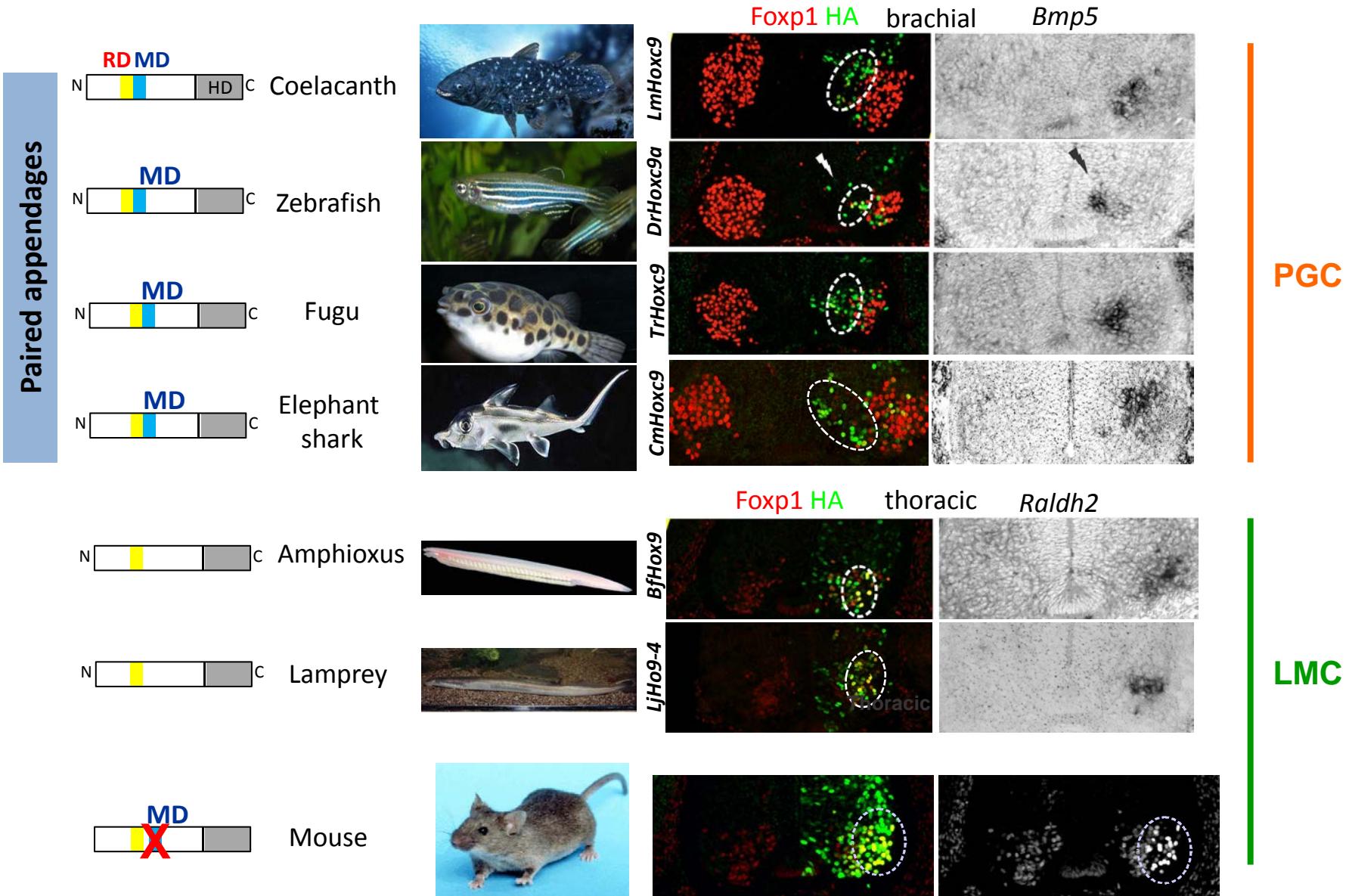


Evolution of Hox9 regulatory motifs in chordates

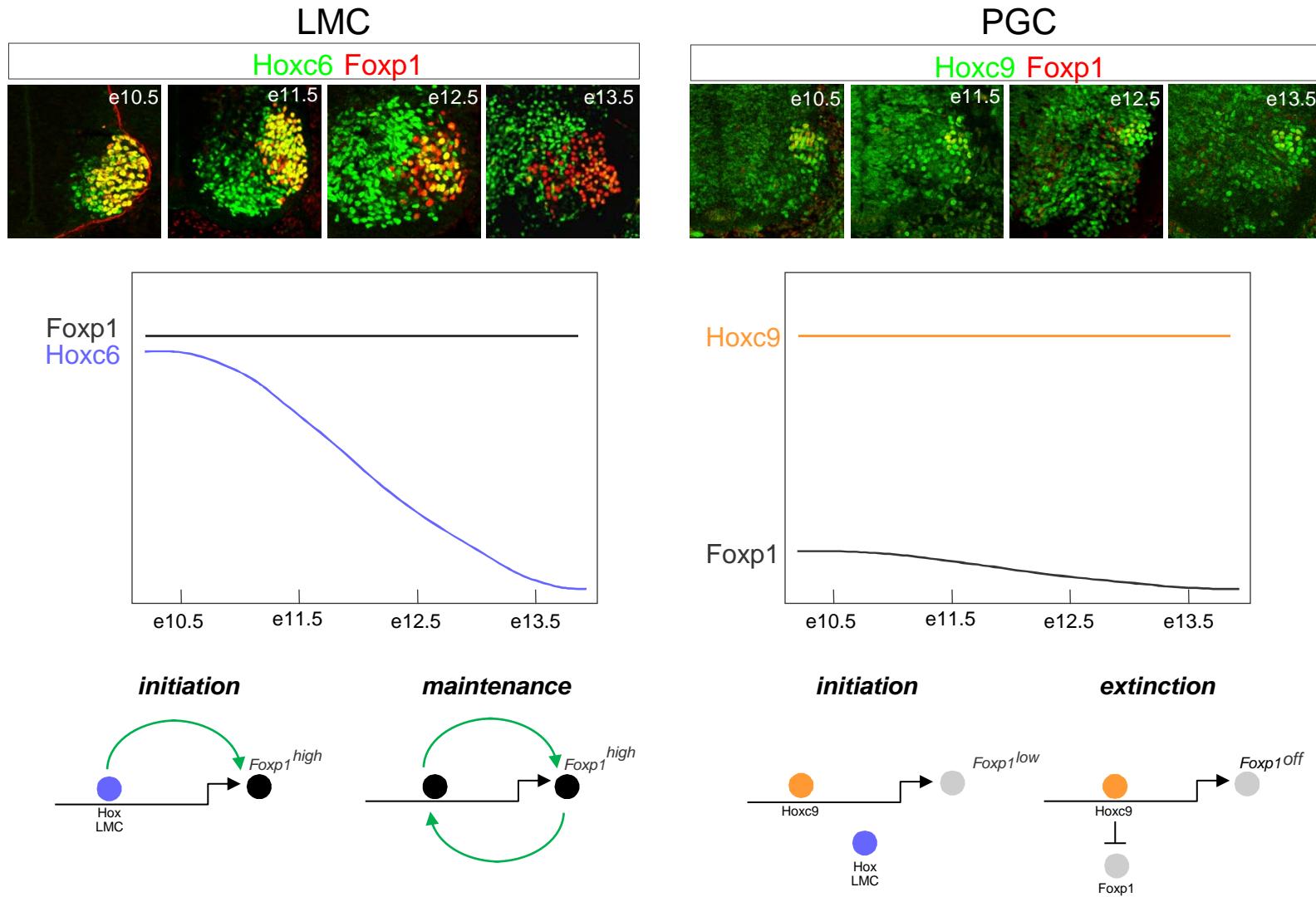
			Hox9 RD	Hoxc9 MD
PGC	mouse	<i>mmHoxa9</i>	HPYVHPQAPVAAAAPDG-- RYMRSWLEPTPGALSFAGLPSS-	RPYGIKPEPLS
	mouse	<i>mmHoxc9</i>	SVVYHPYGPQPHLGADT-- RYMRTWLEPLSGAVSFPS-	FPAGGRHYALKPDAYP
	chick	<i>ggHoxc9</i>	VGYHHPYGPQAPVGAEP-- RYMRTWLEPLAGAVSFPAFAPGAA	RPYGLKPDAF-
	zebrafish	<i>drHoxc9a</i>	SVVYHPYTHQPHLGTDS-- RYVRSWLEPIPGTVSFPG-	YAGNSRHYGLKPDTFQ
"finned"	coelacanth	<i>ImHoxc9</i>	SVVYHPYTHQPHI GTDS-- RYMRSWLEPISGAVSFPG-	FPTNSRHYGLKPDAFP
	fugu	<i>frHoxc9</i>	SVGYHPYSHQPHLATDS-- RYMRSWLEPISGAVPFHG-	YPGNGRHYGLKPDAFQ
	eleph. shark	<i>cmHoxc9</i>	TGVYHPYSHQPHLGTDT-- RYMRSWLEPISGPVPFHGFPSTGRHYGVVKPESF-	
	mouse	<i>mmHoxb9</i>	PSVYHPYLQ-PQGAPAAESRYLRTWLEPAPRAEAAPGQGQAAVKAEPLLGAPG-	
LMC	mouse	<i>mmHoxd9</i>	SGLYHPYVSPPPLAAAEPGRYVRSWMEPLPGFPGGAGGGGSGGGGGGPGPV-	
	lamprey	<i>LjHox9-4</i>	FIPHAAYVGQPHLADEGG-RFVRSWLEPVAAFSGFCGGGGG----- GVRPSYD	
	lamprey	<i>LjHox9-1</i>	FIPHAAYVGQSHLADEGS-RYVRSWLEPVFG-FSGFGGGGGVGGGGGARPYD	
	amphioxus	<i>biHox9</i>	VSCLYPYLPPRHLPNDG-TDGI NPWTEPVPNNHQAAG-- SSYCNGTGLHATAMQ	



