The background of the slide features a complex network of neurons, likely from a C. elegans nervous system. The neurons are stained with two colors: red and green. The red-stained neurons form a more organized, radial-like pattern, while the green-stained neurons are more diffused and form a more continuous, mesh-like structure. They intersect and overlap throughout the field of view.

Neural Specification

DV and AP patterning

And its relation CNS circuit wiring

Outline

I. DV patterning by Shh

- a. Graded signaling and interpretation
- b. TF-mediated patterning
- c. Progenitor and postmitotic codes

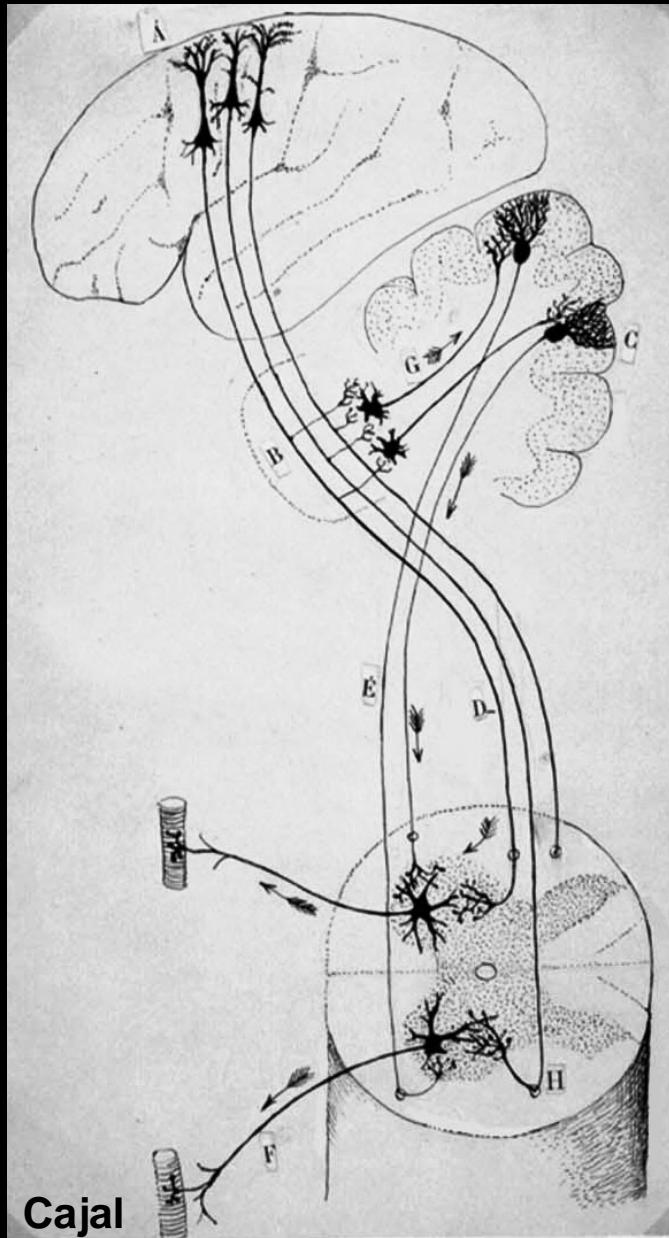
II. AP patterning in the spinal cord

- a. Neuronal diversity along AP axis
- b. Motor neuron diversity
- c. Integration of AP and DV

III. Motor circuits

- a. Sensory-motor circuits
- b. INs and motor behaviors
- c. Identity versus position as determinants of synaptic specificity

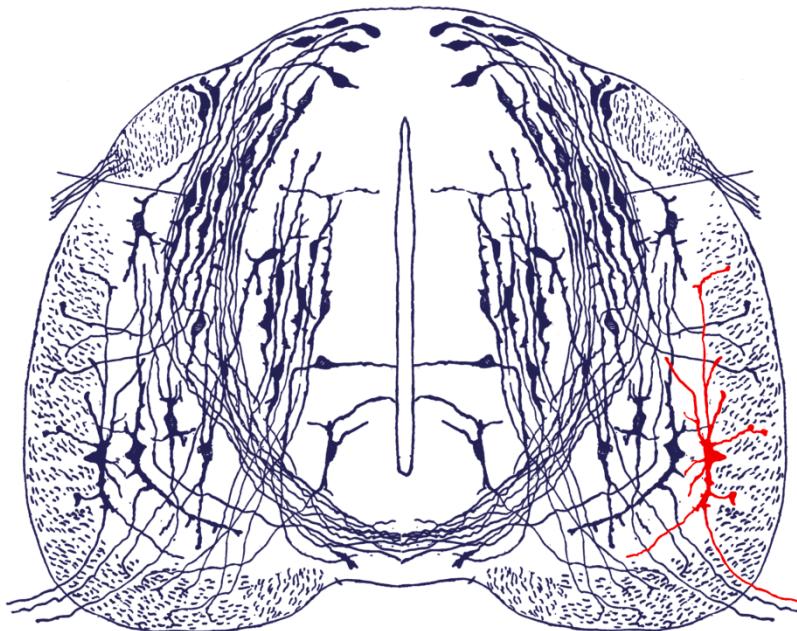
Assembly of neural circuits in the motor system



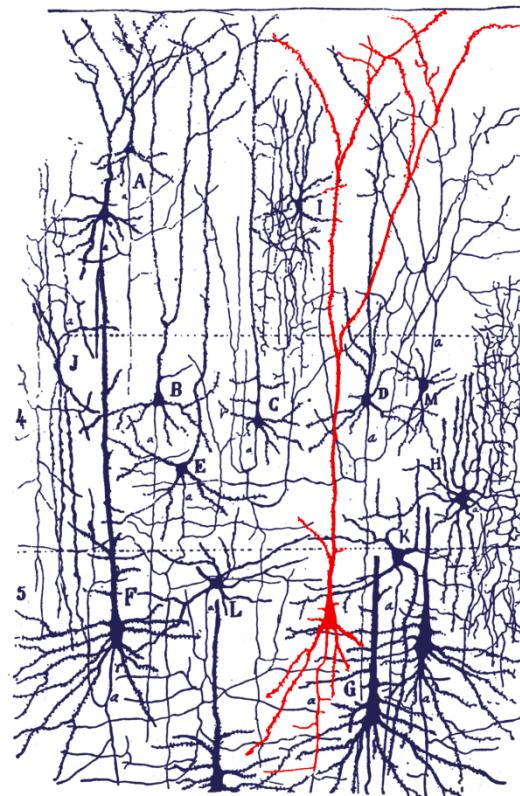
“To move is all mankind can do and for such, the sole executant is muscle, whether in whispering a syllable or felling a forest.”
- Charles Sherrington

Neuronal specification : identity and diversity

Spinal Cord

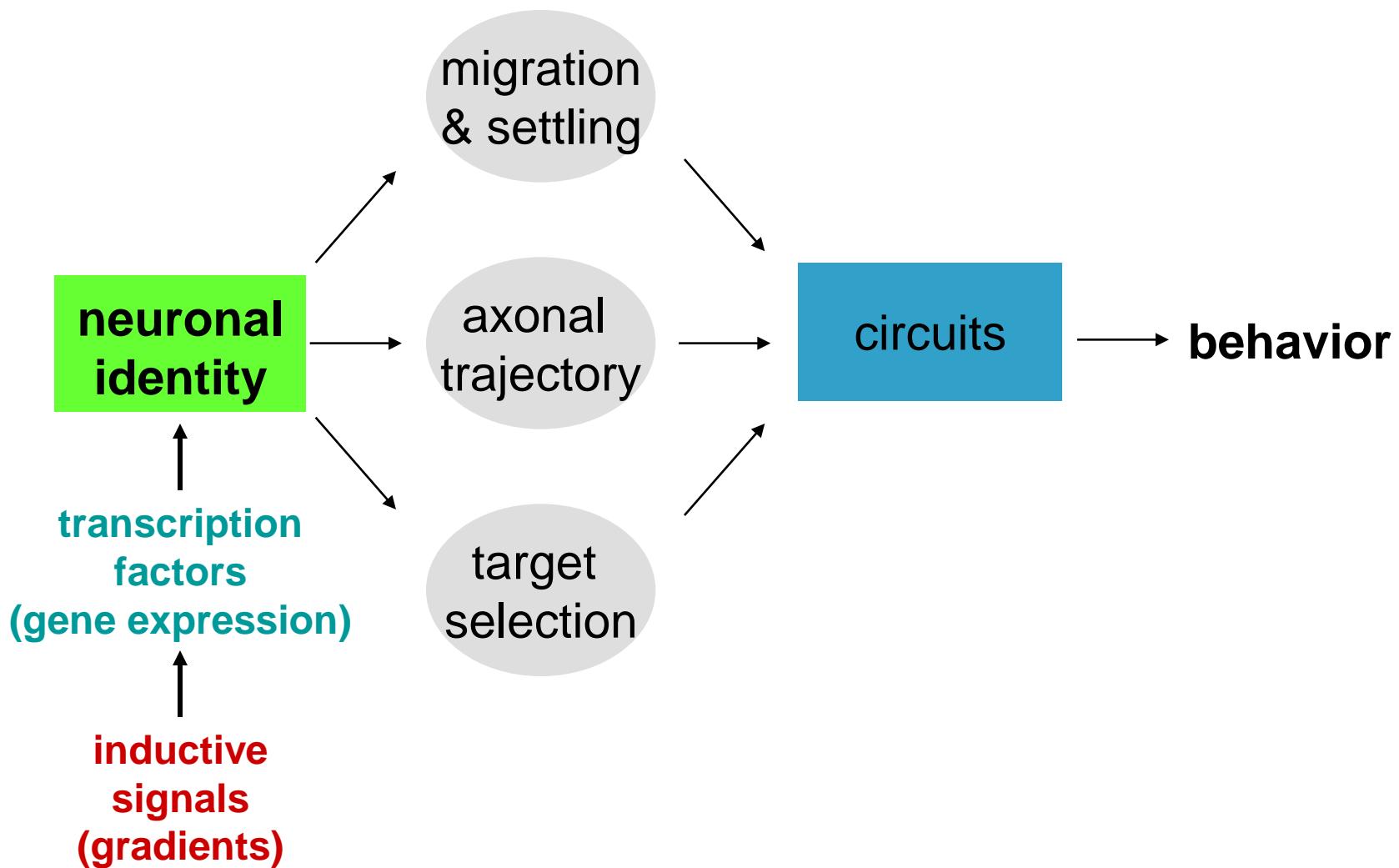


Cerebral Cortex

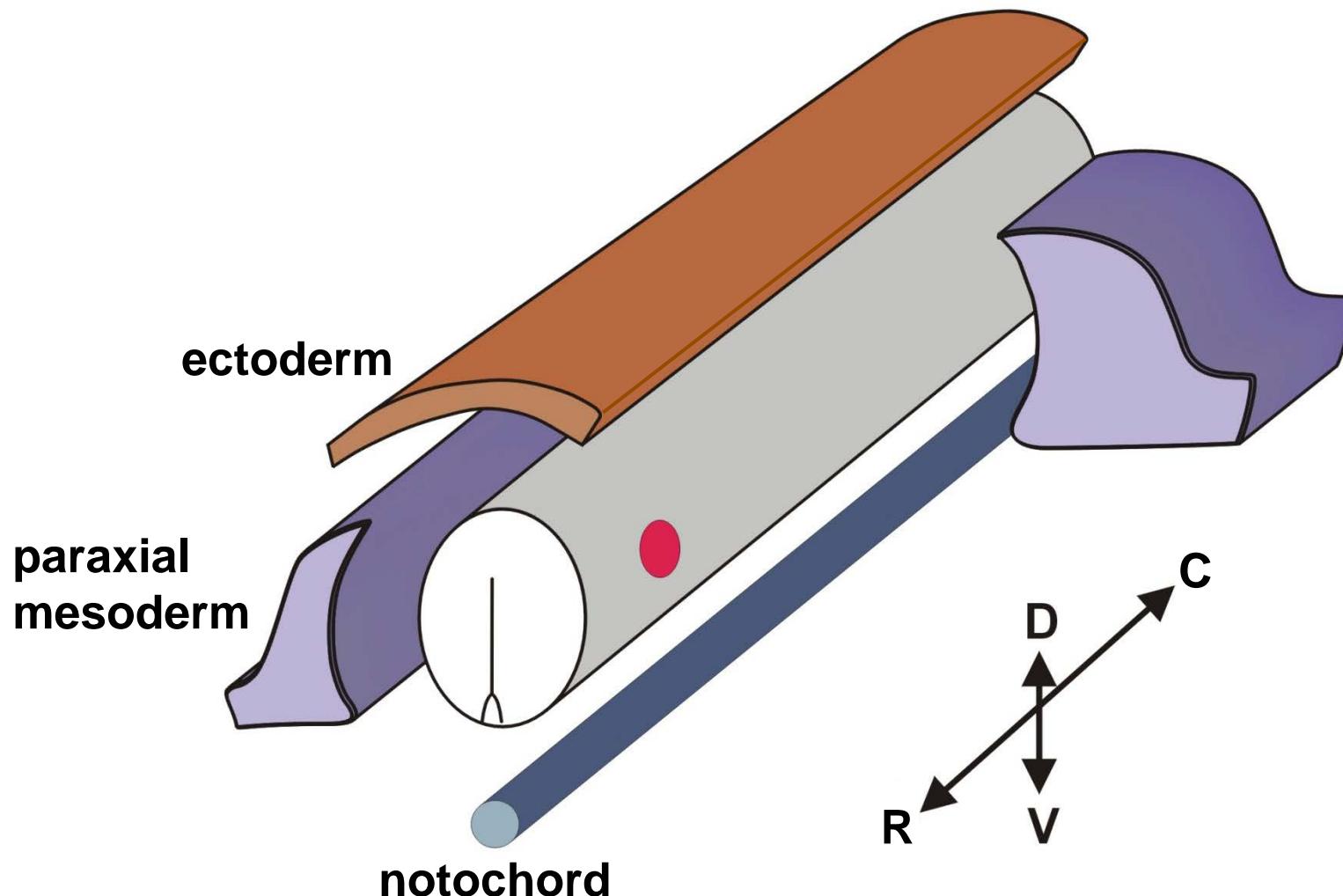


Cajal

Neuronal identity as a determinant of circuit assembly

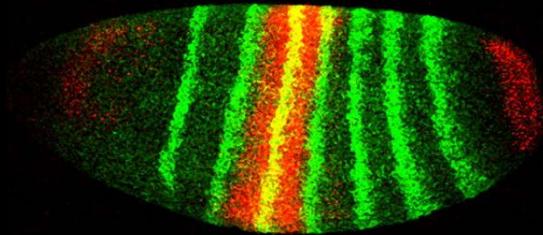


Assigning positional identities along the DV and AP axes

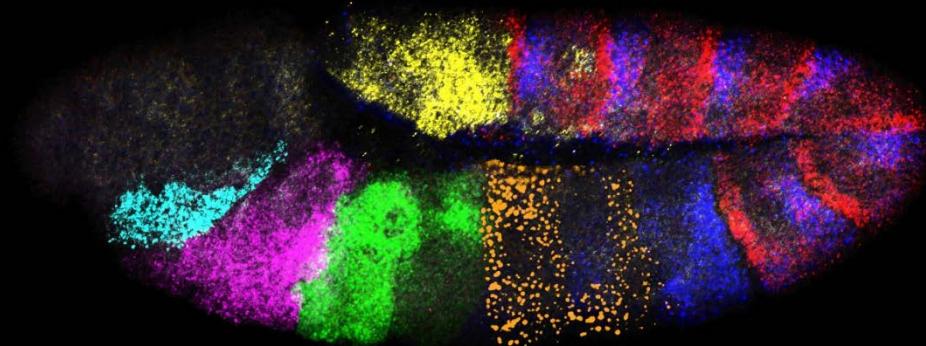


Common strategies for patterning in metazoans

fly segmentation



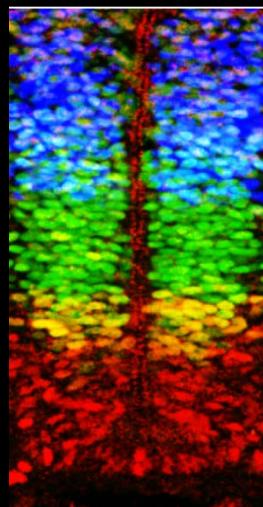
fly AP patterning



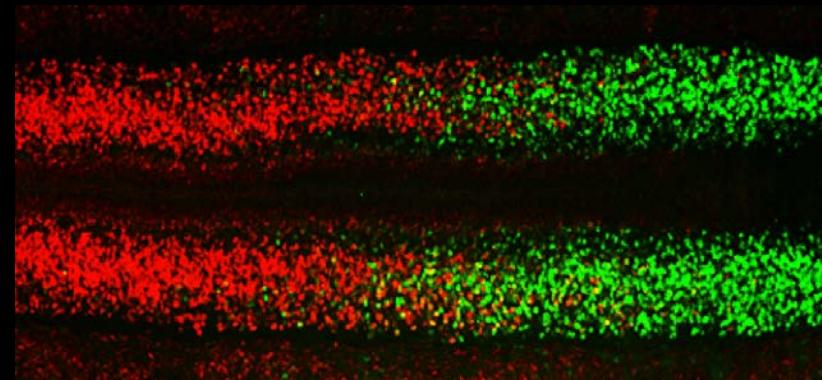
Discrete and combinatorial expression of TFs

- 1) Setting up TF patterns
- 2) How do TFs control identity?