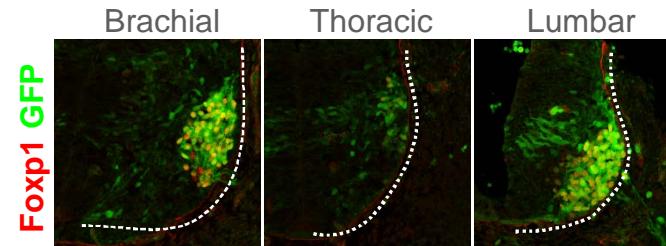
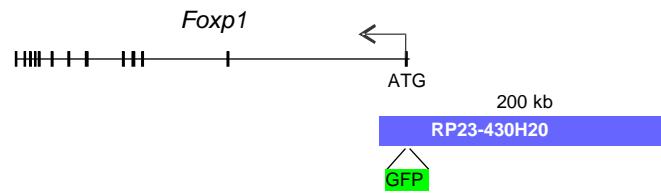
Activity of chordate Hox9 proteins in chick embryos



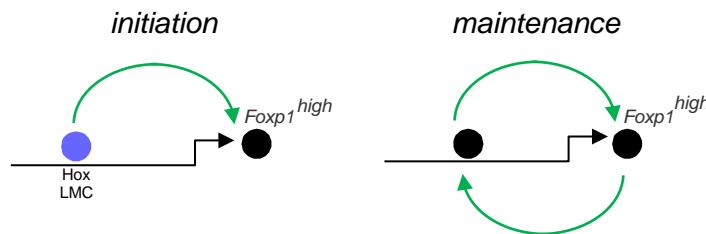
Spatial and temporal profiles of Hox proteins and Foxp1



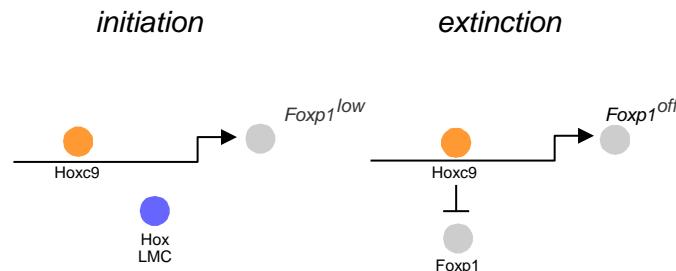
Regulatory interactions controlling *Foxp1* expression in mice



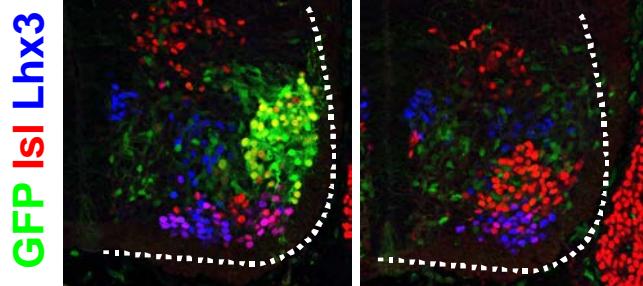
limb levels (LMC)



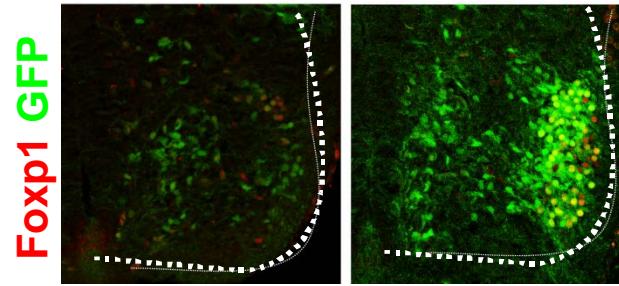
thoracic levels (PGC)



Foxp1::GFP brachial
Foxp1^{+/−} *Foxp1*^{−/−}

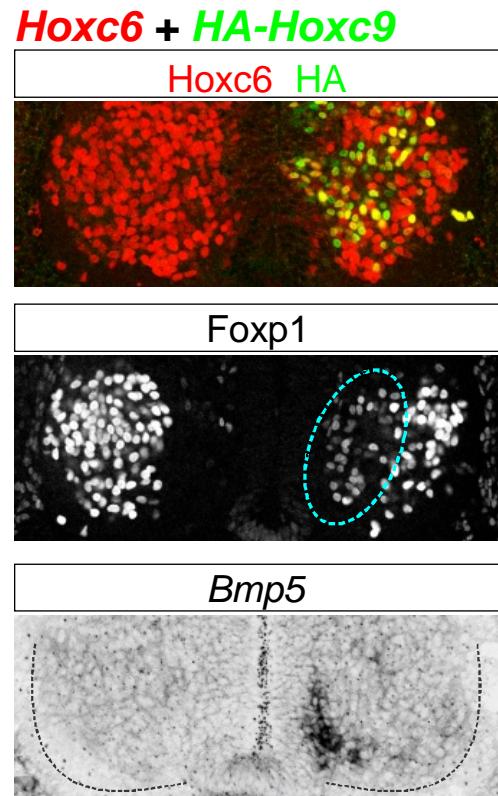
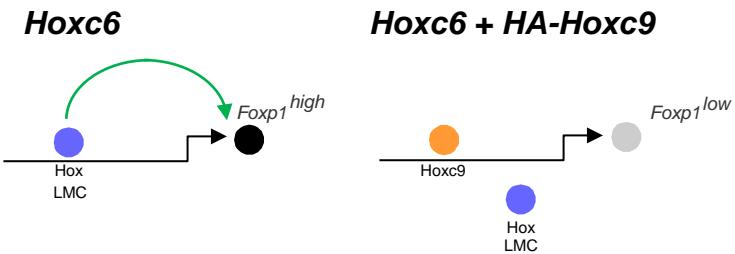
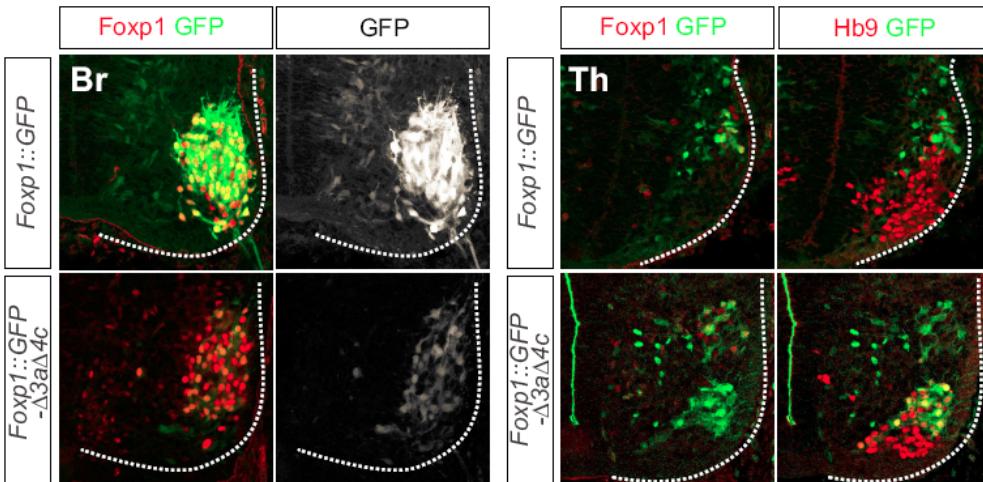
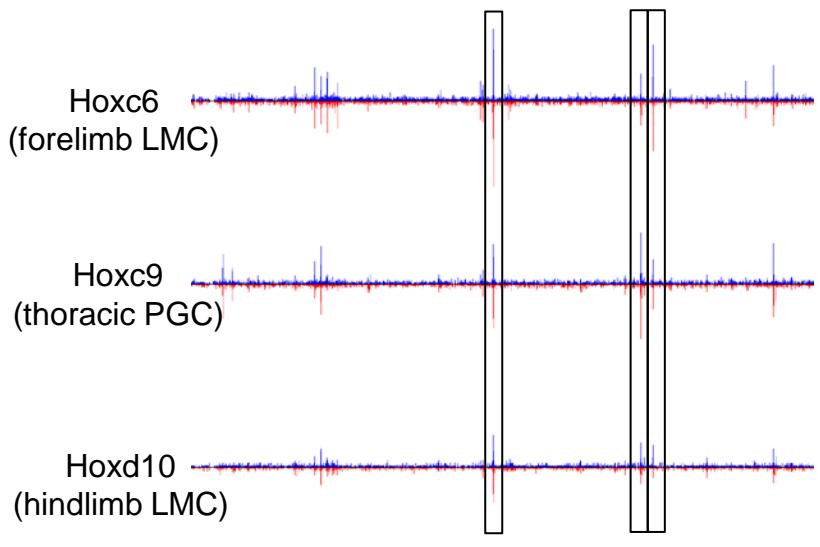


Foxp1::GFP thoracic
Hoxc9 ^{+/−} *Hoxc9* ^{−/−}

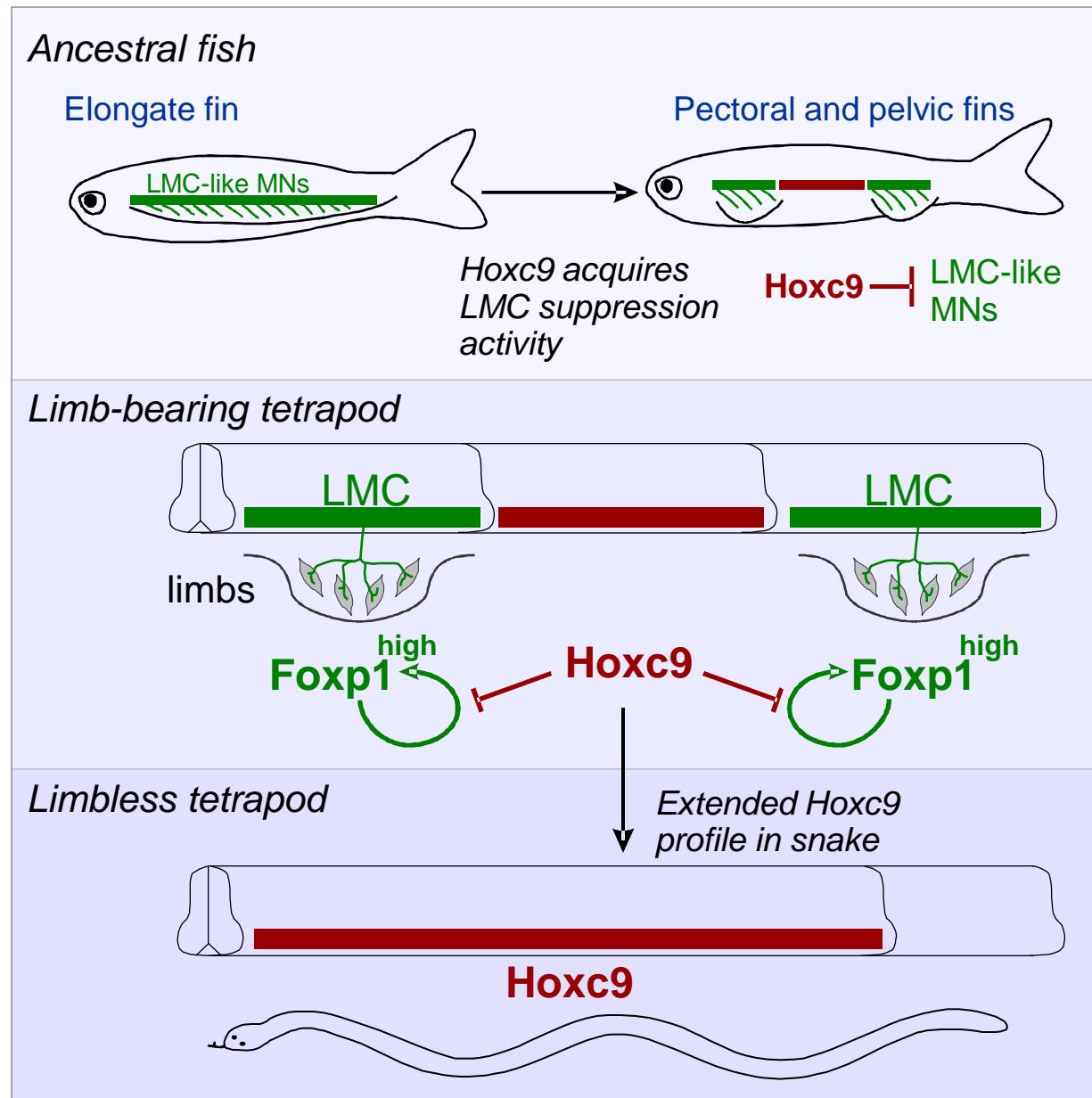


Competitive Hox interactions at the *Foxp1* locus

ES-MN ChIP-seq (Mazzoni & Wichterle)



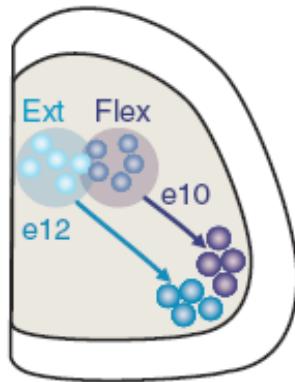
Model for the evolution of vertebrate limb innervation programs