vertebrate dorsoventral



vertebrate AP

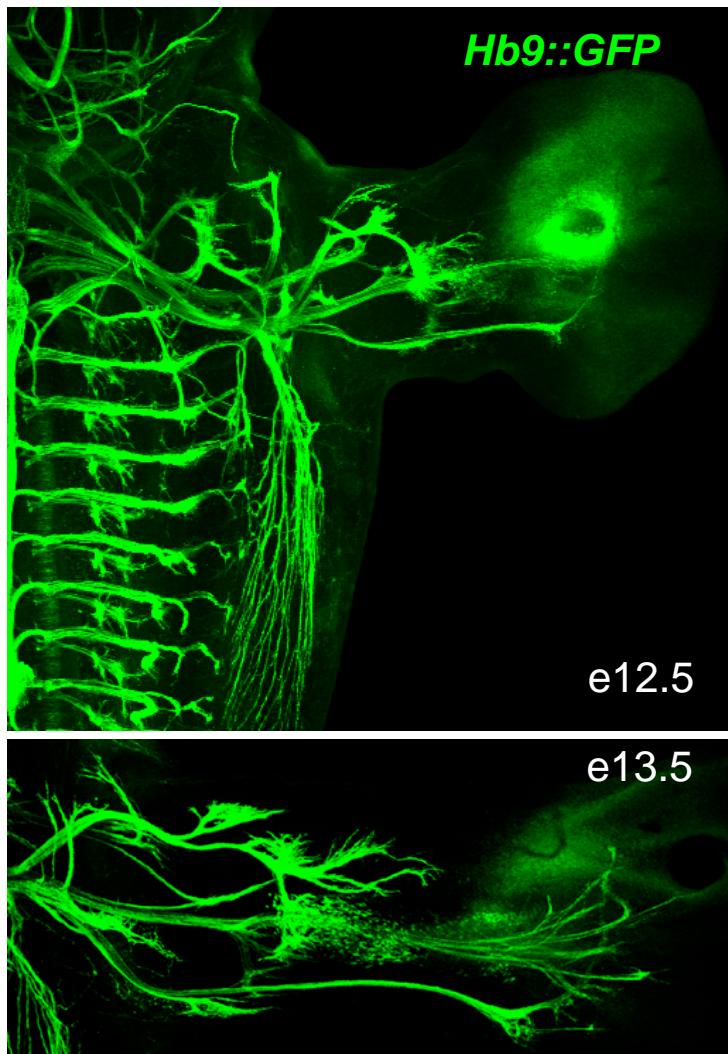


Diversity of locomotor behaviors



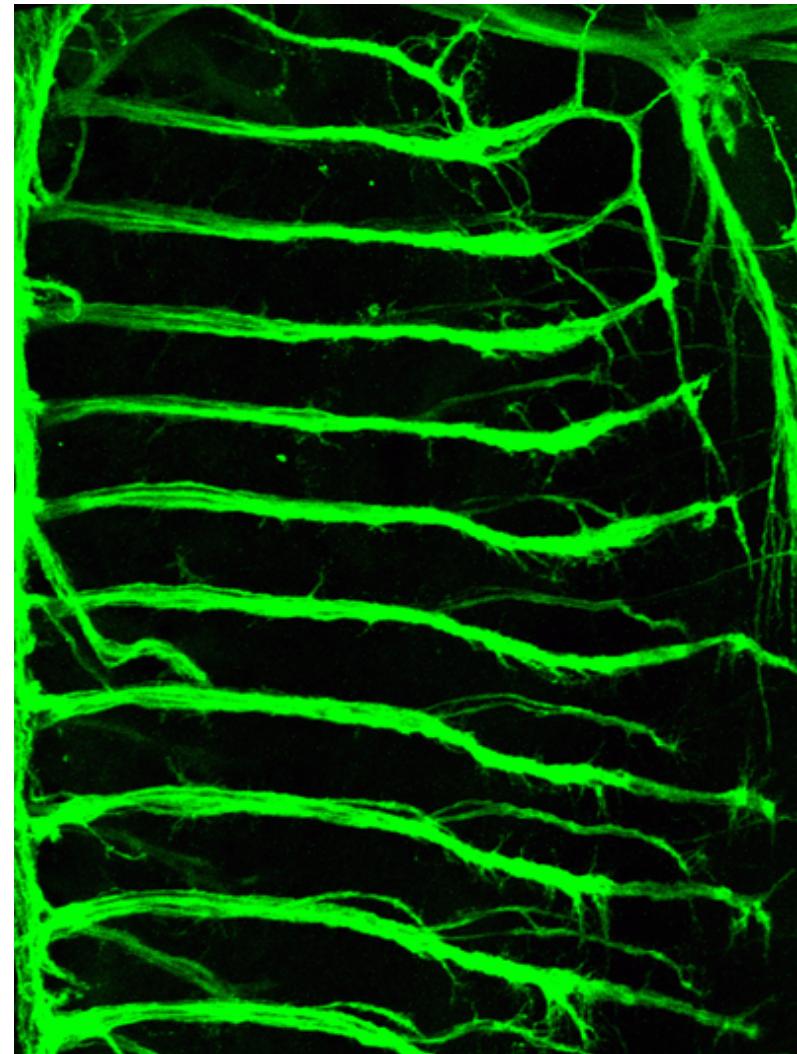
Regional diversity of MNs and innervation patterns

Limb innervation



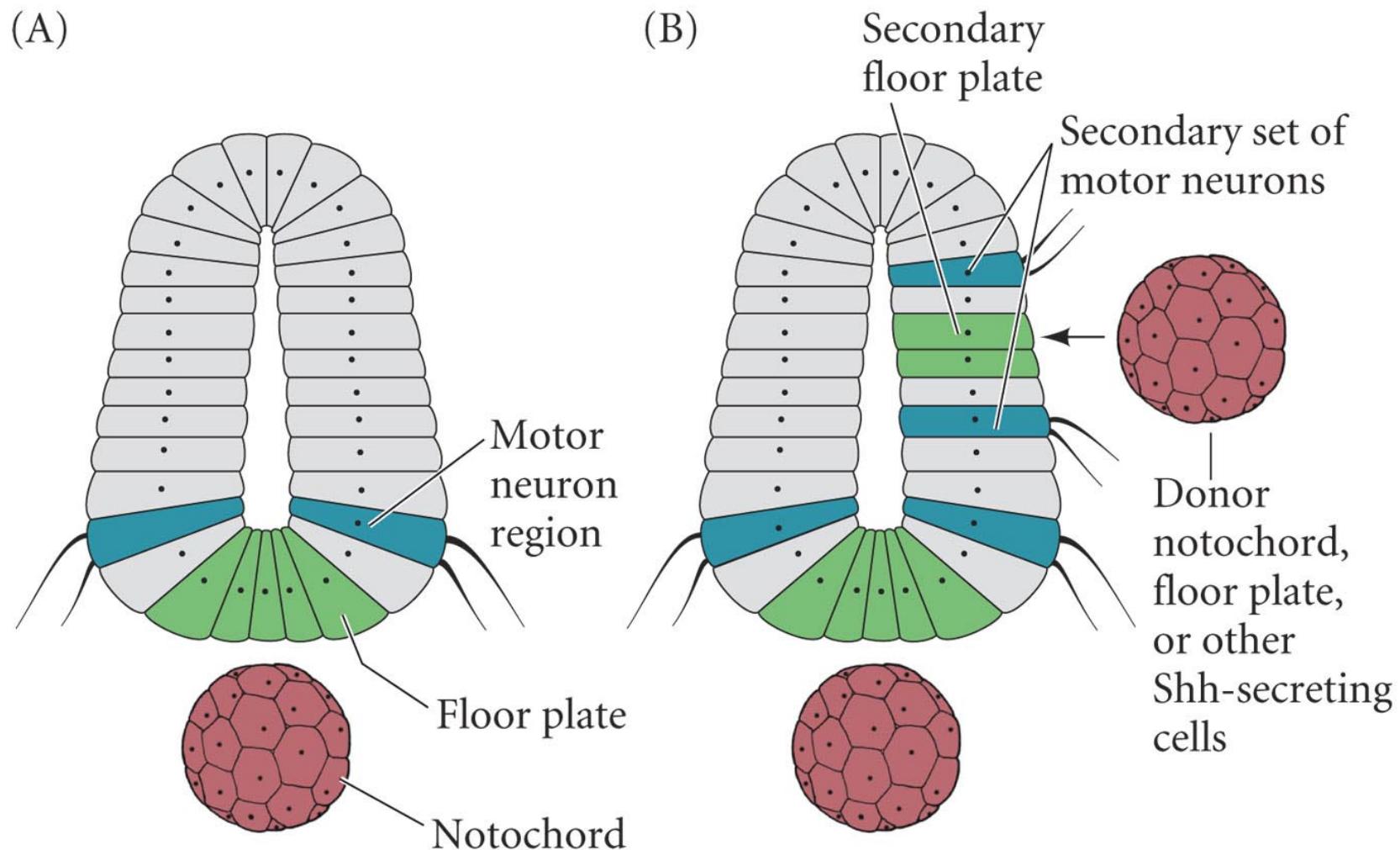
100s of MN subtypes

Body wall innervation

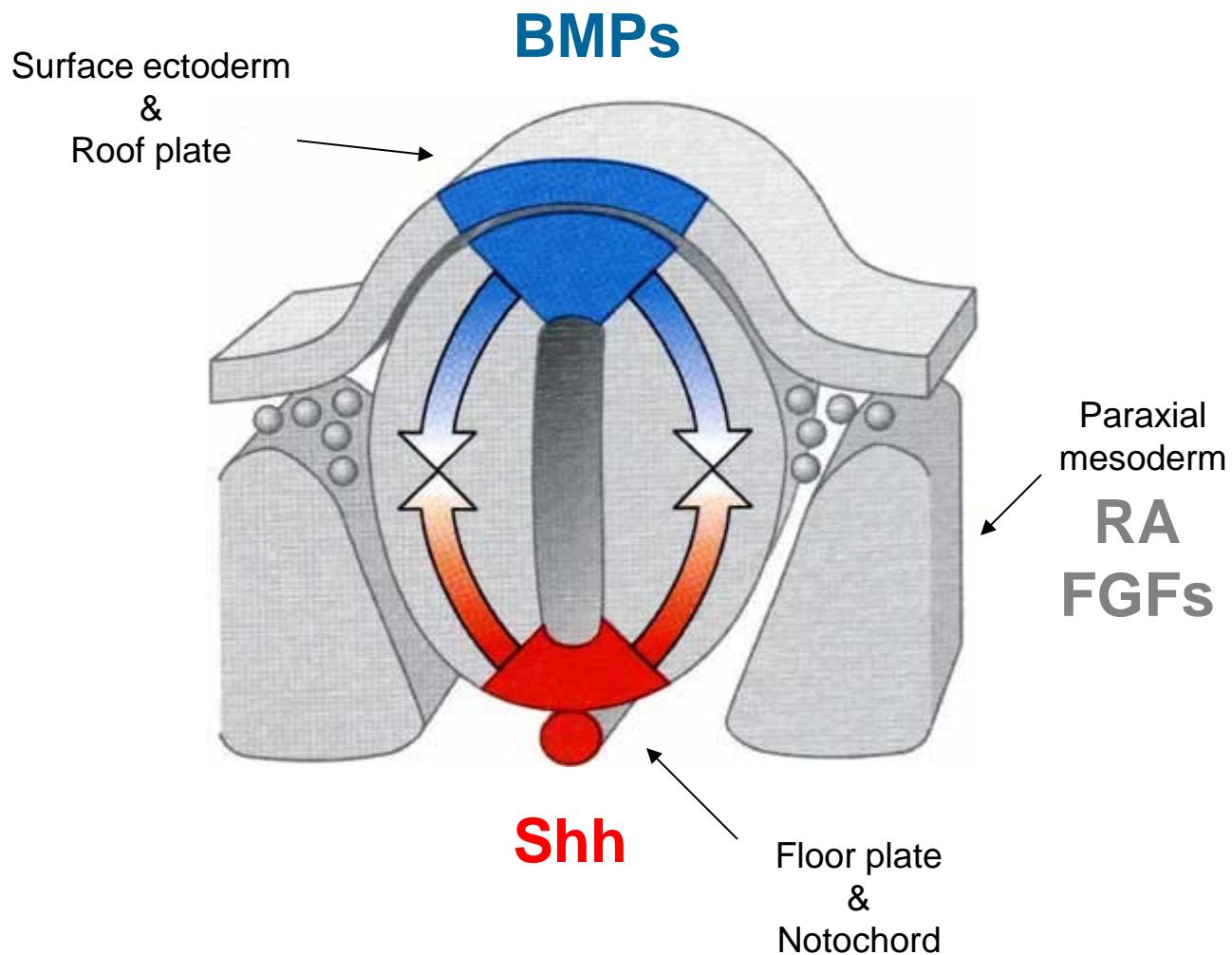


3 MN subtypes

Evidence that the notochord patterns the ventral neural tube

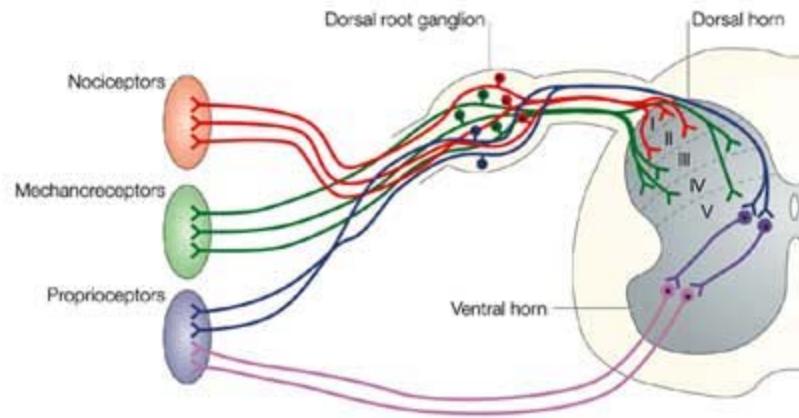


Signals and their sources along the DV axis of the neural tube



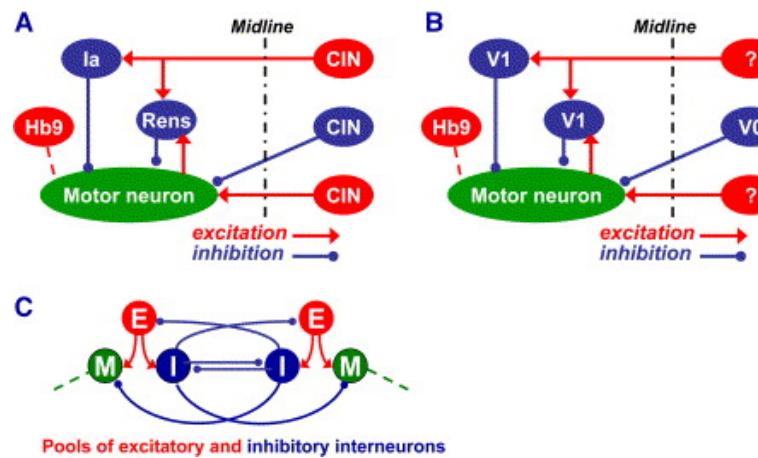
Cell types and neural circuits along the DV axis of the spinal cord

Sensory circuits
(dorsal)

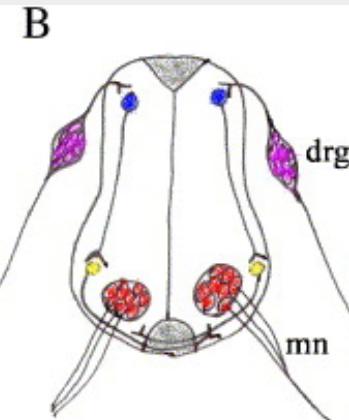
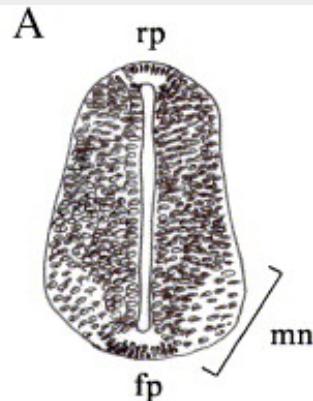


Nature Reviews | Neuroscience

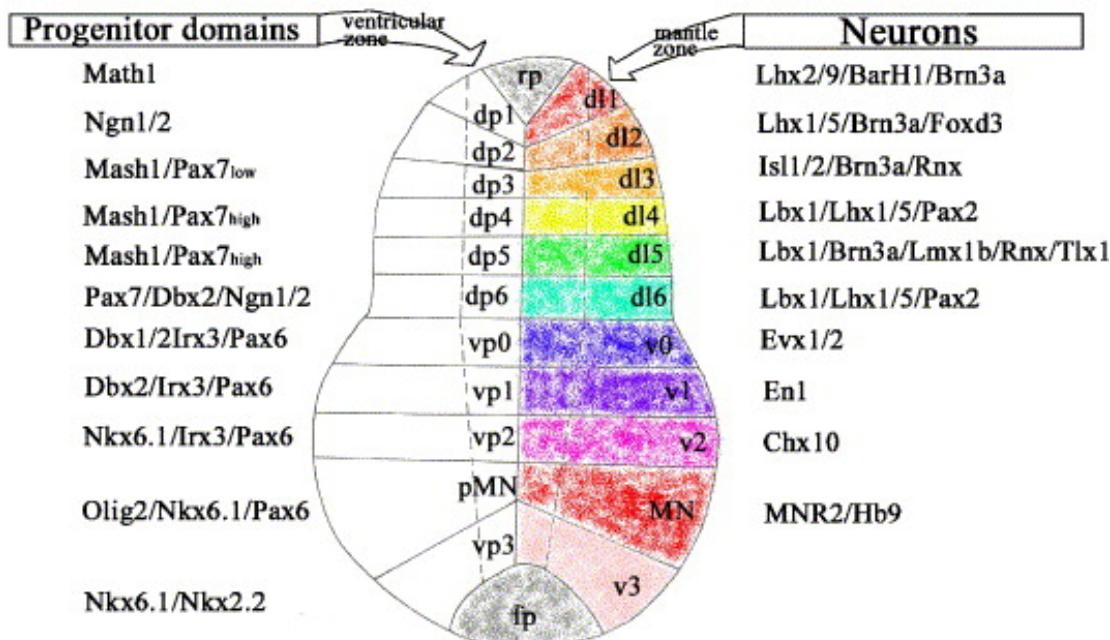
Motor circuits
(ventral)



Diversity of neuronal classes in the vertebrate spinal cord



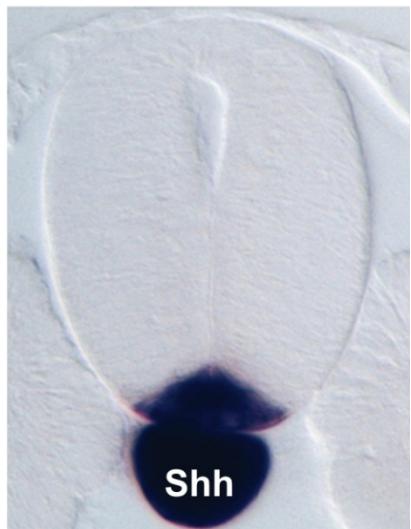
C



dorsal: "sensory"

ventral: "motor"

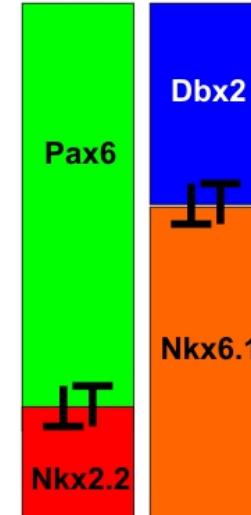
Establishing neuronal identity in the ventral spinal cord