Organization of MNs in zebrafish

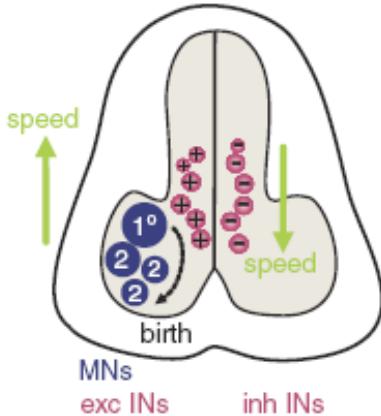
mouse

(a) Extension-Flexion



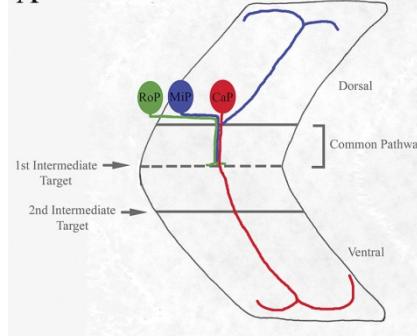
zebrafish

(b) Swimming speed

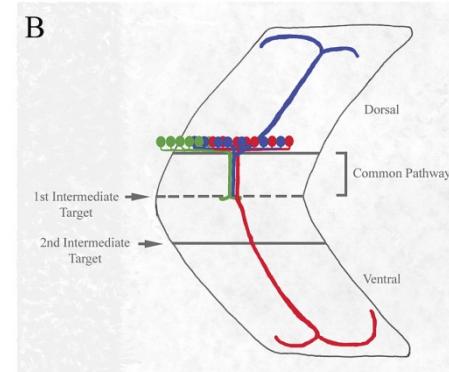


Primary axial MNs

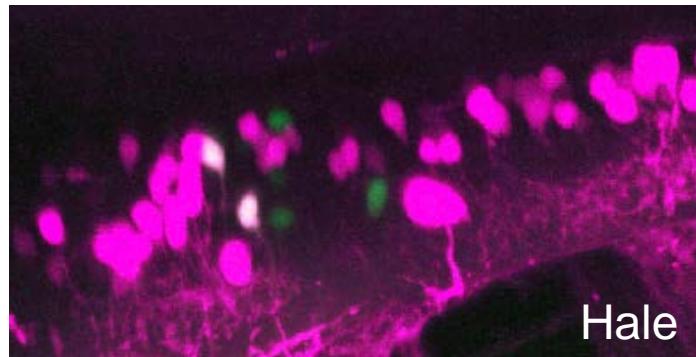
A



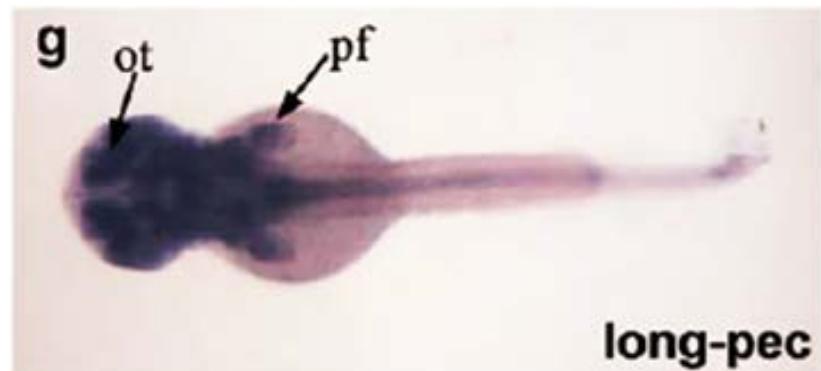
B



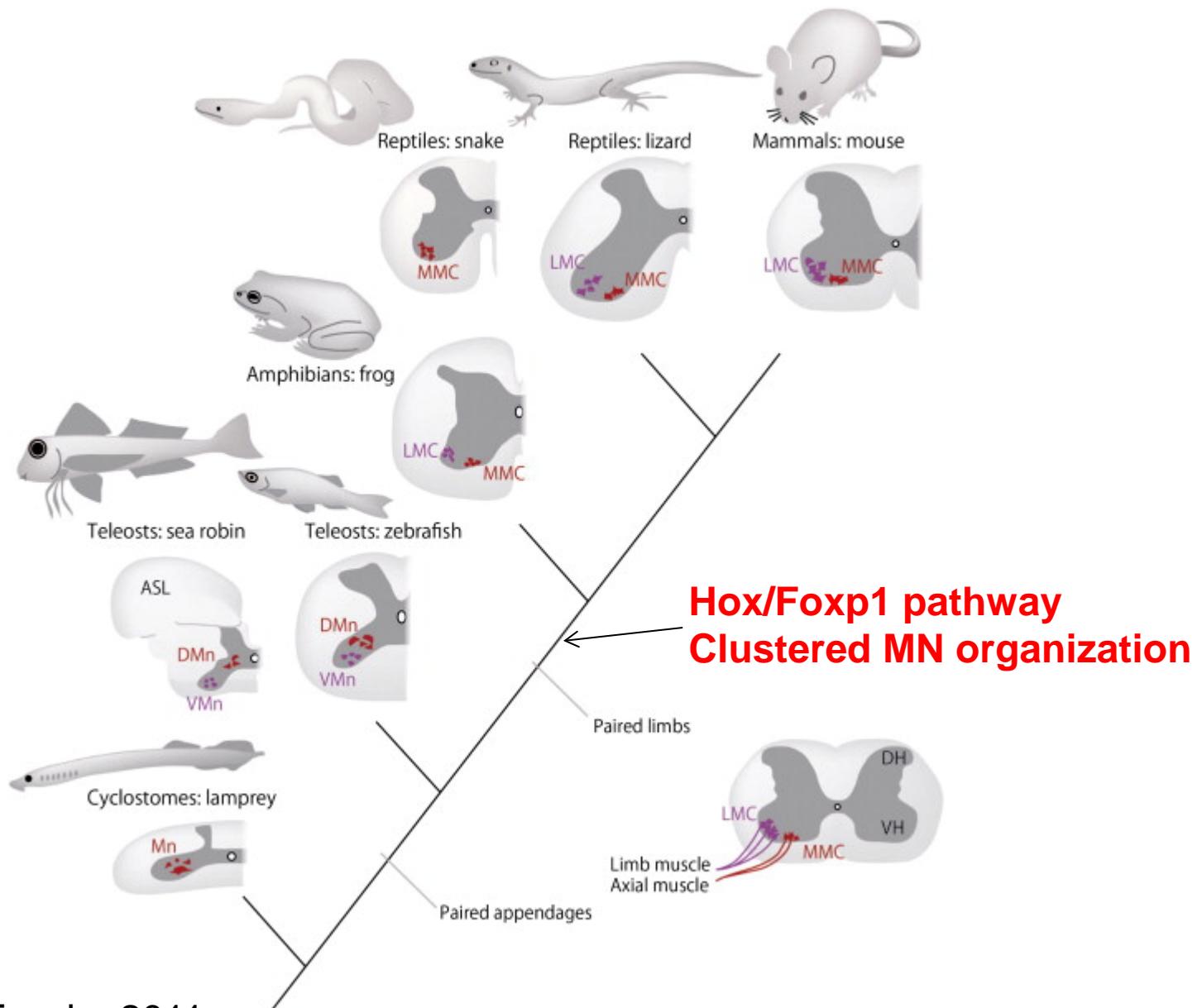
Pectoral fin MNs



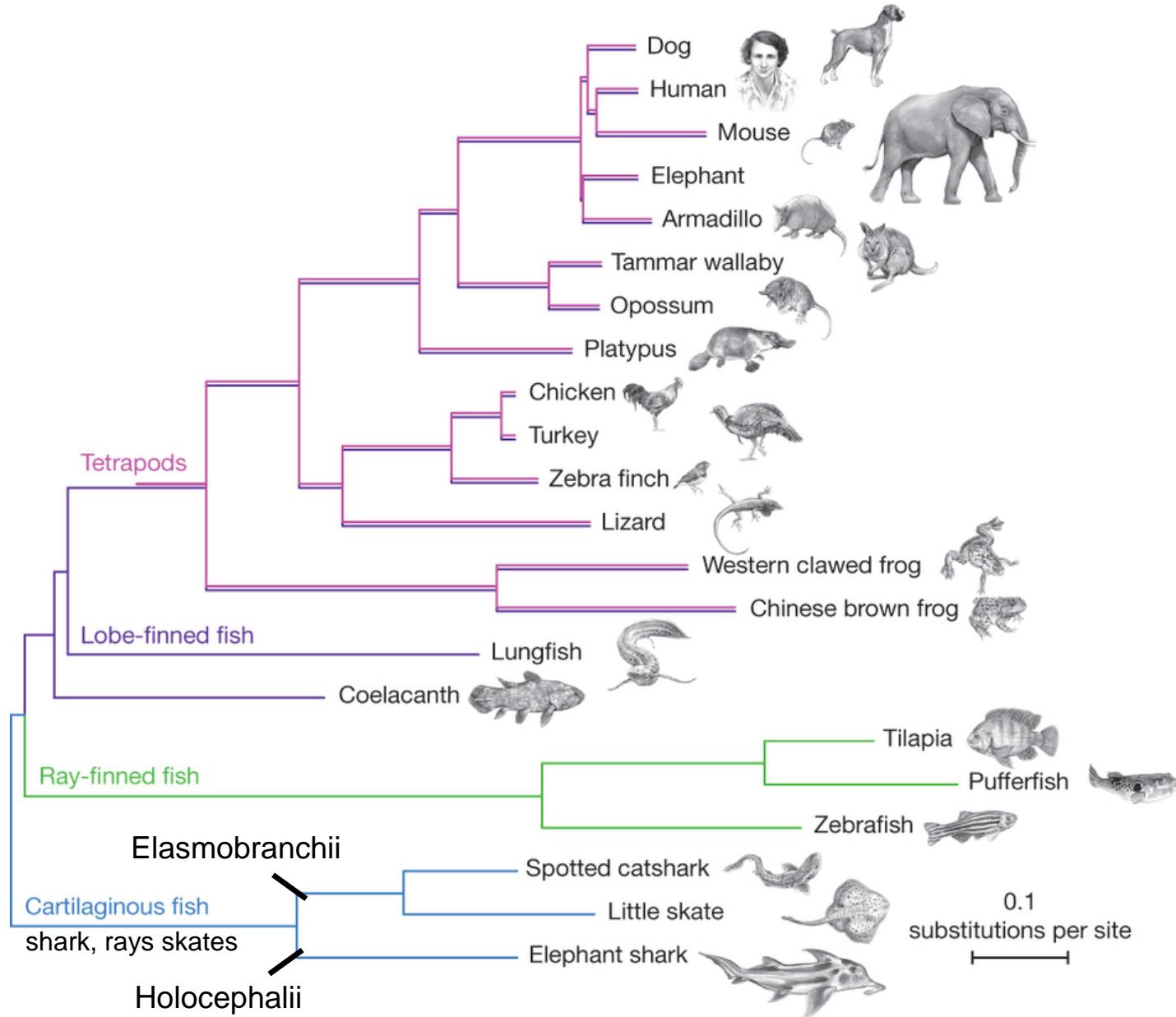
zFoxp1



Model for the emergence of appendage innervation programs



Cartilaginous fish : the most basal fin-bearing vertebrates



Agonist/antagonist muscle pairs in the fins of sharks



rotating cradle

RF

LF

LSD

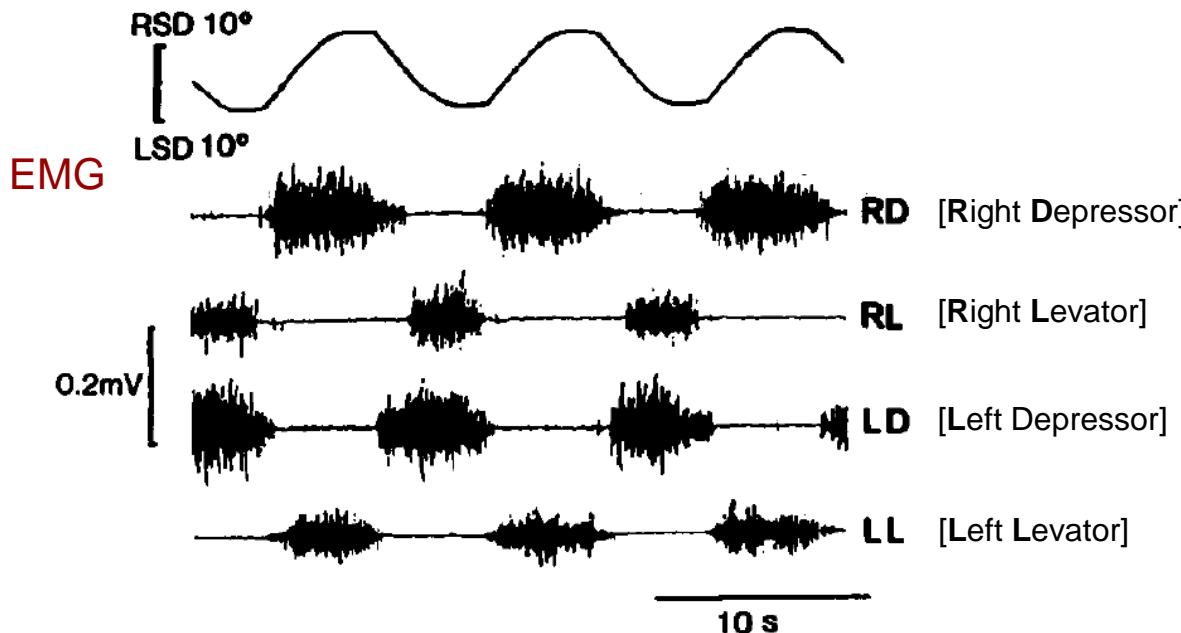
RF