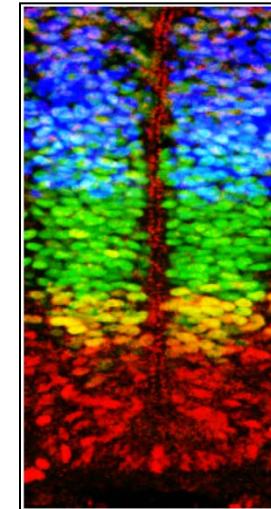
*Graded
Inductive signals*



*Transcription
factor
expression*



*Cross-repressive
interactions*

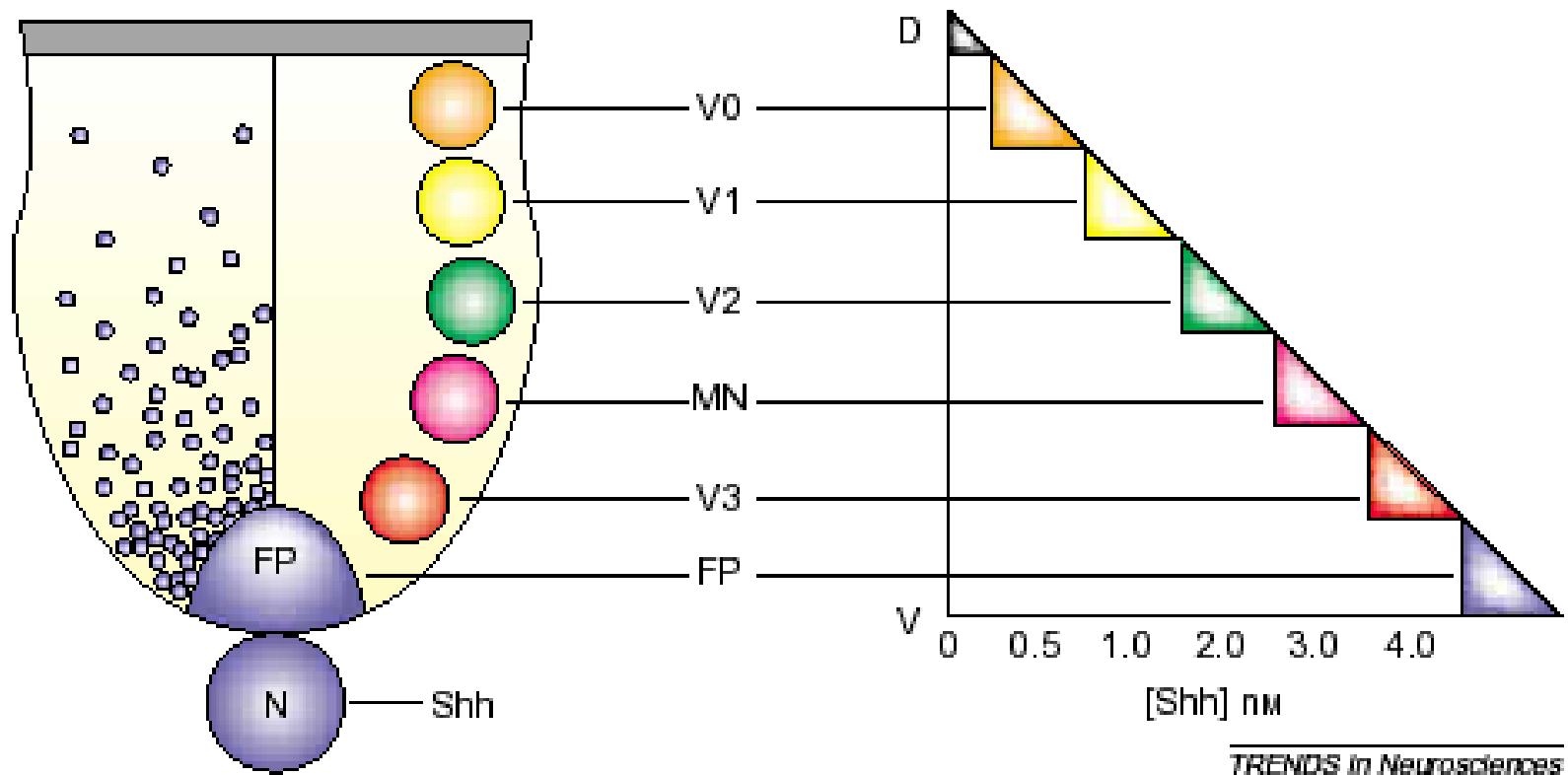


*Neural
progenitor
cell types*

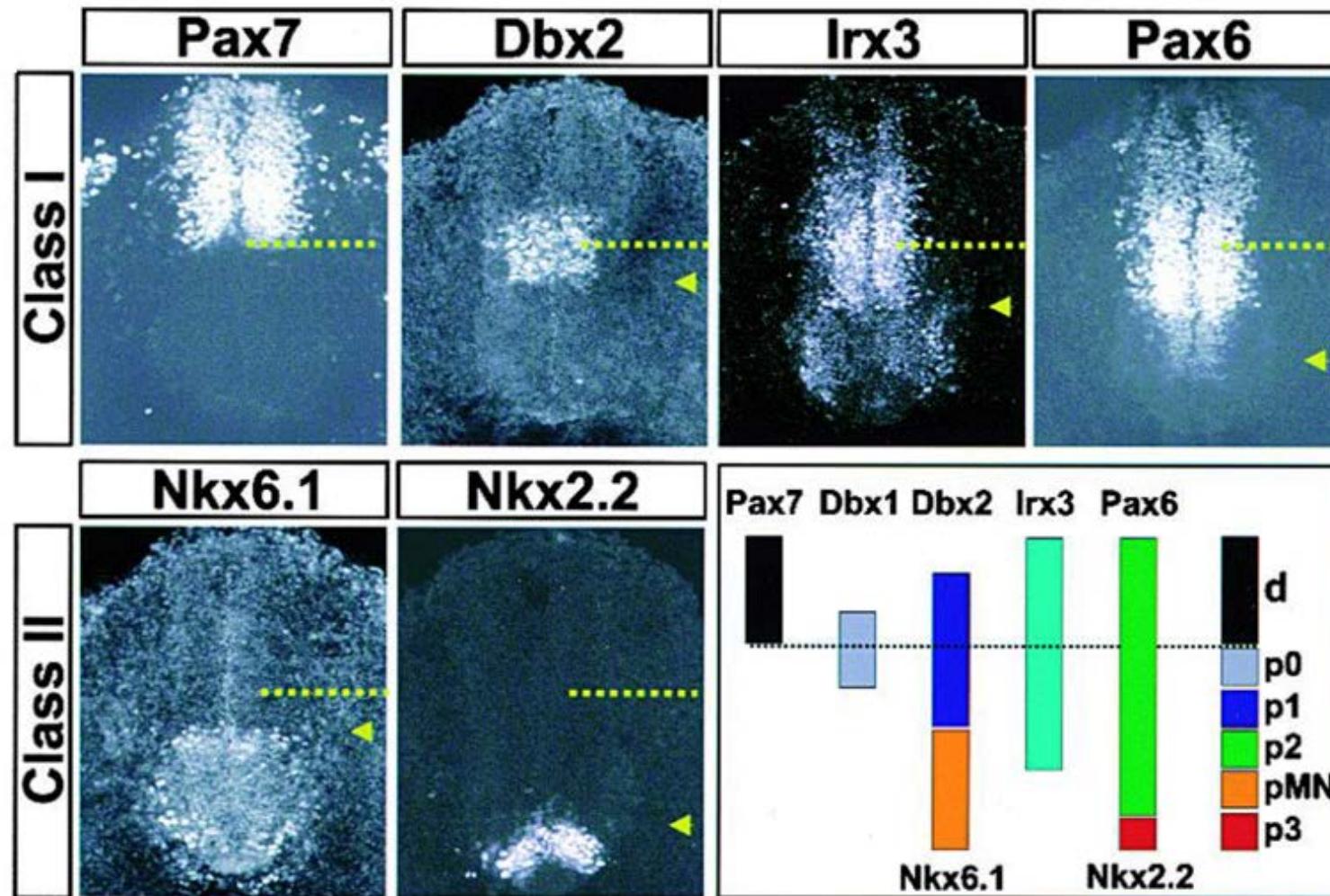
- ● V0
- ● V1
- ● V2
- ● MN
- ● V3

*Postmitotic
neuronal
classes*

Graded Shh signaling specifies distinct classes on ventral neurons

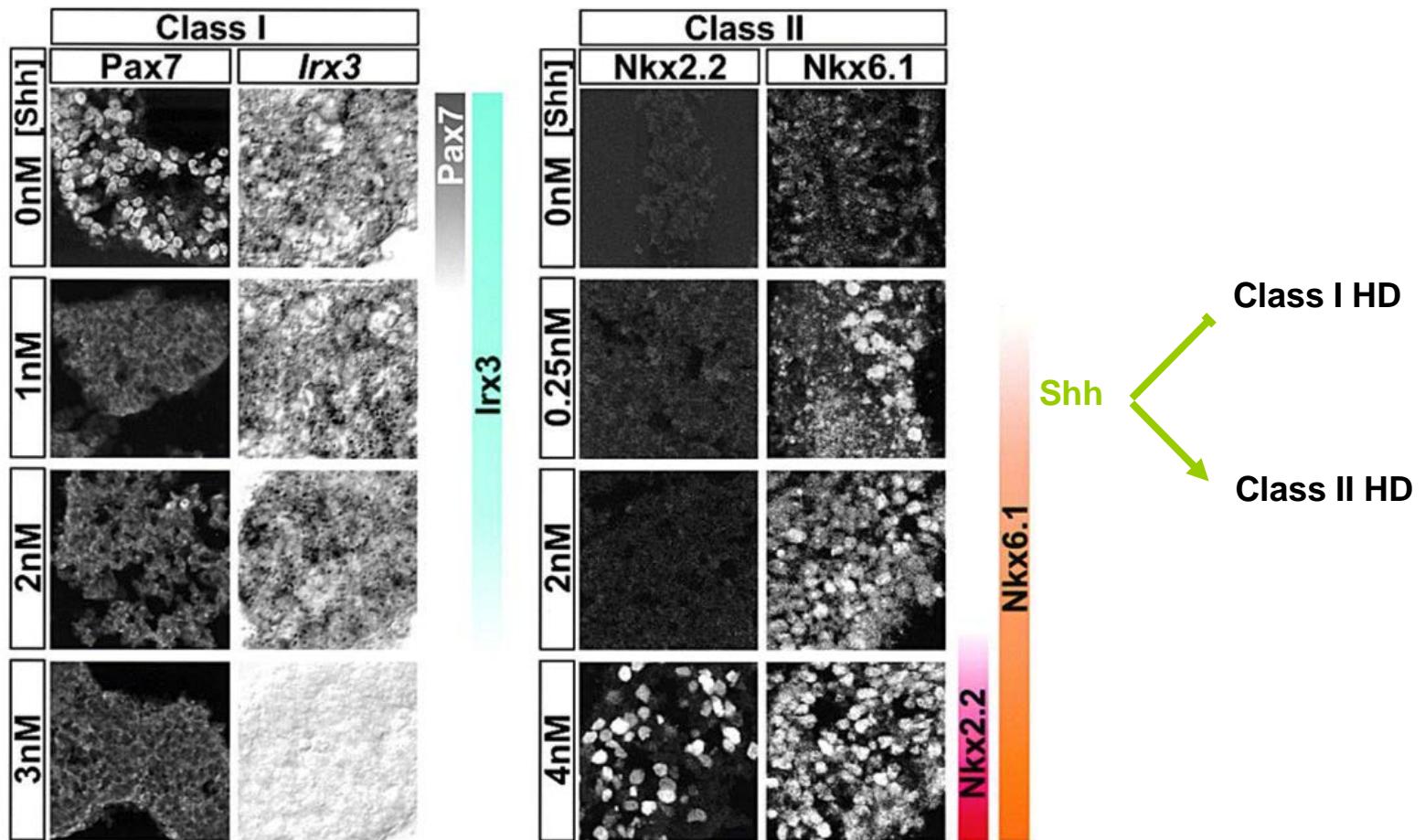


Expression of TFs by neural tube progenitor cells

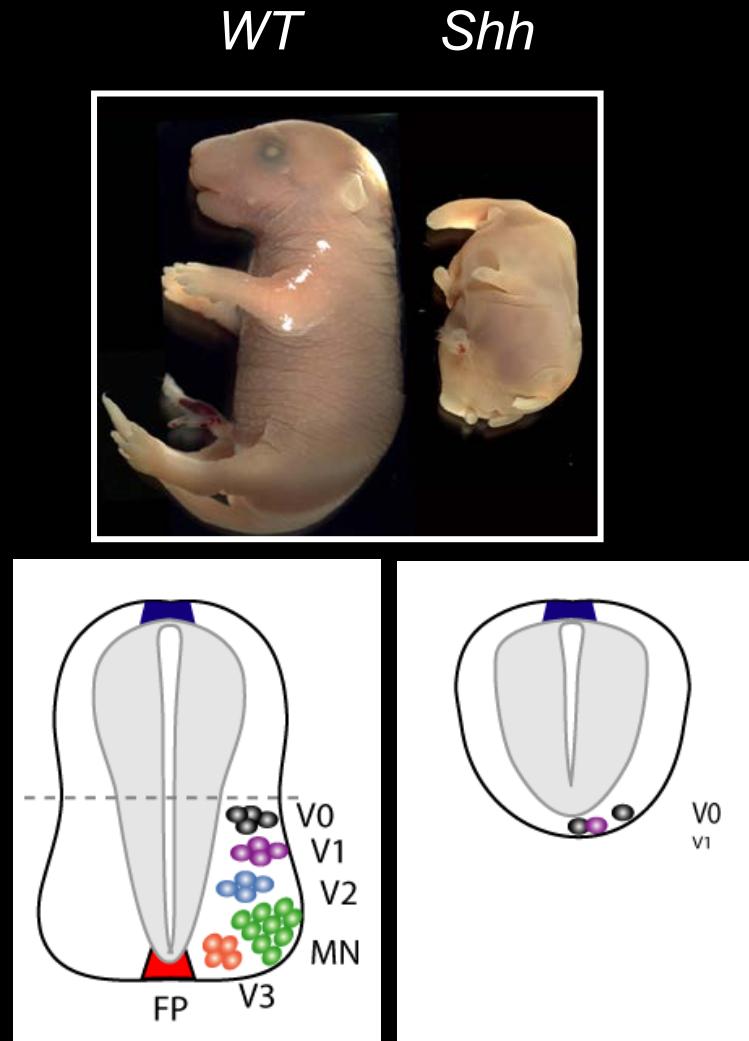


Shh signaling controls TF expression in the ventral neural tube

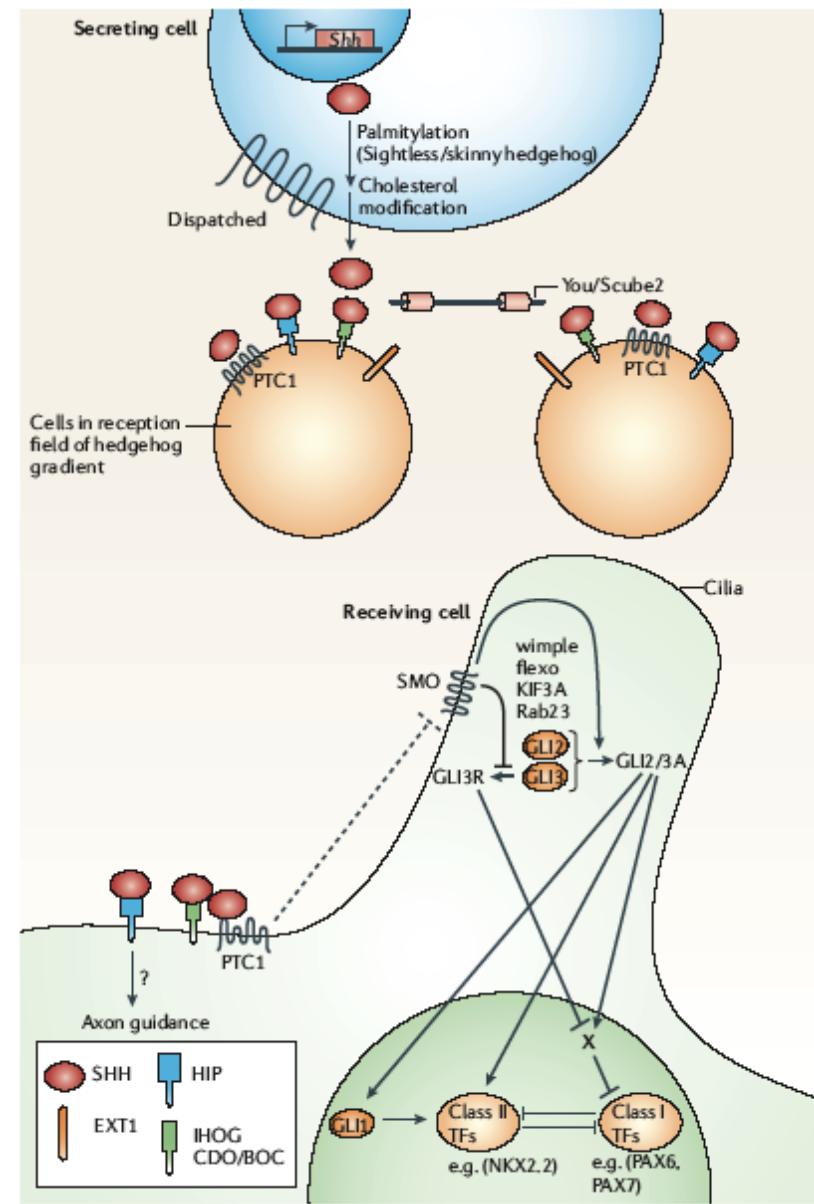
i-explants:
naive neuroectoderm



Loss of *Shh* has severe developmental consequences



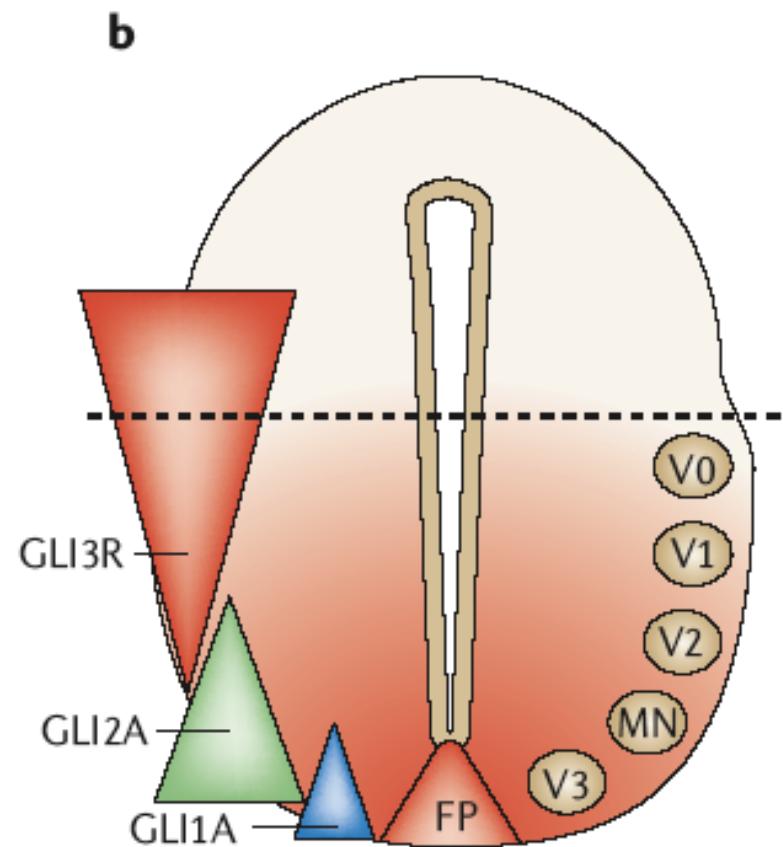
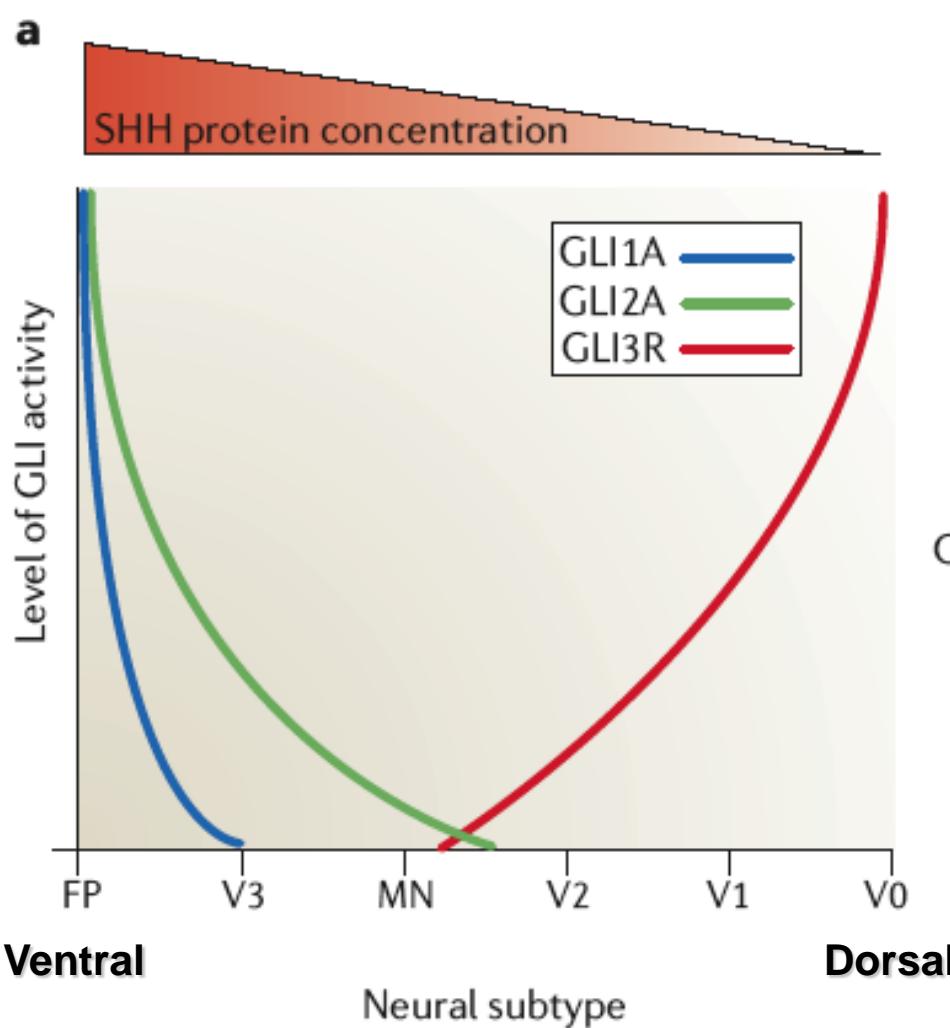
Hedgehog signaling is both complex and context dependent