LF

RSD

RF

LF



spotted catshark, *Scyliorhinus canicula*

Timerick et al 1990

A clearnose skate is shown swimming over a sandy ocean floor. The fish has a light-colored body with dark spots and a long, thin tail. The background consists of clear blue water and a sandy bottom.

Clearnose Skate

Walking Behavior

©2012 TheLivingSea.com

The little skate *Leucoraja erinacea*





Expression of MN Subtype Determinants in *Leucoraja*

Little Skate (*Leucoraja erinacea*)

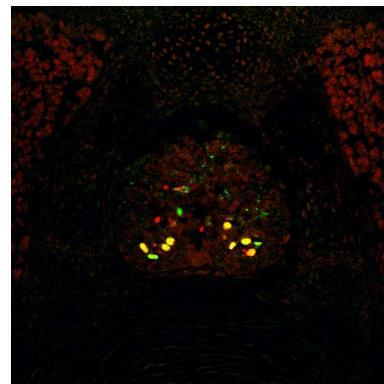
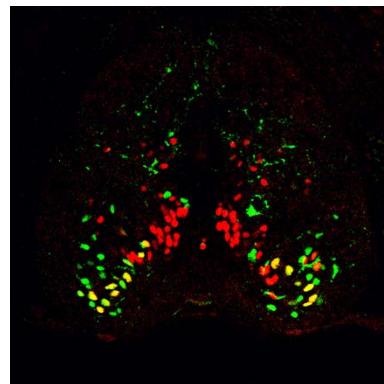
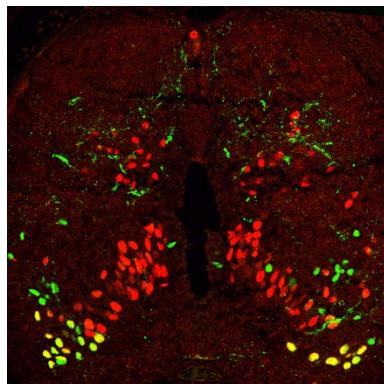
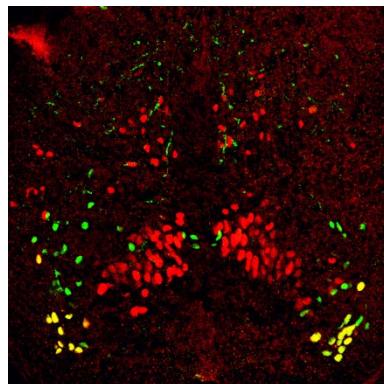
st32 (27~29 weeks)

pectoral fin
(Pec) pelvic fin
(Pelv)