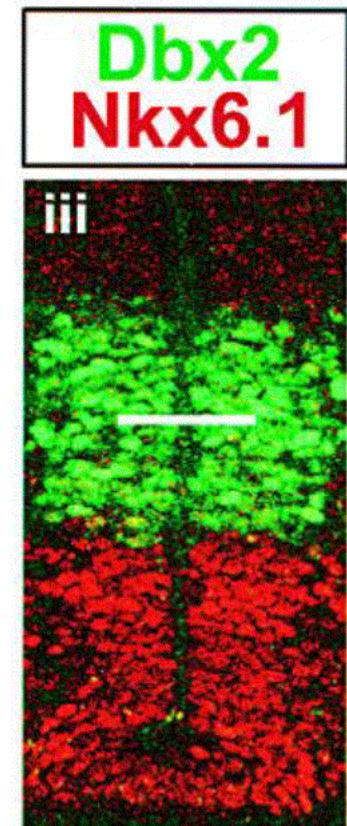
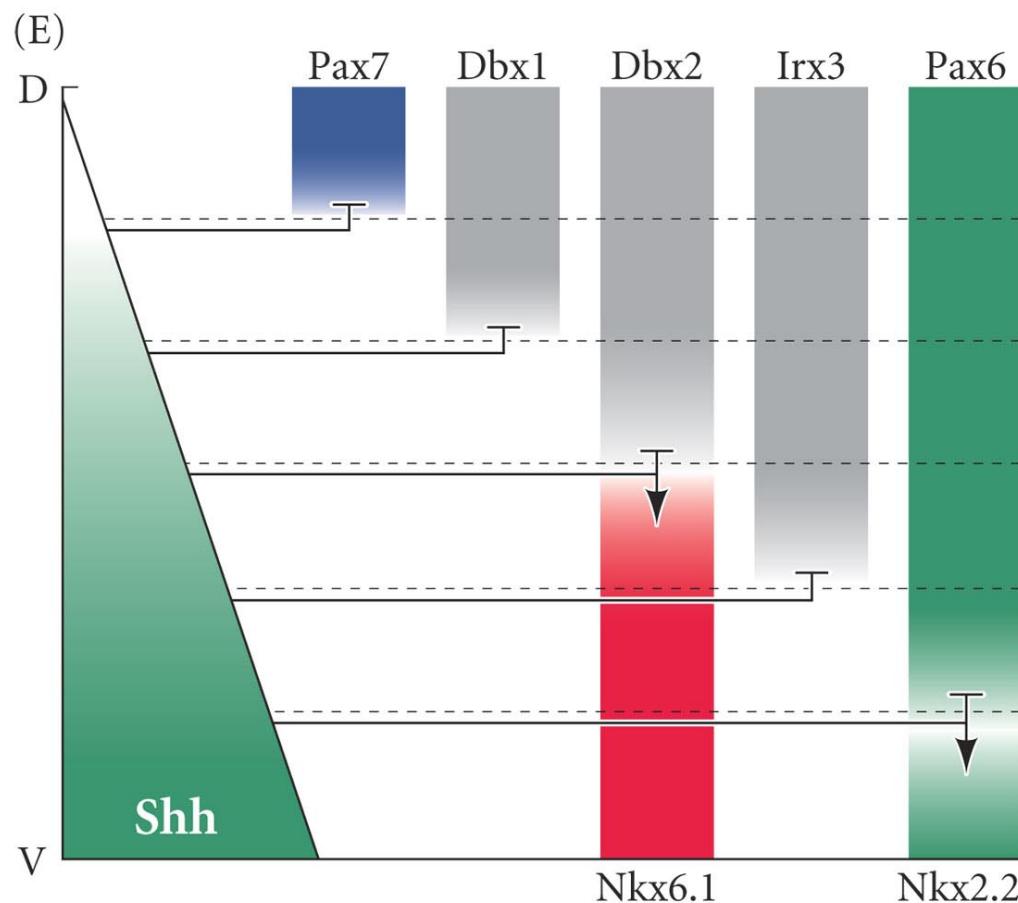
GliA : turn on ClassII genes

GliR : repress a presumed repressor
(Allows ClassI gene expression)

Model for mediation of graded Shh signaling by Gli TFs

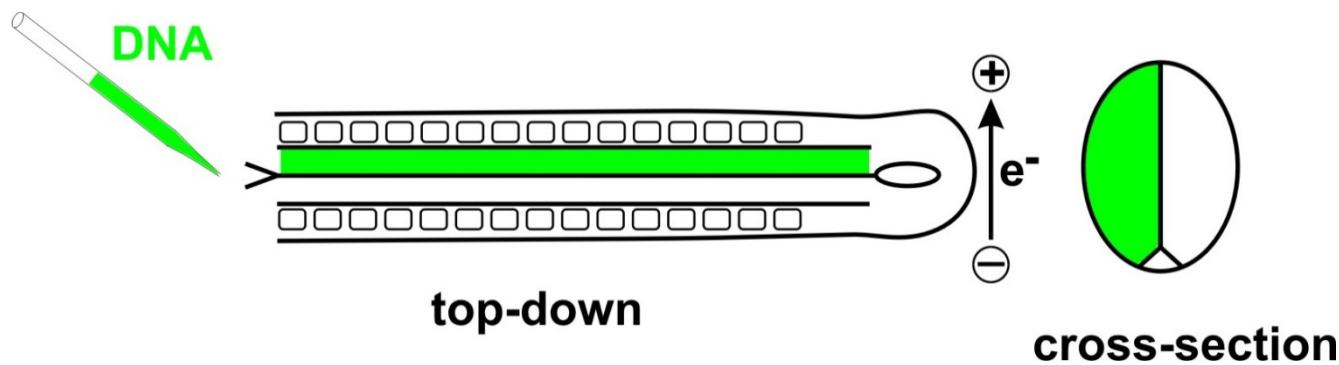
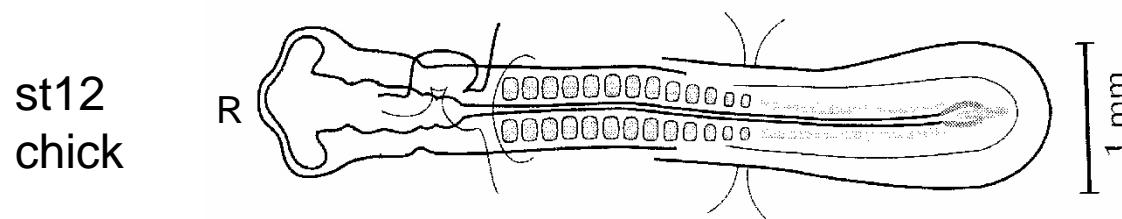


How are sharp boundaries established?

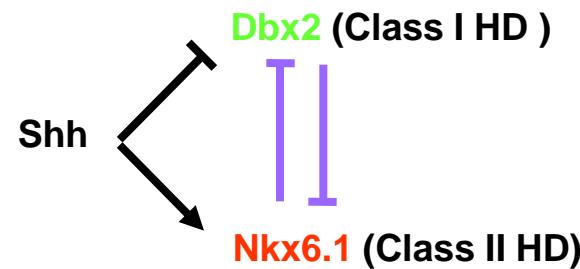
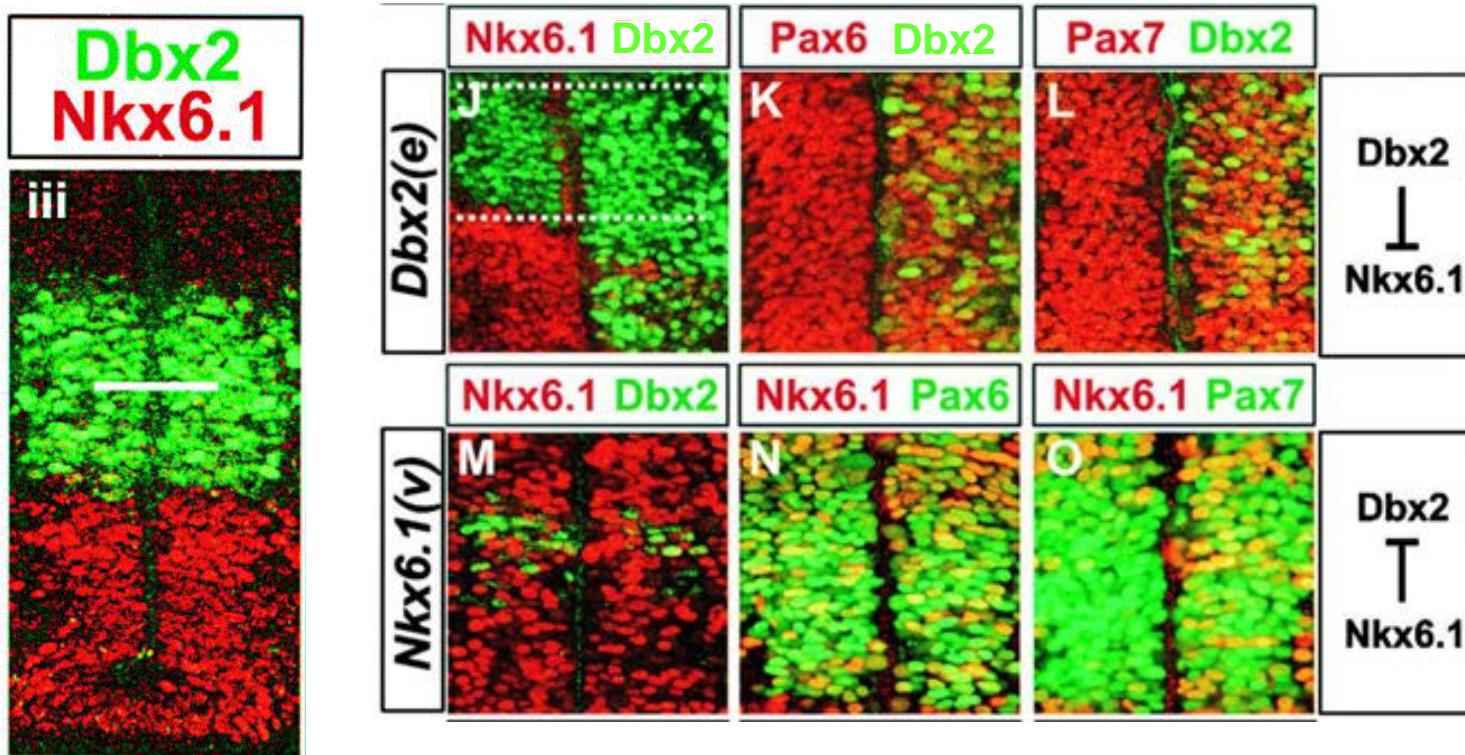


DEVELOPMENTAL BIOLOGY, Seventh Edition, Figure 12.12 (Part 3) Sinauer Associates, Inc.
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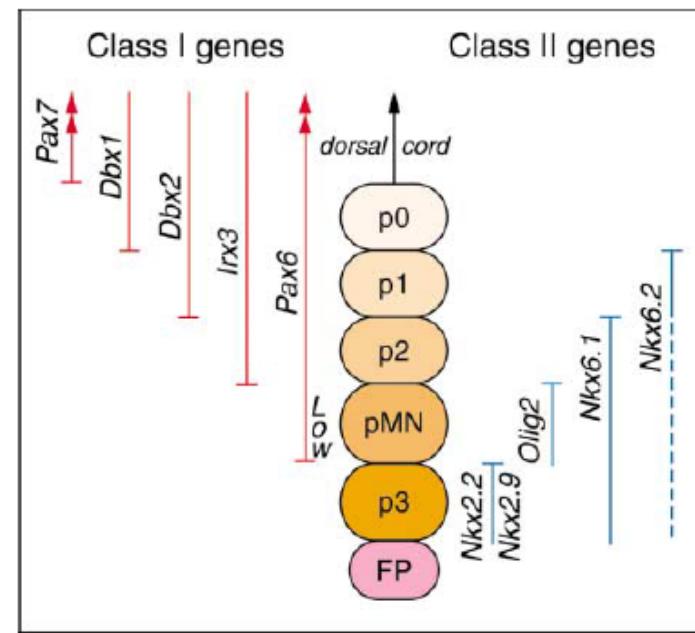
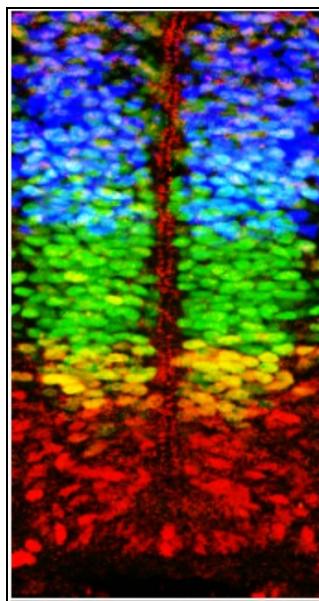
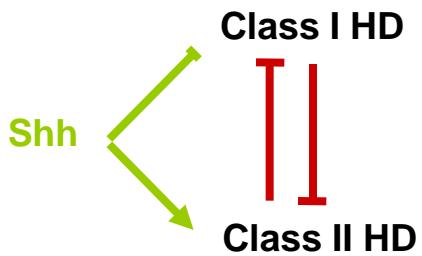
Neural tube electroporation in chick embryos



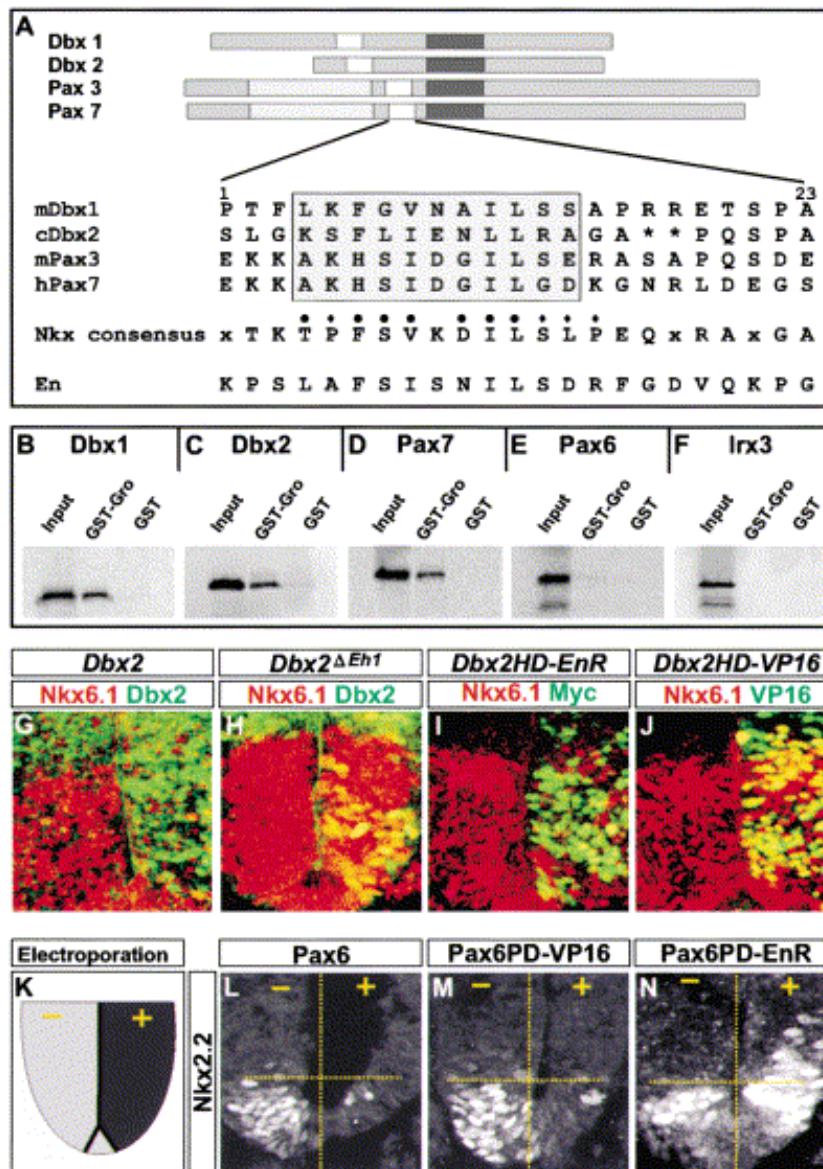
Ventral patterning via selective cross-repressive interactions



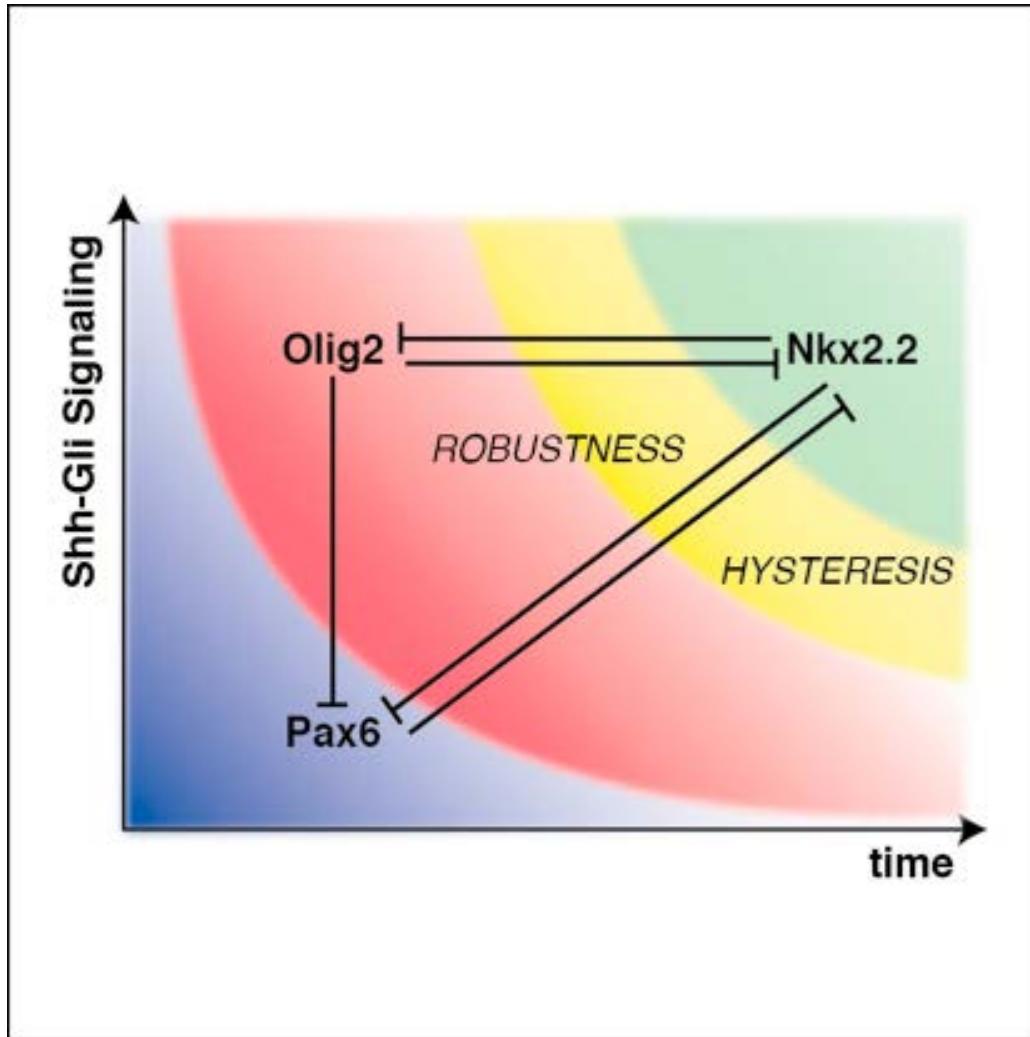
Mutual repression of Class 1 (Shh inhibited genes) and Class 2 (Shh induced genes)
Cross regulate to specify different spinal cord populations.



Boundaries shaped along the DV axis by Groucho co-repressors



TF network interactions as a memory of the signal

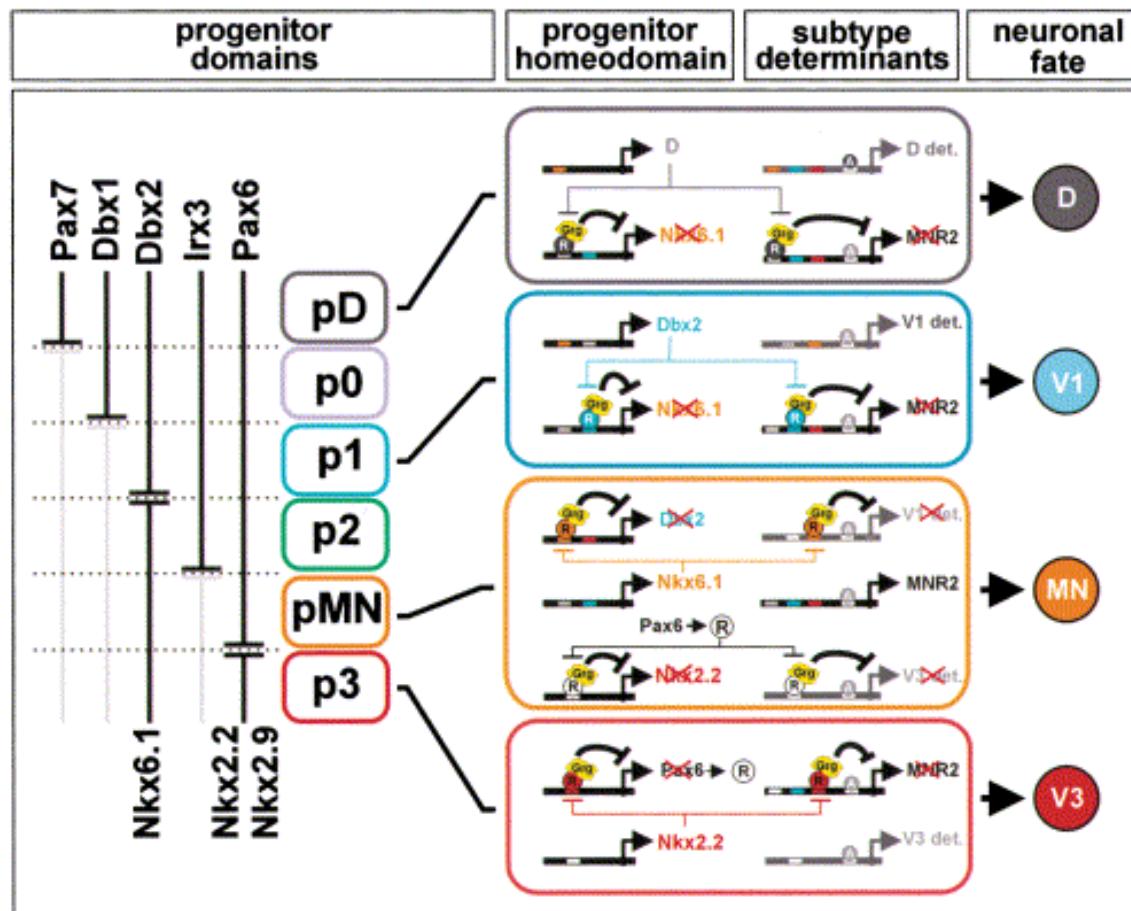


TF network:

“Memory” of the patterning signals

Renders cells refractory to fluctuations in signaling

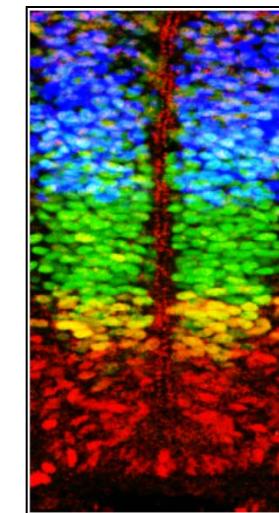
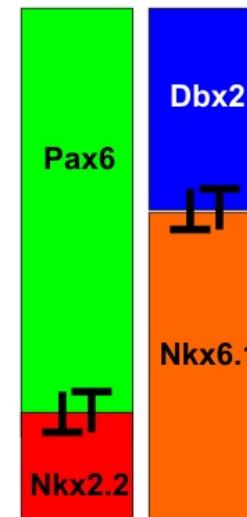
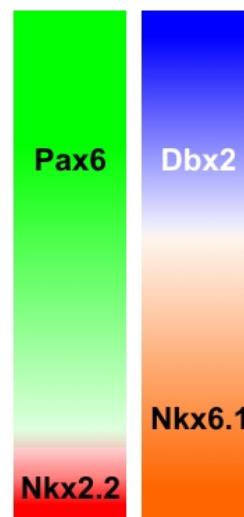
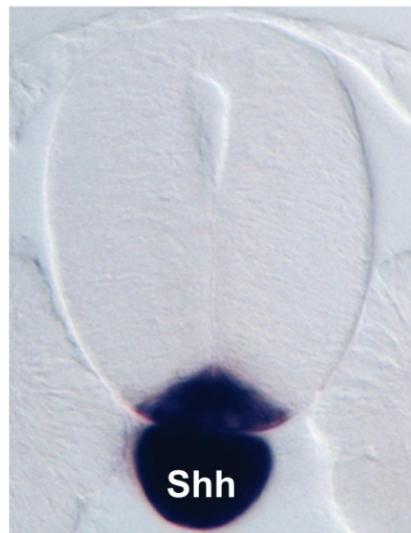
A “derepression” strategy specifying classes of neural progenitors



Are there
Any specific activators
In the system?

To what extent do
postmitotic factors
control identity?

Establishing neuronal identity in the ventral spinal cord



- ● V0
- ● V1
- ● V2
- ● MN
- ● V3

*Graded
Inductive signals*

*Transcription
factor
expression*

*Cross-repressive
interactions*

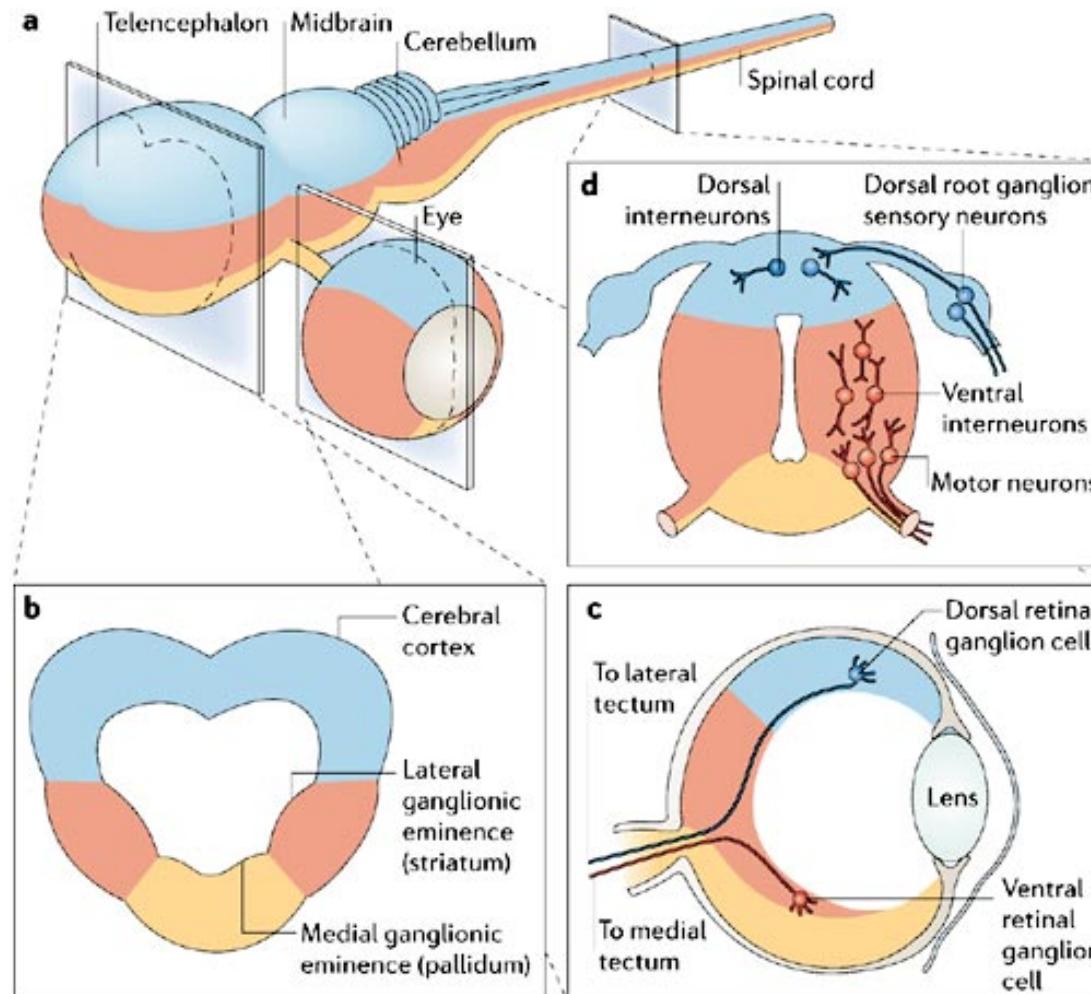
*Neural
progenitor
cell types*

*Postmitotic
neuronal
classes*

**How the Shh gradient is interpreted not well understood
Few targets for any of the TFs are known**

**Appears to be a highly conserved mechanism for generating
diverse CNS cell types**

Dorsoventral patterning in the nervous system



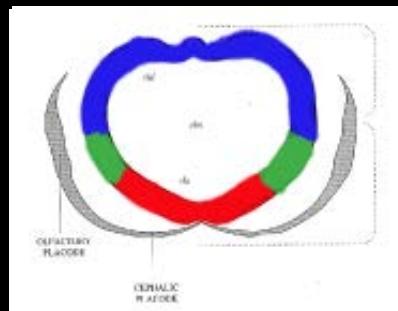
Dorso-ventral regionalization in the telencephalon

E9.5

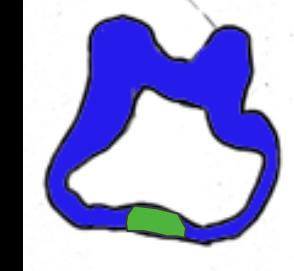
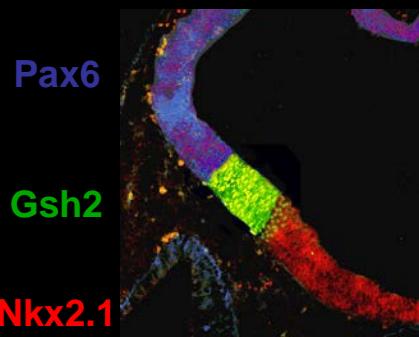
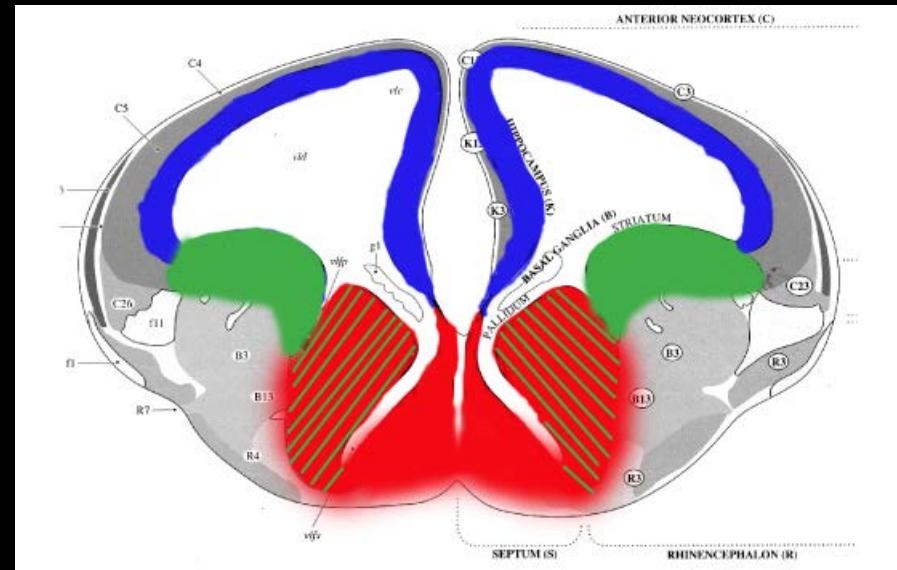
Dorsal
Pax6,
Emx1/2,...

Lateral
Gsh2;
Dlx1/2;...

Ventral
Shh; Nkx2.1;...



E12.5

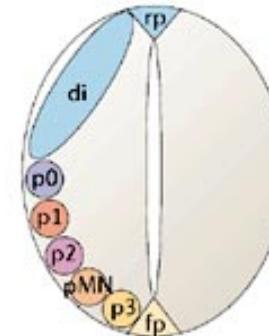
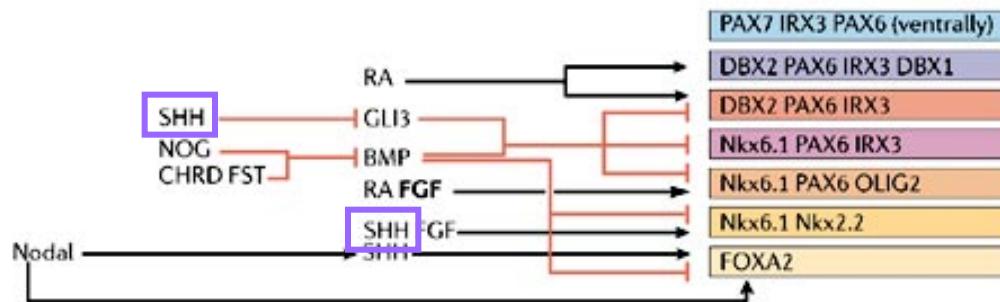


Shh -/-

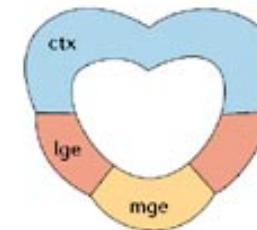
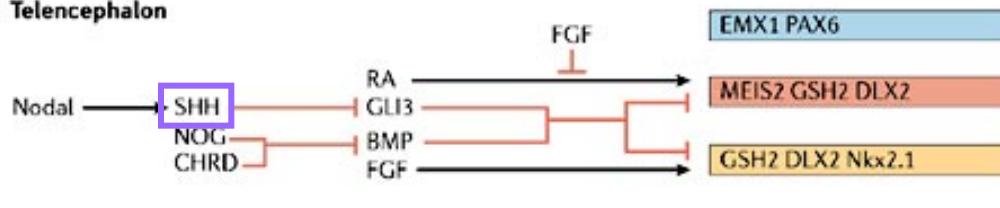
These region-specific genes are necessary for the proper development of the region in which they are expressed