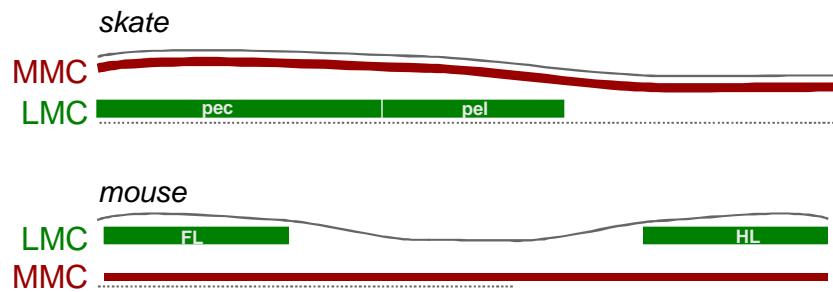
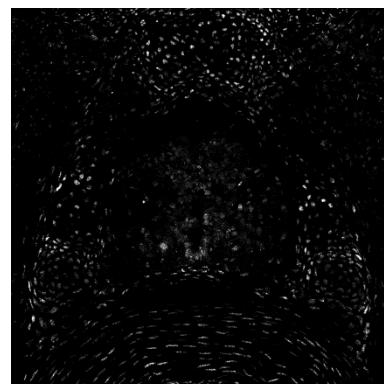
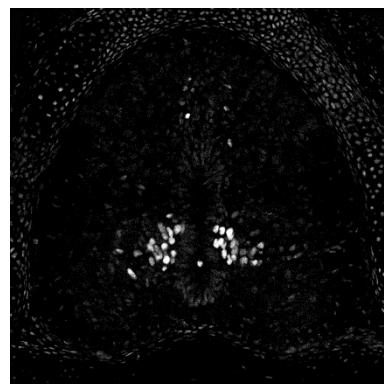
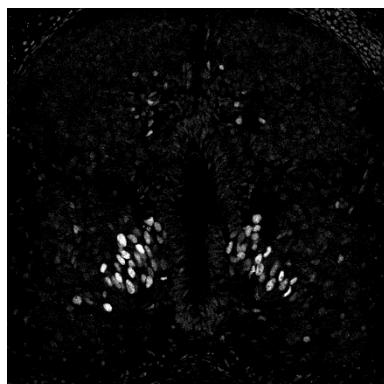
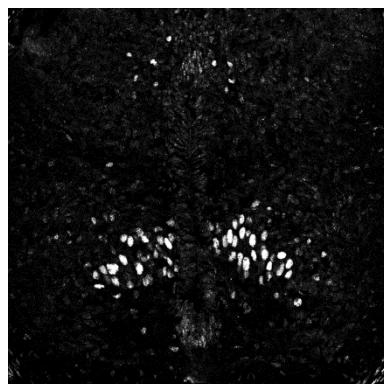
rPec

cPec

Lsl1/2 Lhx3



Foxp1



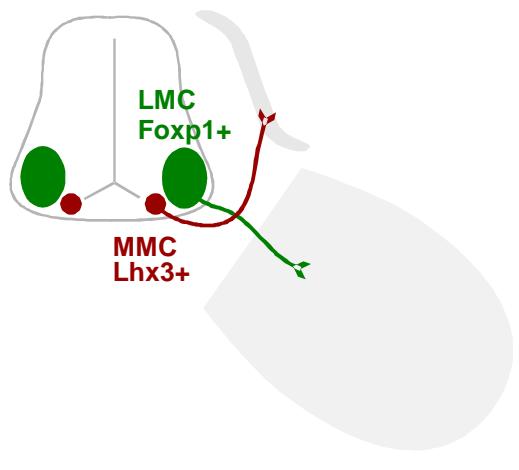
Pelv

Tail

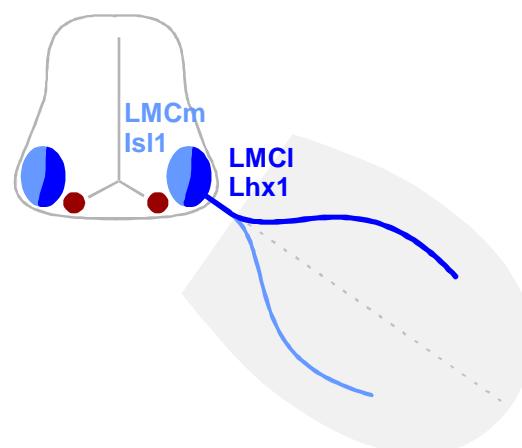
Jung

The early genetic pathway for limb innervation

Columnar specification



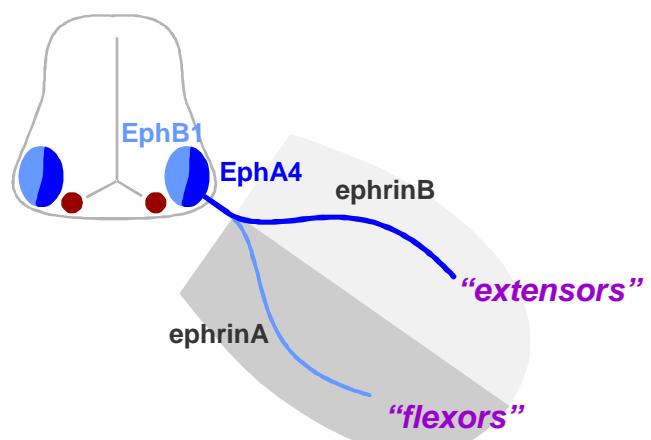
Divisional specification



$\text{Hox} \rightarrow \text{Foxp1} \rightarrow \text{limb}$
T
 Lhx3

$\text{Hox/Foxp1} \rightarrow \text{Raldh2 (RA)} \rightarrow \begin{cases} \text{Lhx1} \\ \text{Isl1} \end{cases}$

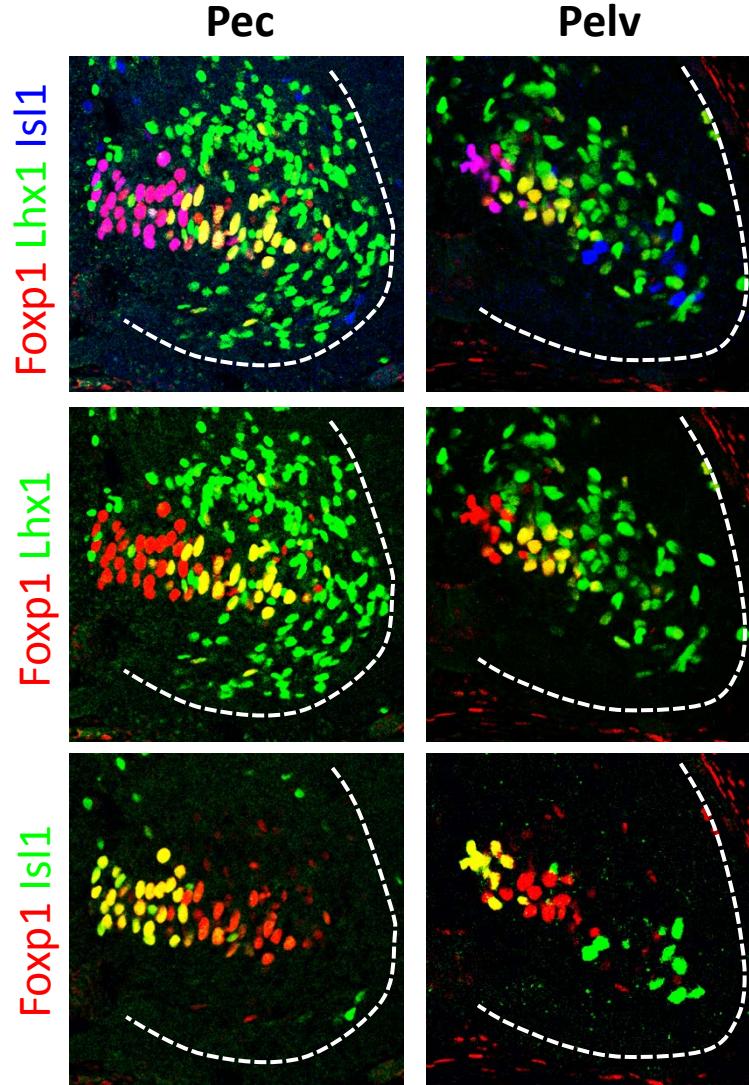
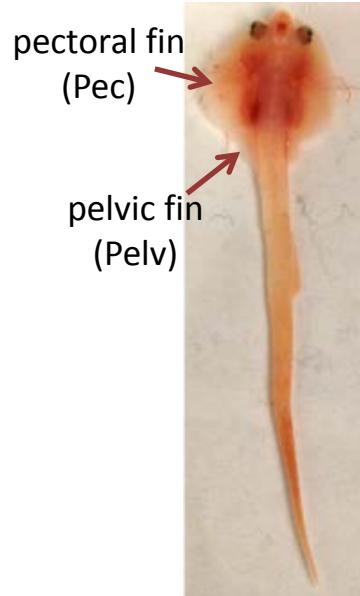
Dorsal-ventral guidance



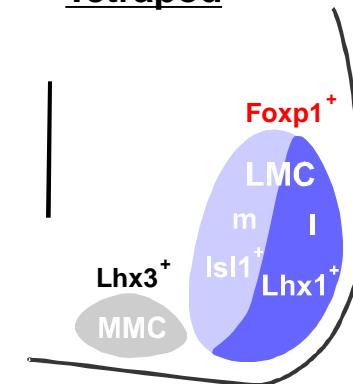
$\text{Lhx1} \rightarrow \text{EphA4} \rightarrow \text{Dorsal}$

$\text{Isl1} \rightarrow \text{EphB1} \rightarrow \text{Ventral}$

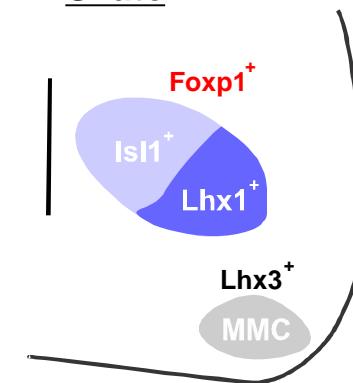
Evidence for divisional identity in *Leucoraja*



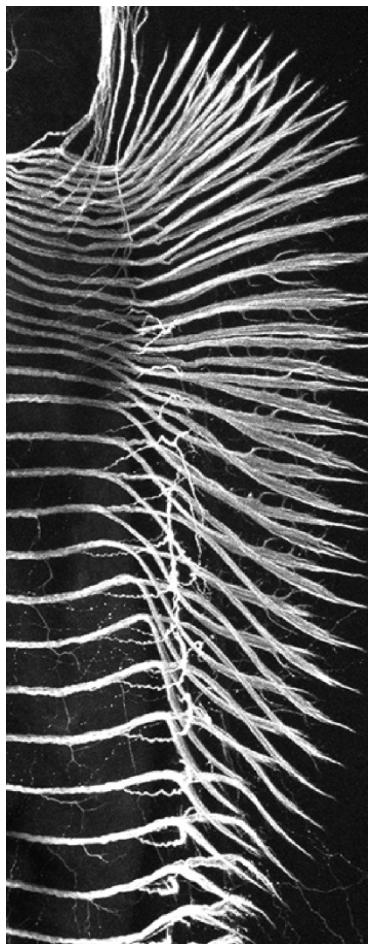
Tetrapod



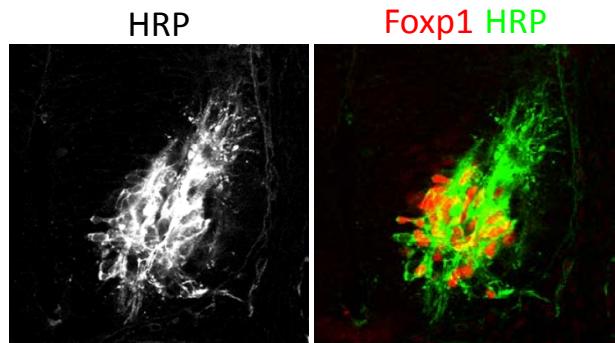
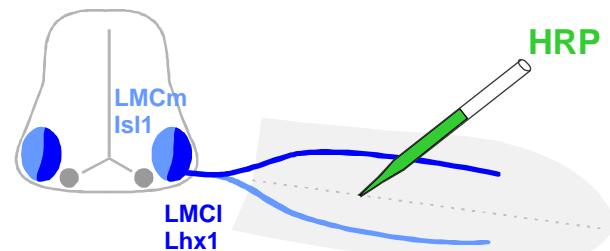
Skate



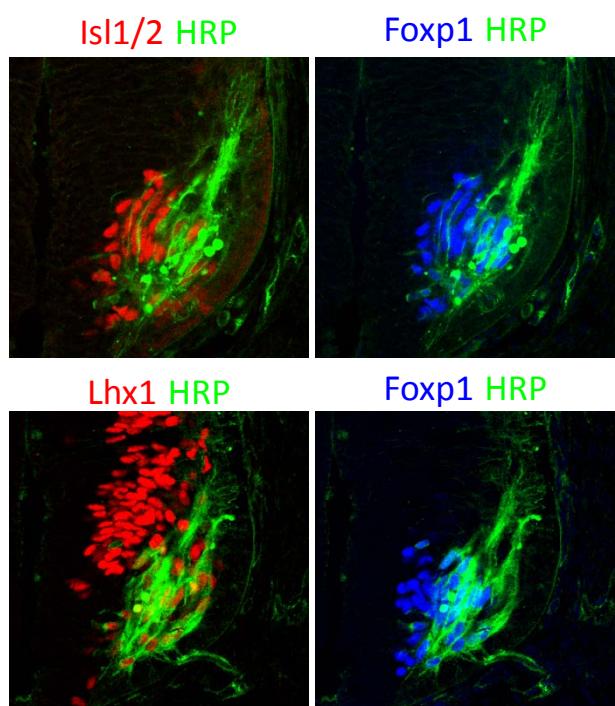
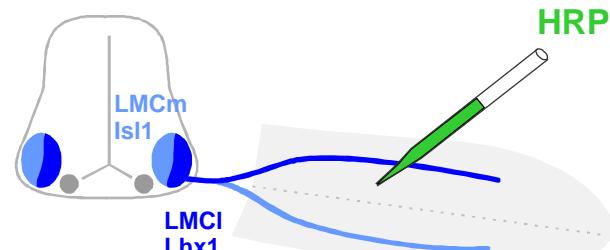
Further evidence for divisional identity in *Leucoraja*



whole fin



dorsal fin



st29 (16-26 weeks)

Jung

Natural loss of the *HoxC* cluster in elasmobranchs

BREVIA

A Natural Deletion of the *HoxC* Cluster in Elasmobranch Fishes

Benjamin L. King,^{1*} J. Andrew Gillis,² Heather R. Carlisle,³ Randall D. Dahn^{1†}

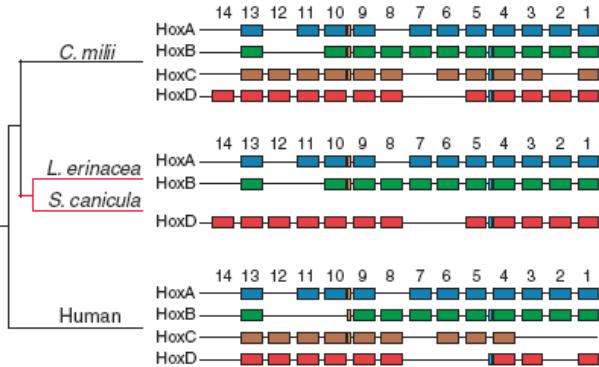
Jawed vertebrates typically possess four *Hox* clusters, with up to 14 genes each, that arose from an ancestral cluster by genome duplication events. An additional round of whole-genome duplication in teleost fishes permitted the *Hox*

215, respectively; table S1). Expression of the 11 *HoxC* genes was undetectable in *S. canicula* [consistent with (2)] and *L. erinacea* ($P = 2.60 \times 10^{-7}$).