Common signals regulate DV patterning in the CNS

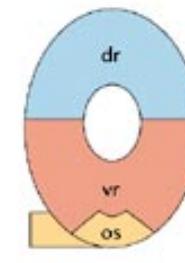
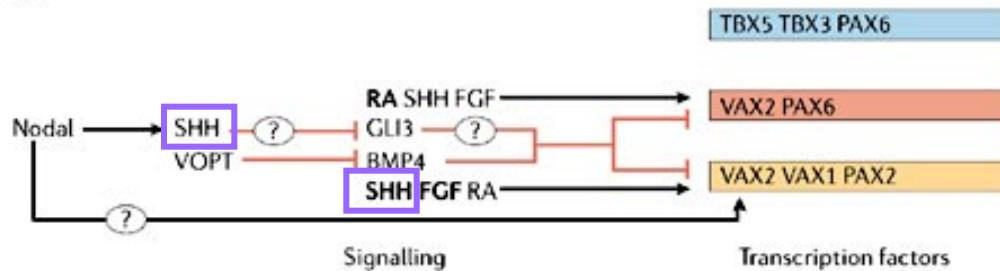
a Spinal cord



b Telencephalon

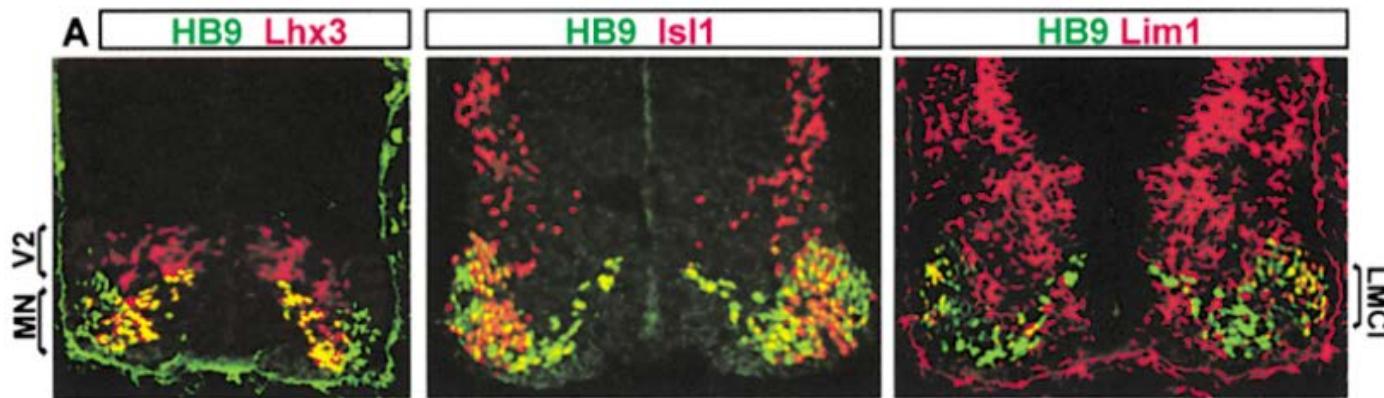
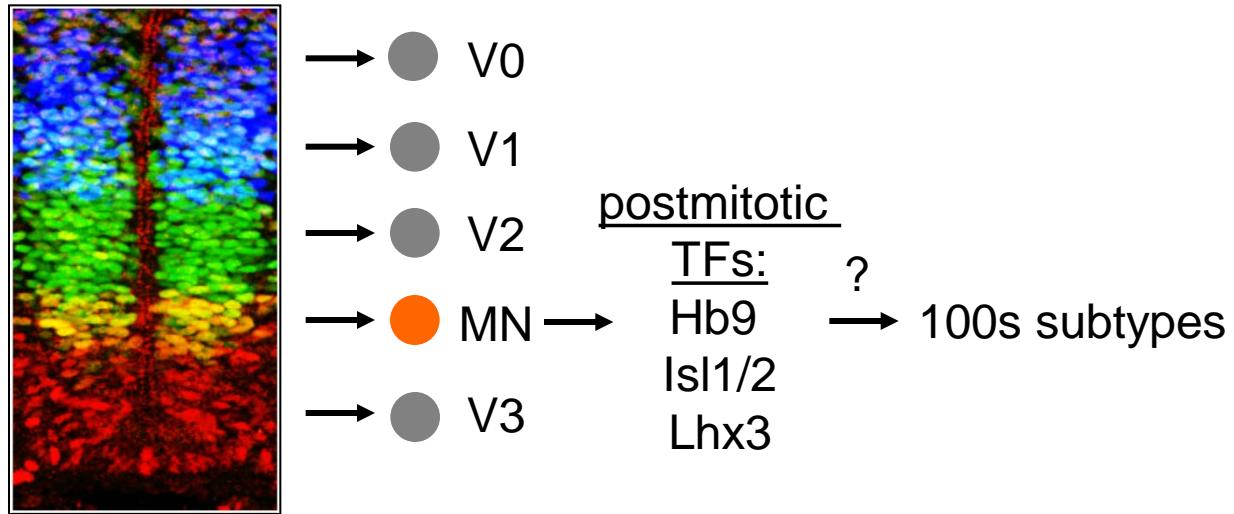


c Eye



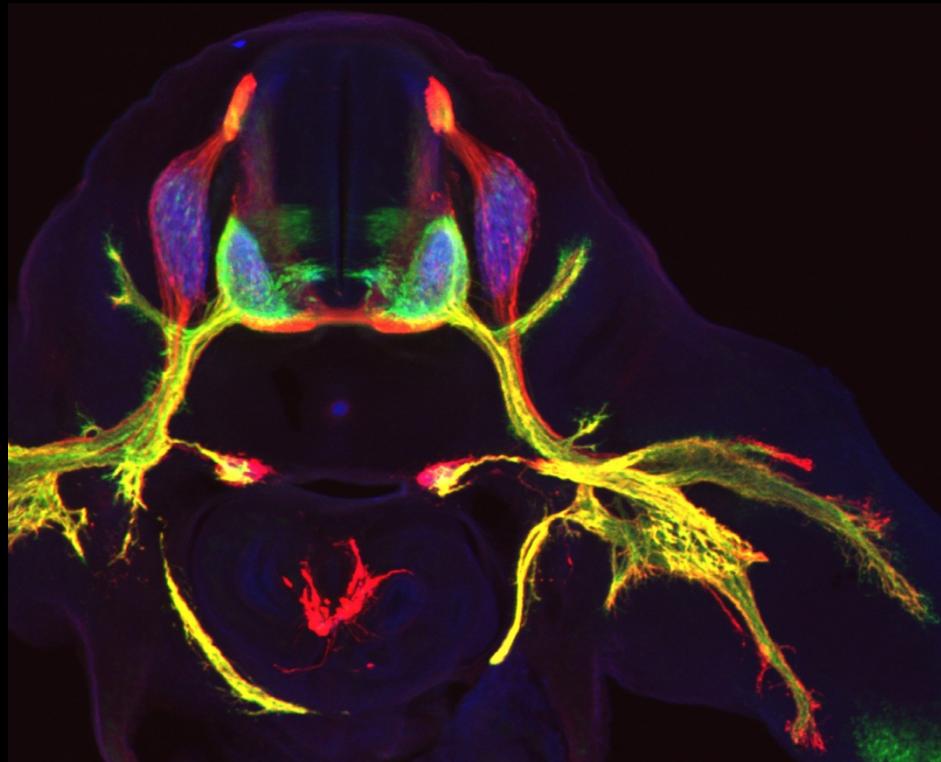
Beyond D/V patterning

How are neurons within a specific class further diversified?

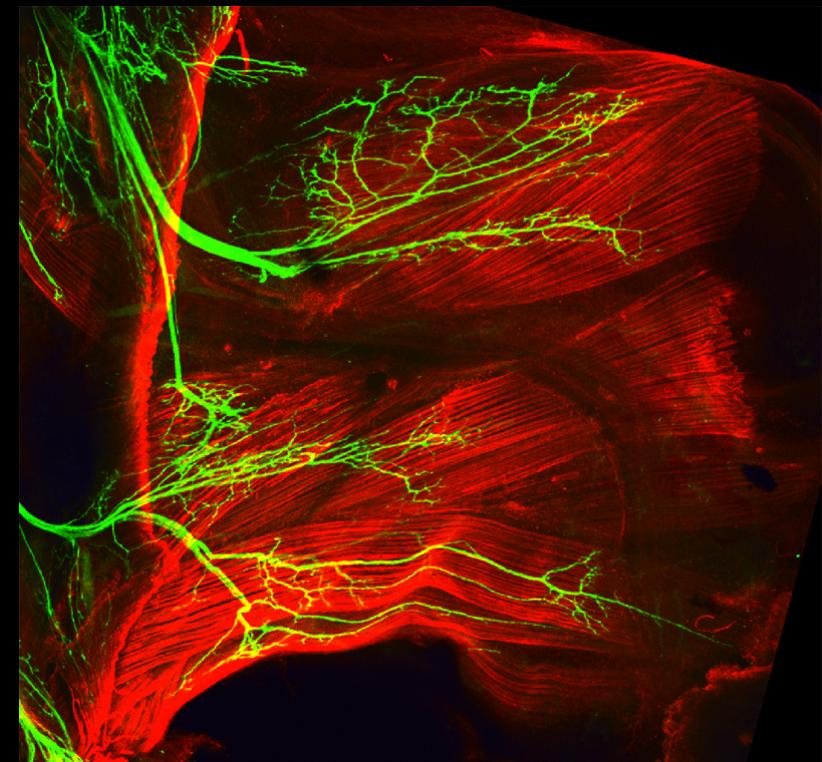


Motor neuron diversity and connectivity

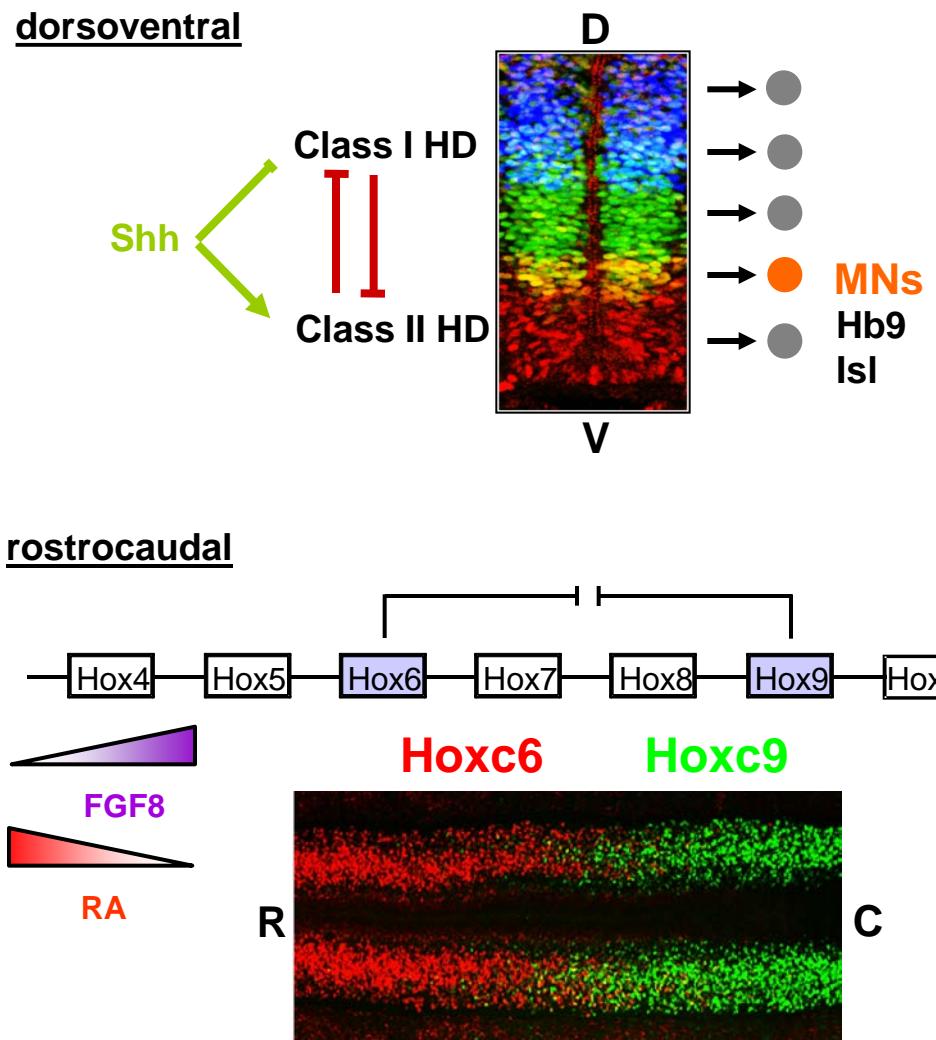
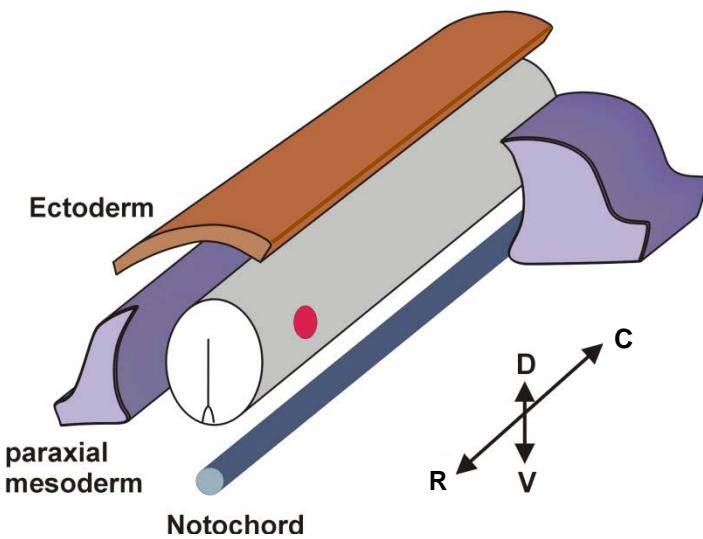
Hb9-GFP NF



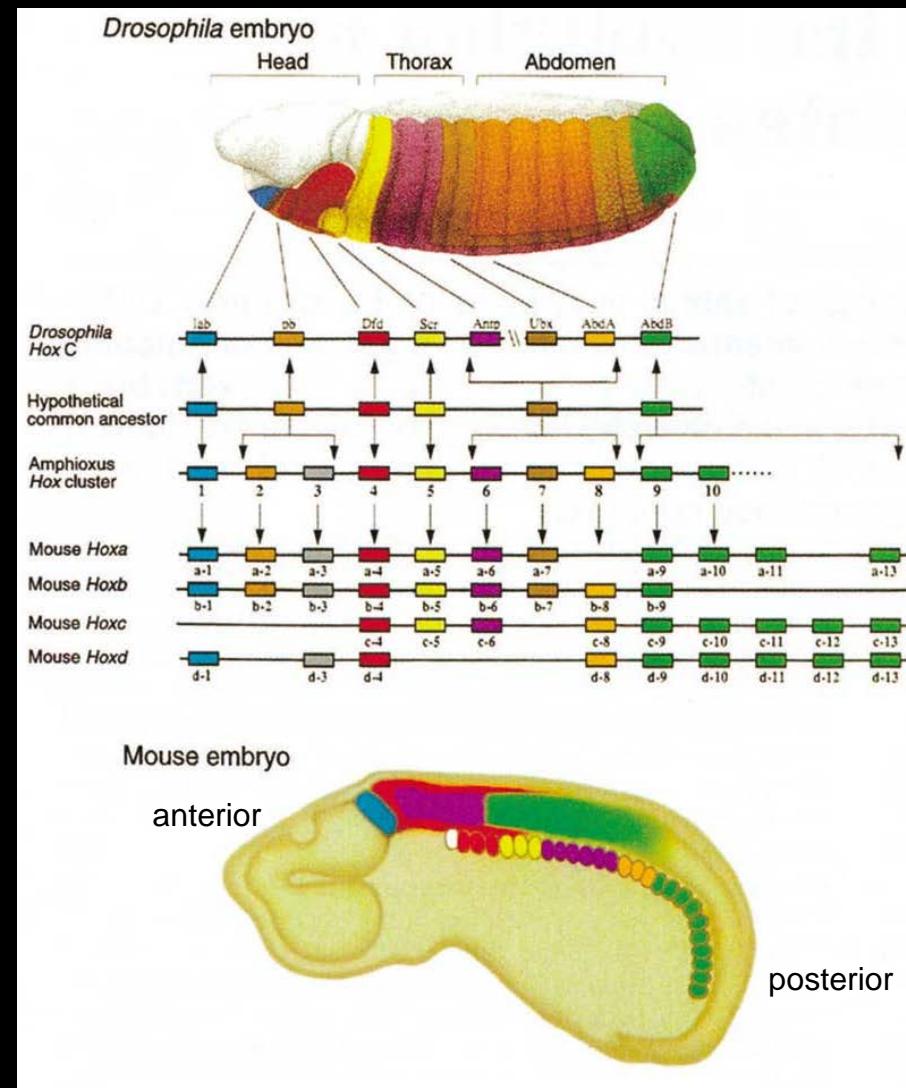
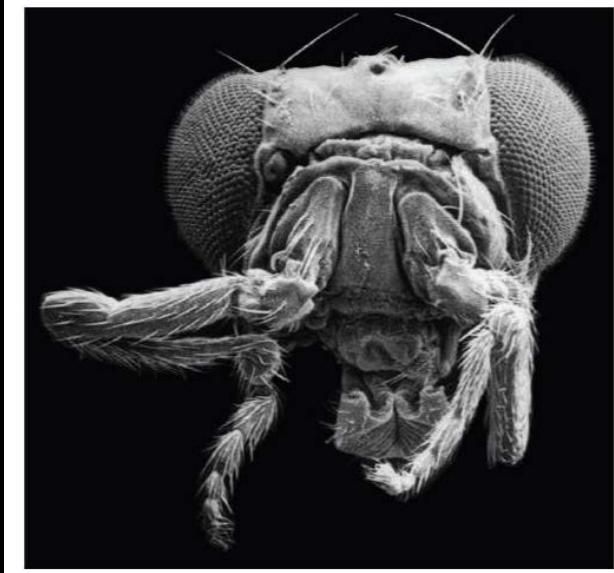
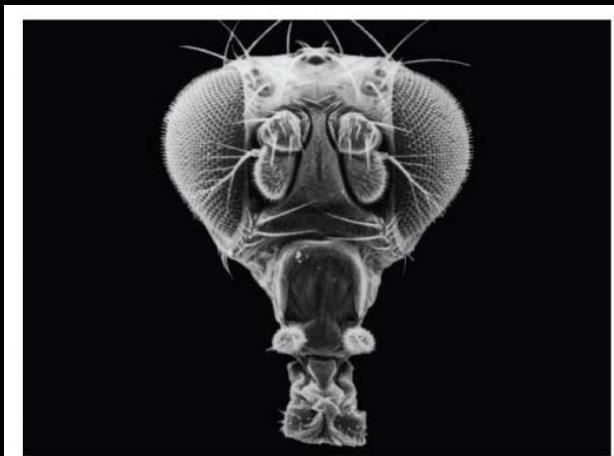
Hb9-GFP Myo