To distinguish between genomic deletion and transcriptional silencing of the *HoxC* cluster in

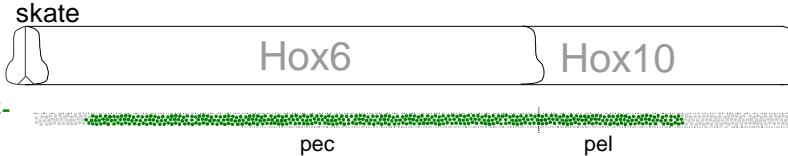
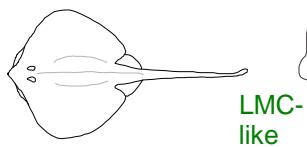
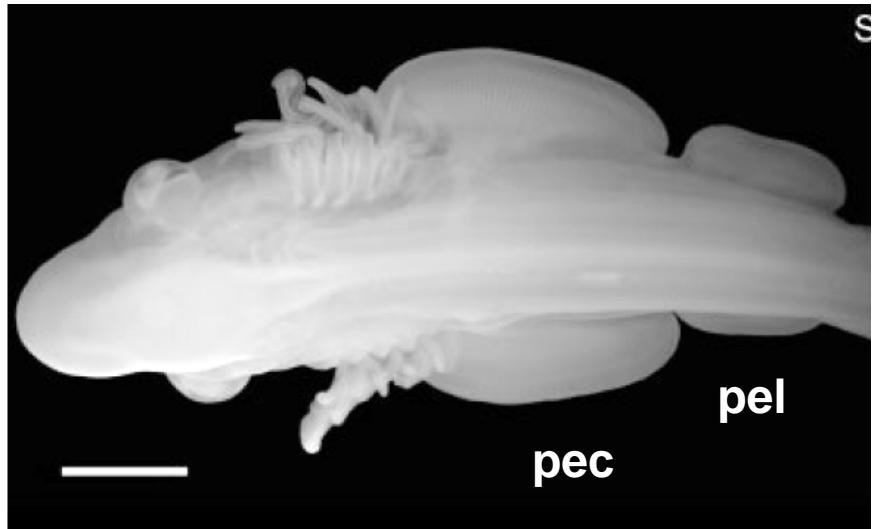
man *HoxA*, *B*, and *D* clusters (4), 51% of the 249 elements were identified in the *L. erinacea* genome, but none of the 25 elements from within the *HoxC* cluster were detected ($P = 1.01 \times 10^{-7}$; table S2).

Our data suggest that the lack of *HoxC* gene expression during *L. erinacea* and *S. canicula* development is attributable to a genomic deletion of the entire *HoxC* cluster in these taxa (Fig. 1). The most likely scenario is that the entire *HoxC* cluster was lost in a single genomic reduction event after the divergence of holopelicans and elasmobranchs but before the divergence of batoids and sharks (Fig. 1); however, regulated chromosomal diminution cannot be excluded on the basis of embryonic genomic DNA sequence (5). Homozygous mice lacking the *HoxC* complex exhibit only minor transformations of axial identity but die perinatally because of pulmonary defects (6). The unique dispensability of the *HoxC* cluster for body plan development may have enabled elasmobranchs to survive the challenge of a genome reduction abrogating all *HoxC* cluster function.



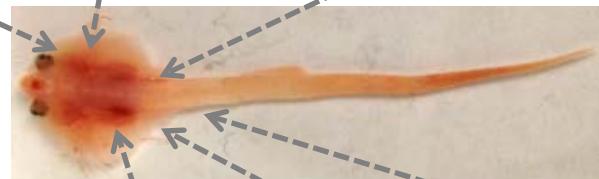
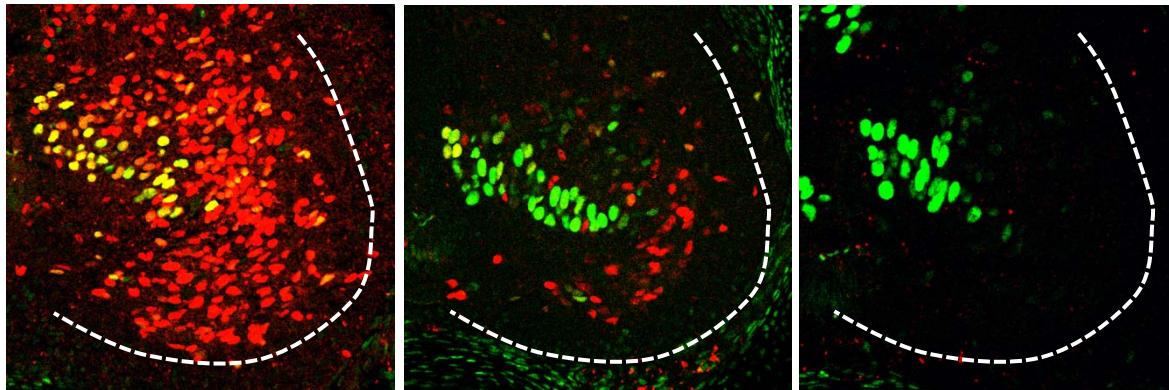
- References and Notes
1. J. M. Webbing, A. J. Duson, *Nat. Genet.* **38**, 601 (2006).
2. S. Oskin et al., *Mol. Biol. Evol.* **27**, 2829 (2010).
3. A. H. Lund, *Cell Death Differ.* **17**, 209 (2010).
4. V. Ray et al., *Proc. Natl. Acad. Sci. U.S.A.* **106**, 16327 (2009).
5. J. J. Smith, W. B. Stuart, T. Sado, Springer, New York, NY, America, Chromosome **23**, 391 (2010).

Winter skate embryo (St.29)

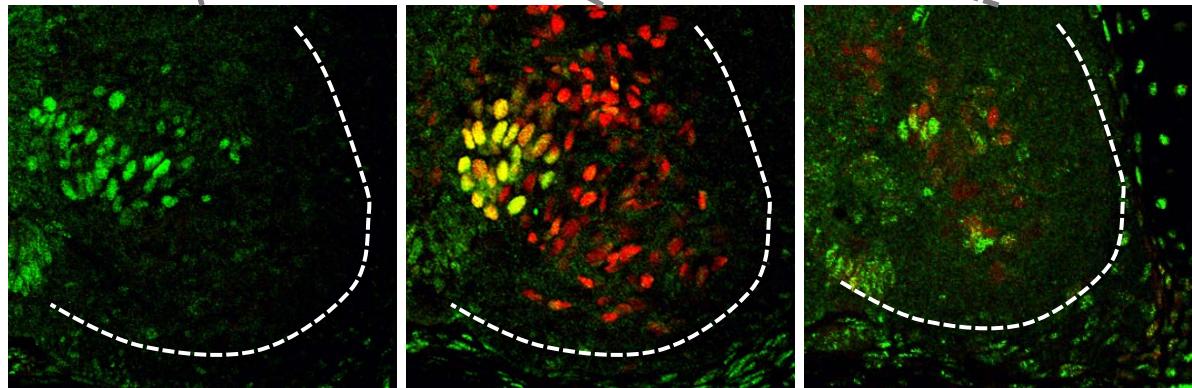


HoxA protein expression in *Leucoraja*

Hoxa5 Foxp1



Hoxa10 Foxp1



The ancient origins of circuit elements for terrestrial locomotion