Generation of motor neuron identity and diversity

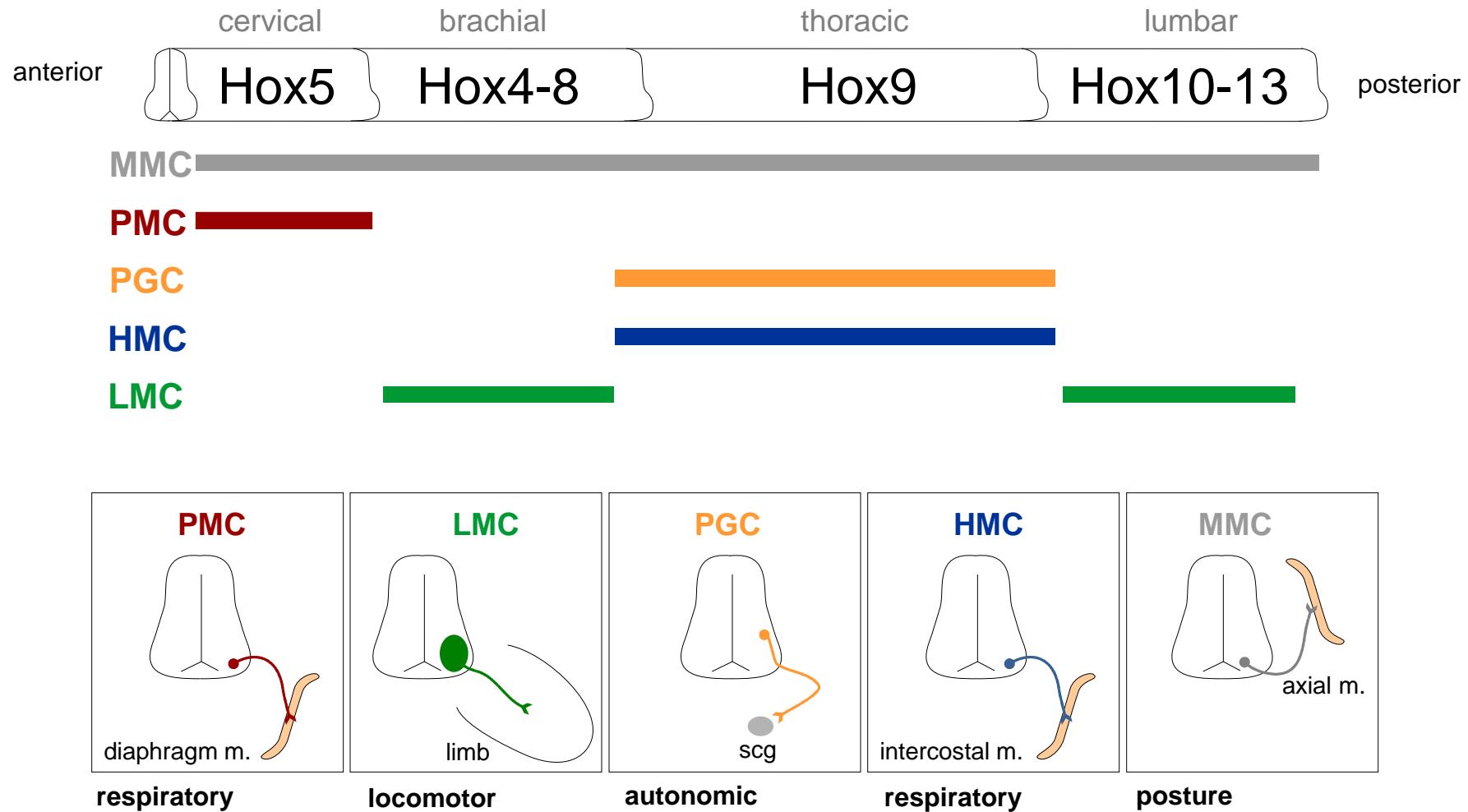


Hox genes as master regulators of metazoan development

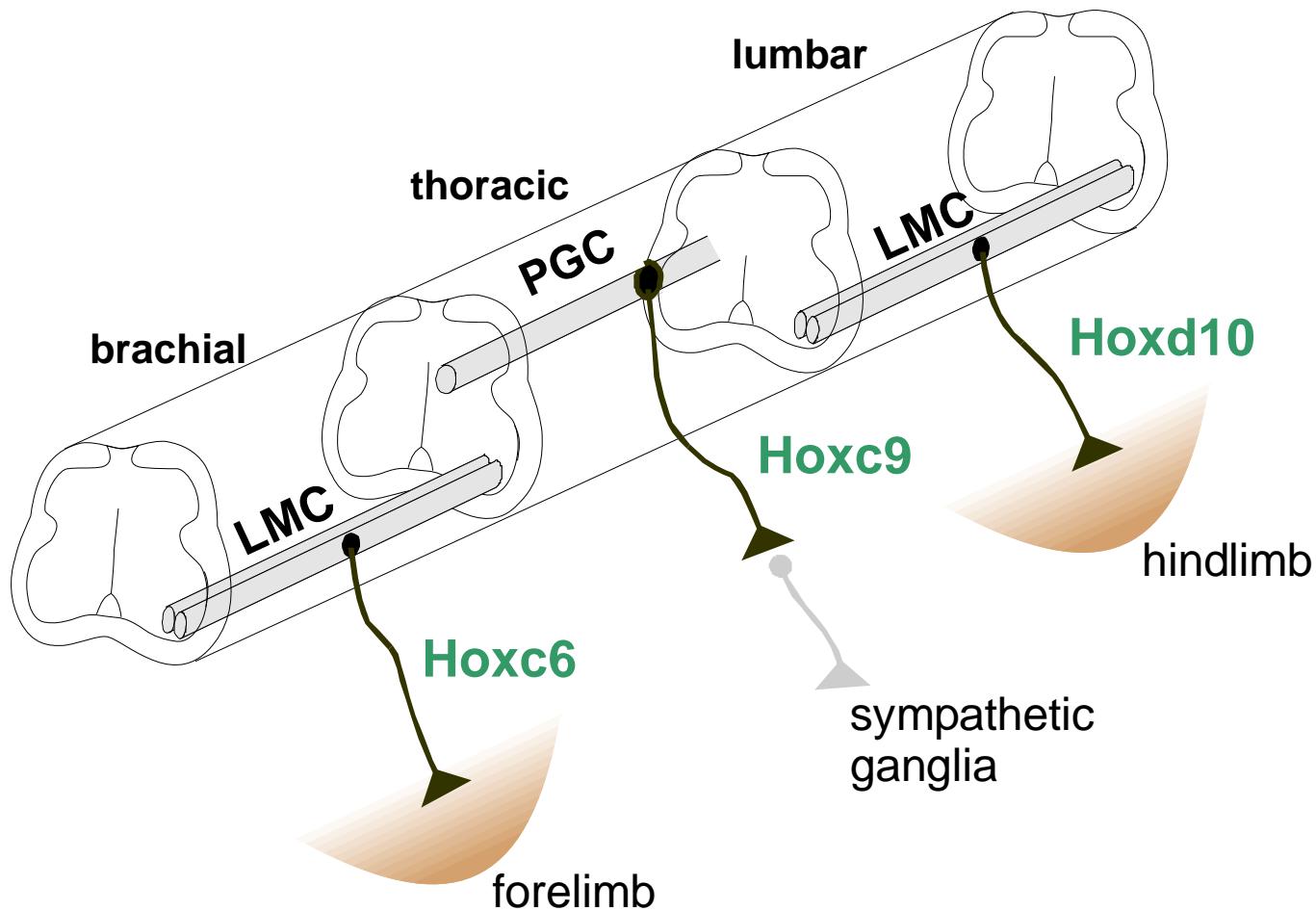


Antennapedia (Antp)

Columns and modularity of motor behaviors



Motor neuron columnar identity and connectivity



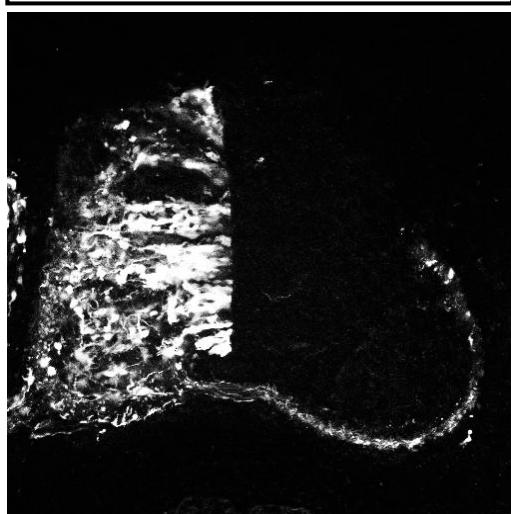
migration & settling

axonal trajectory

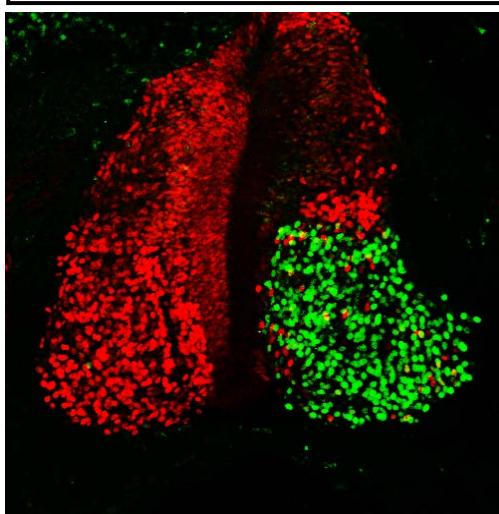
target selection

Hox gene induction and MN columnar fates

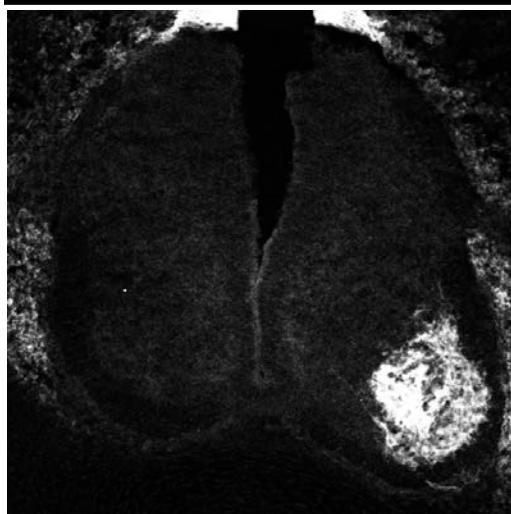
FGF8 / GFP



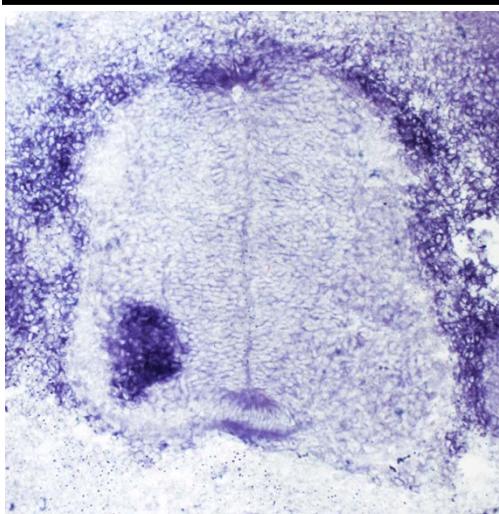
Hoxc9 Hoxc6



Raldh2

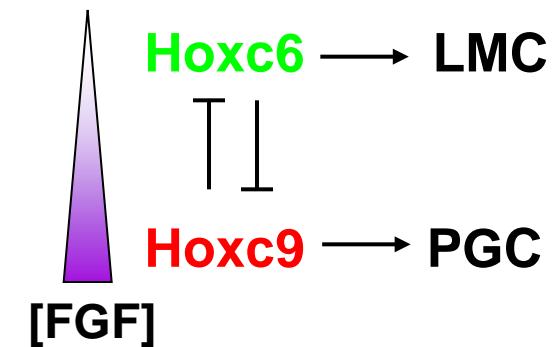


Bmp5

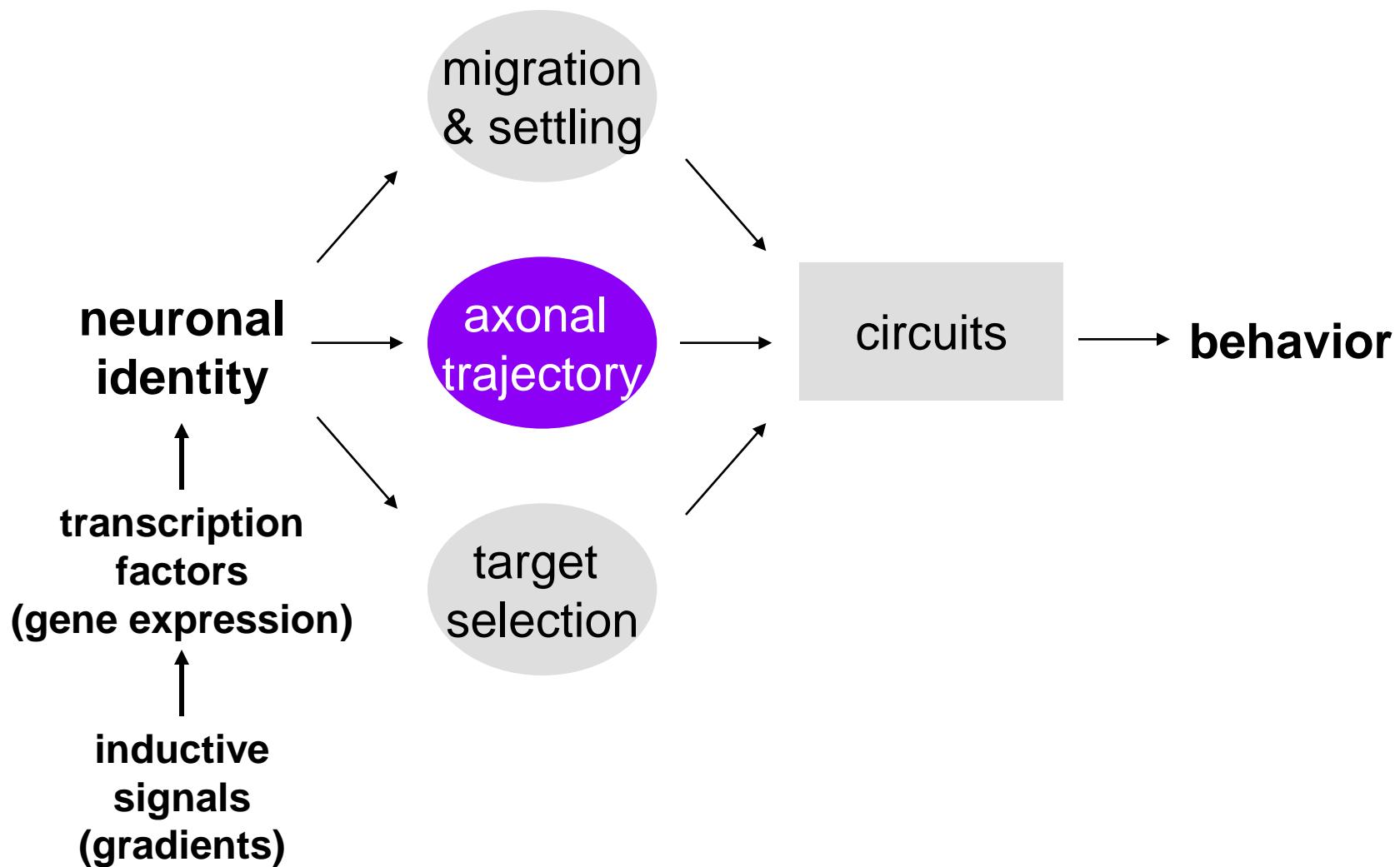


LMC

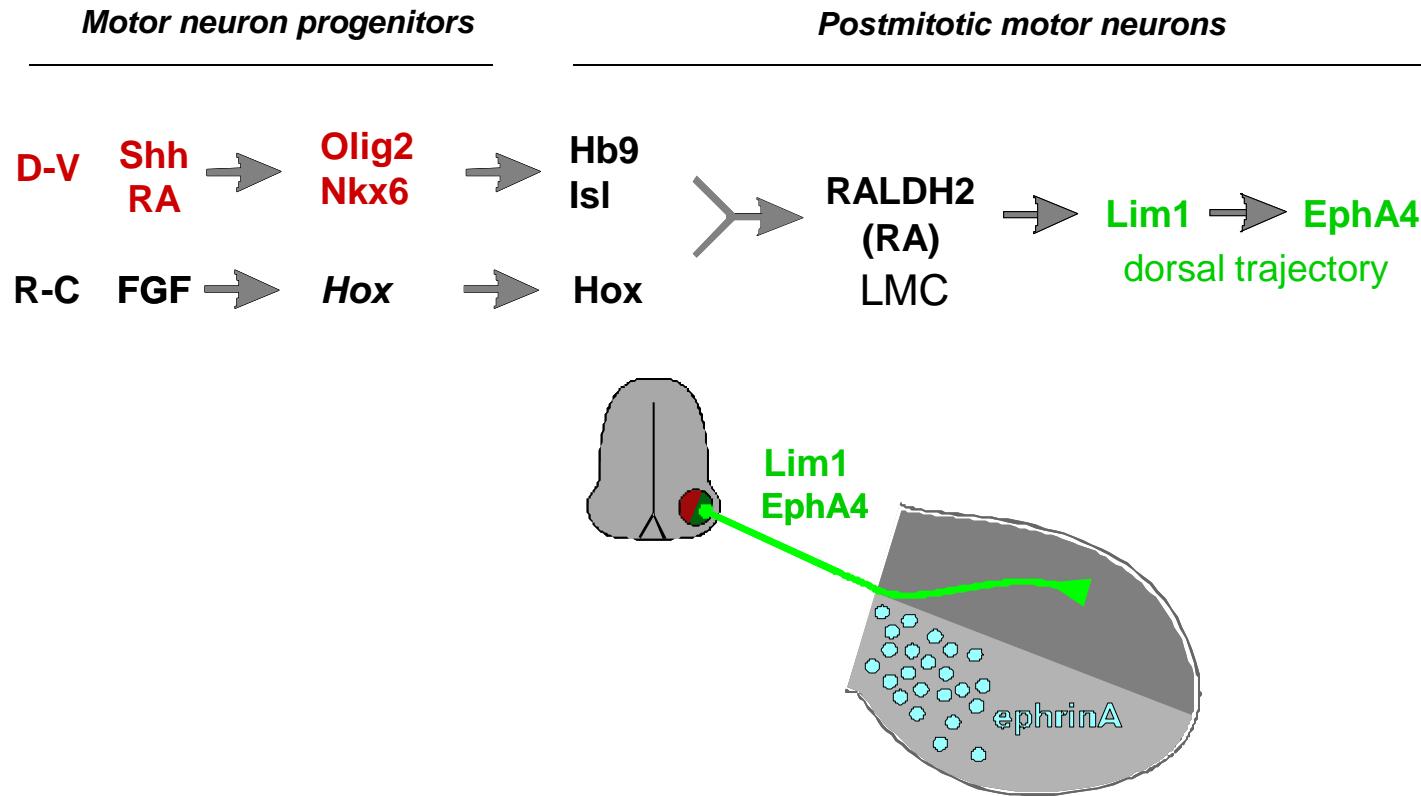
PGC



Neuronal identity as a determinant of circuit assembly



Convergence of DV and AP in determining projection specificity

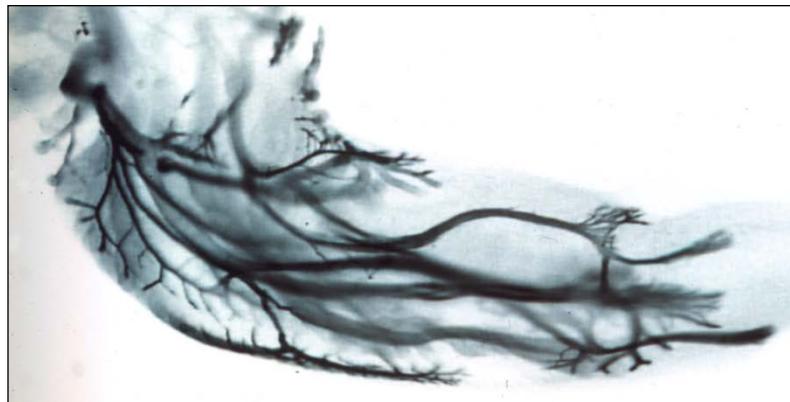


Innervation of limb musculature

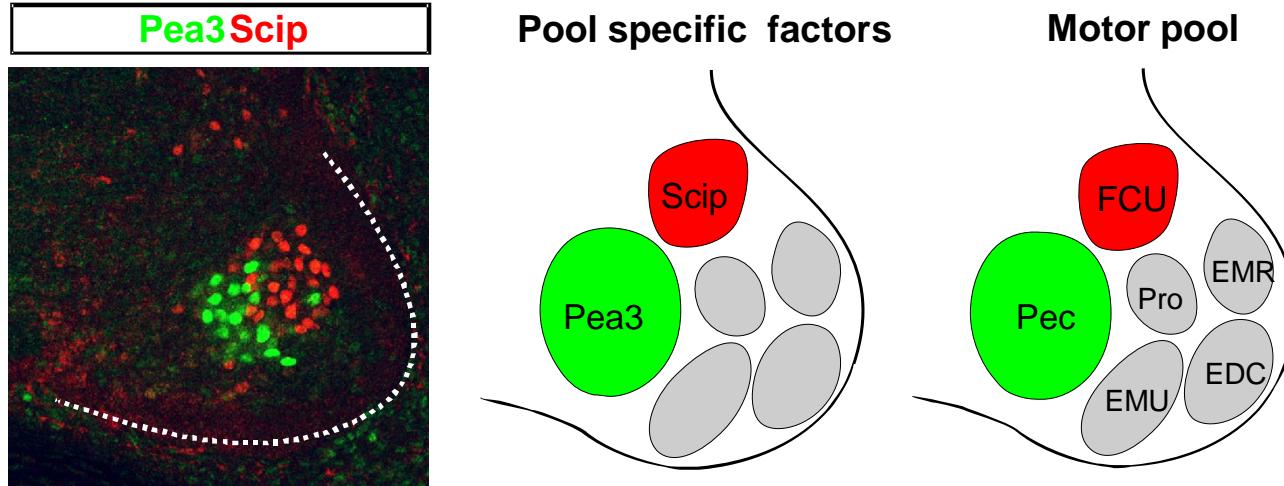
**forelimb
muscles**



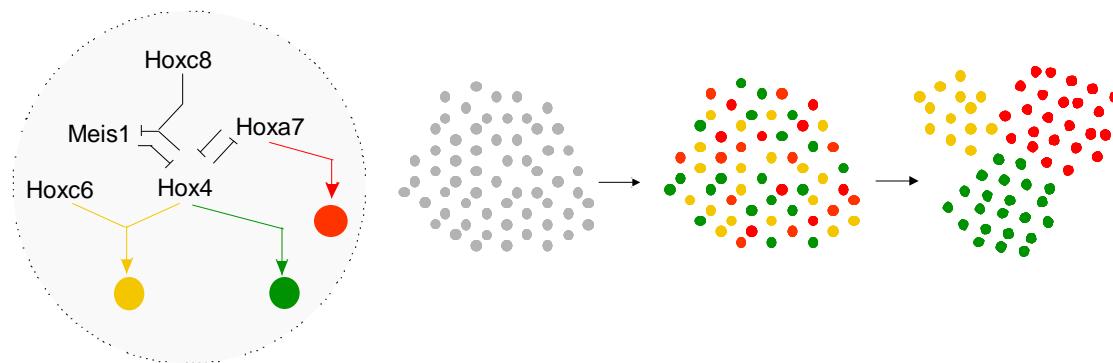
**motor
axons**



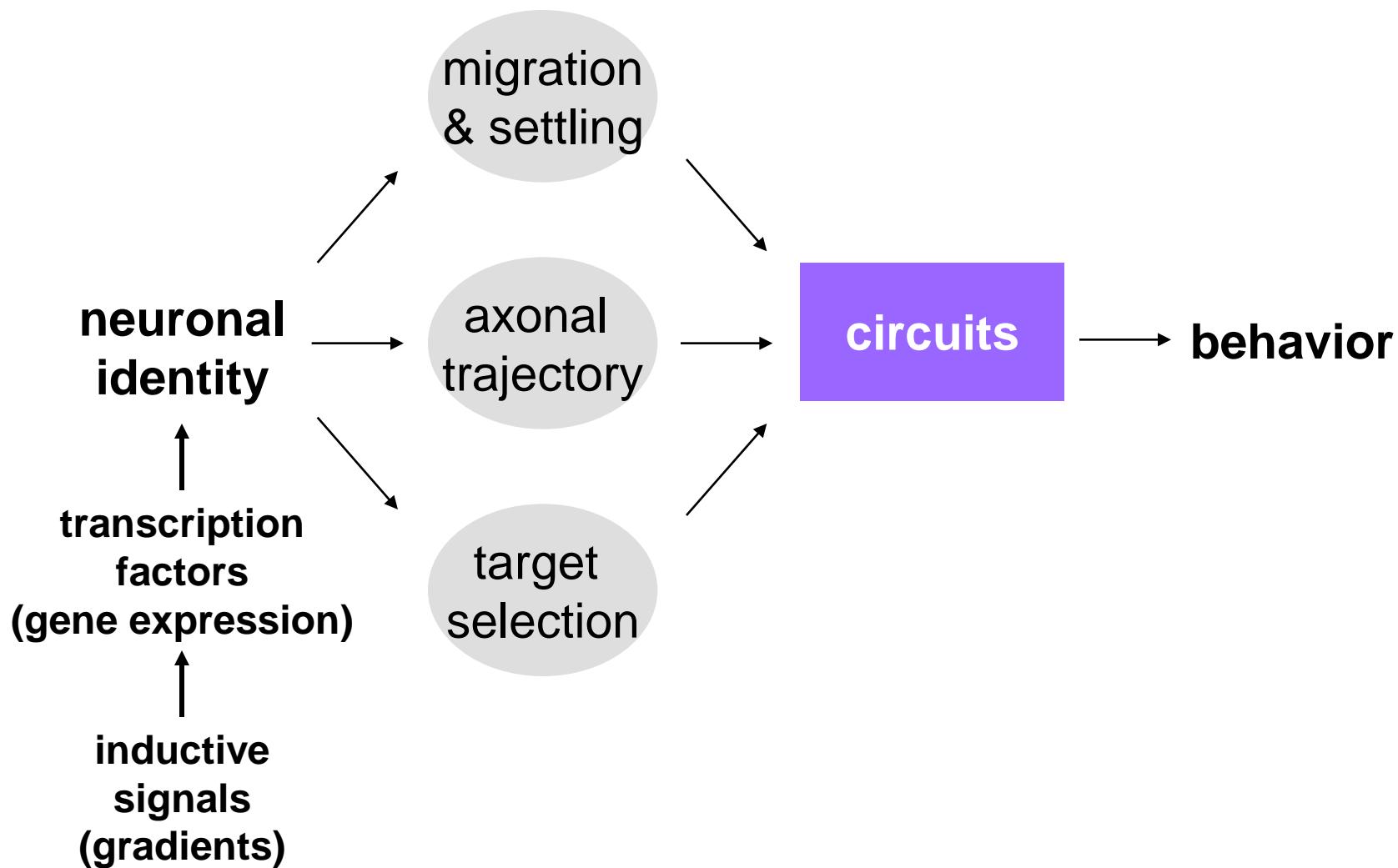
The intrasegmental diversity of motor pools



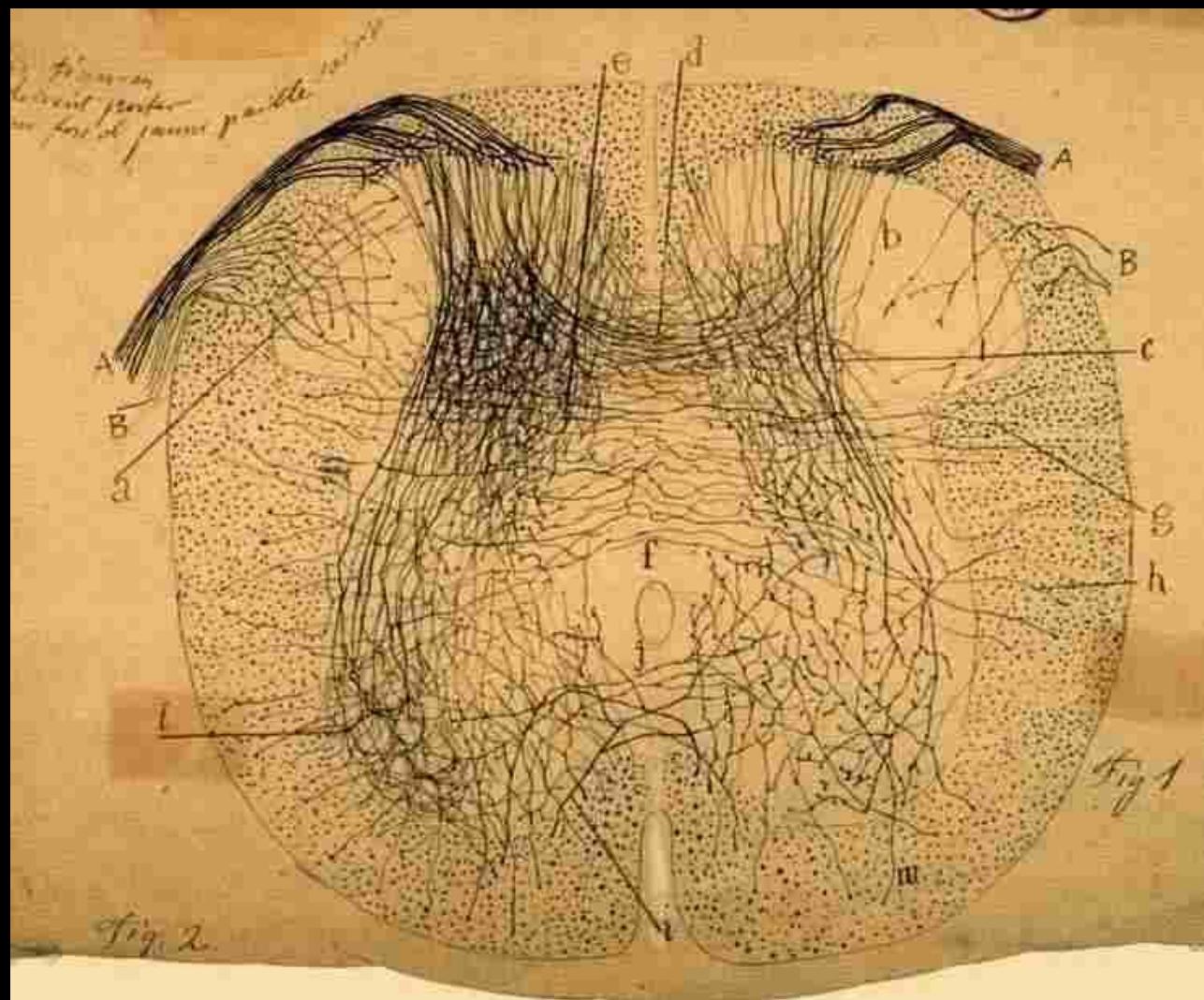
“repressilator” network



Neuronal identity as a determinant of circuit assembly

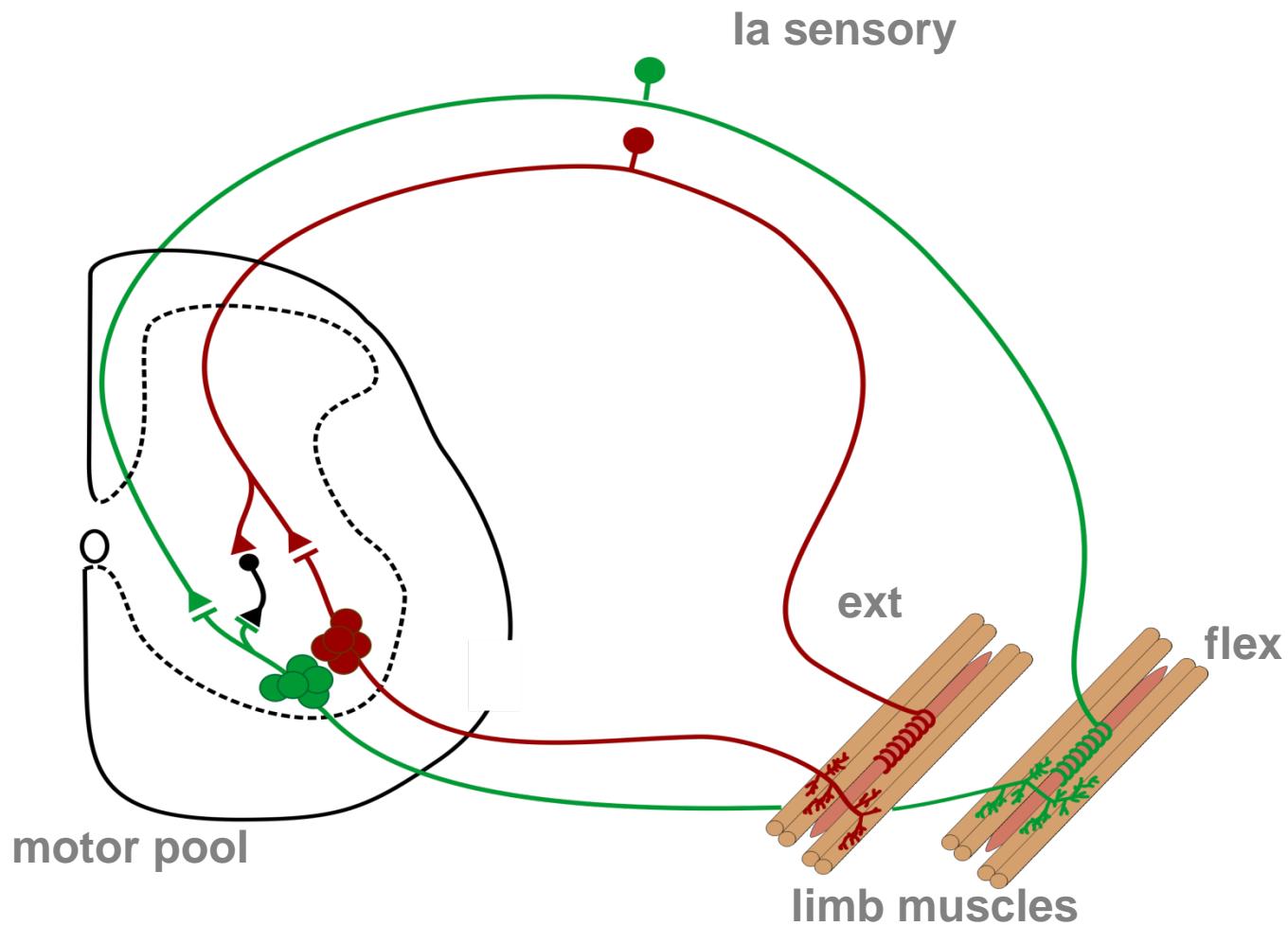


Sensory projections in the spinal cord



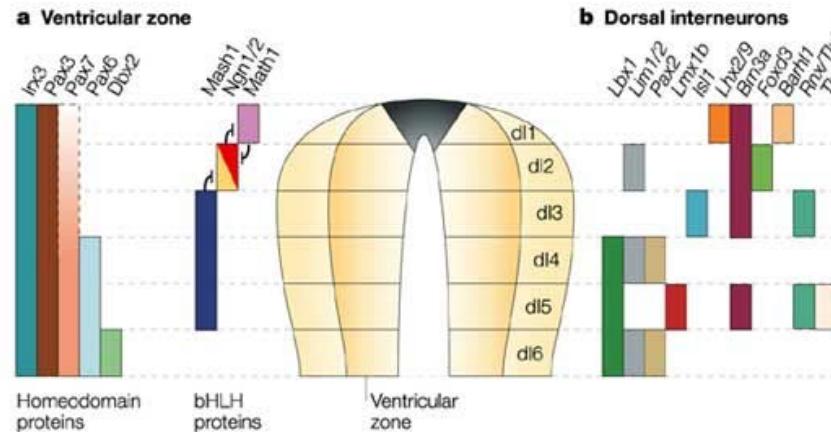
Cajal

The monosynaptic stretch reflex circuit



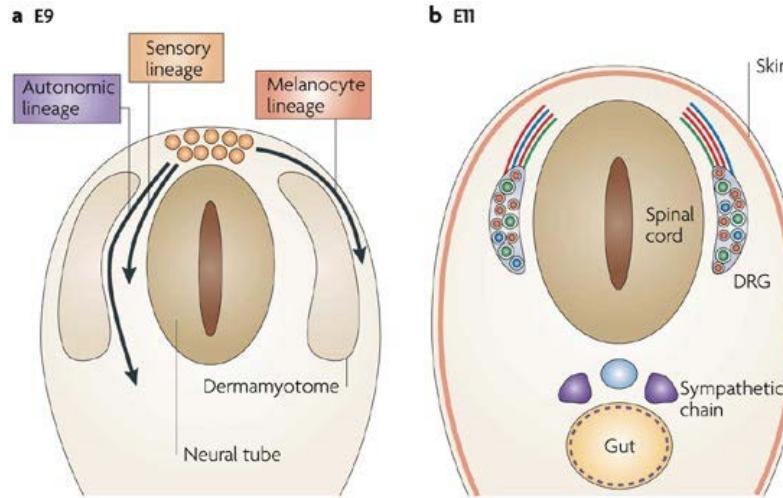
Specification of neural cell types in the dorsal spinal cord

Dorsal interneurons

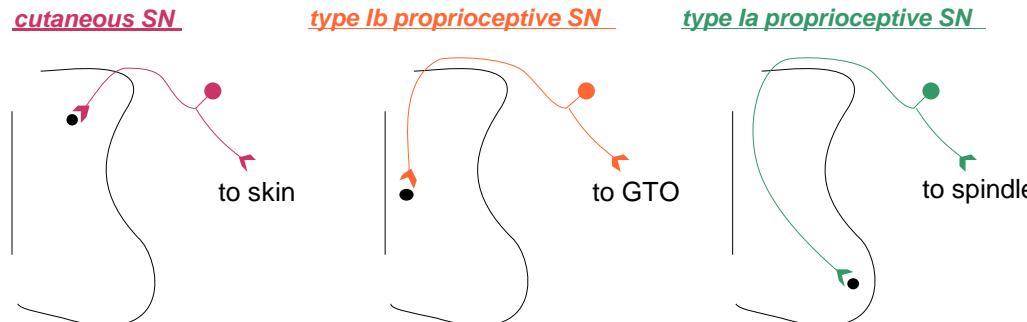
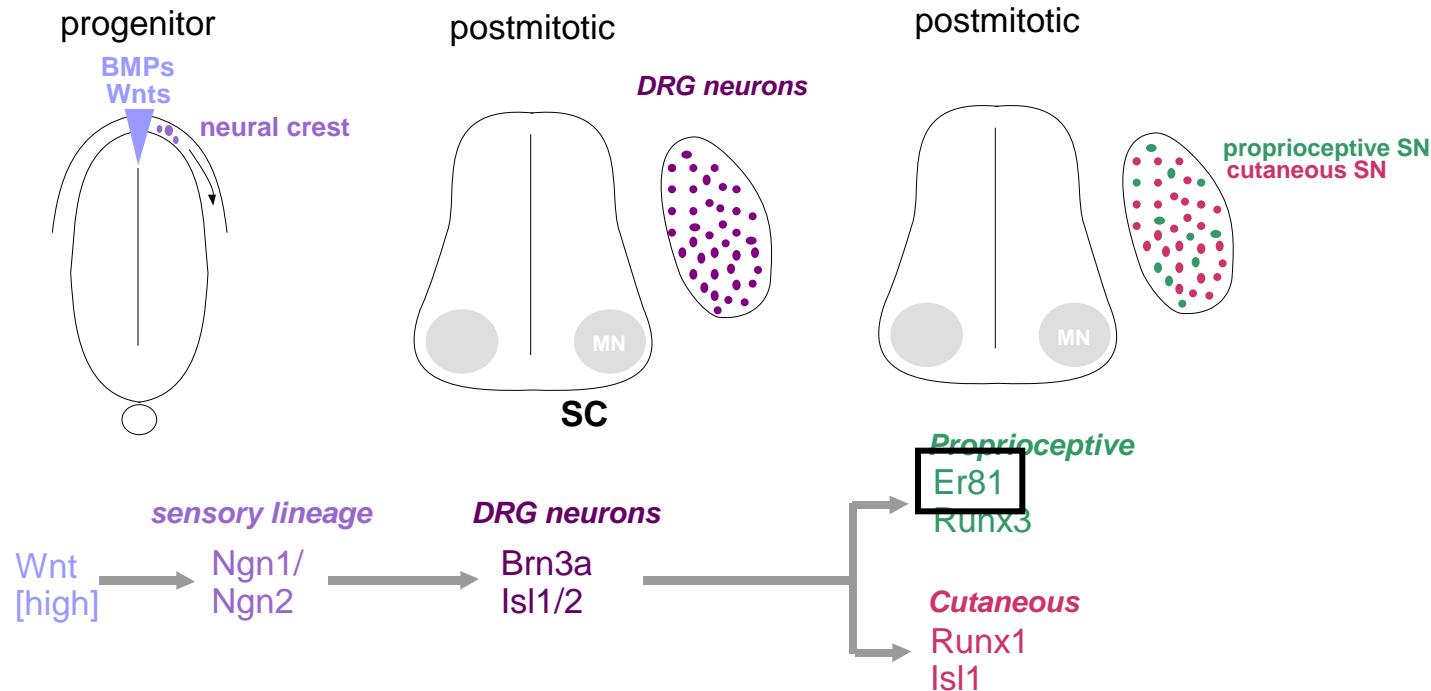


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Neural crest-derived

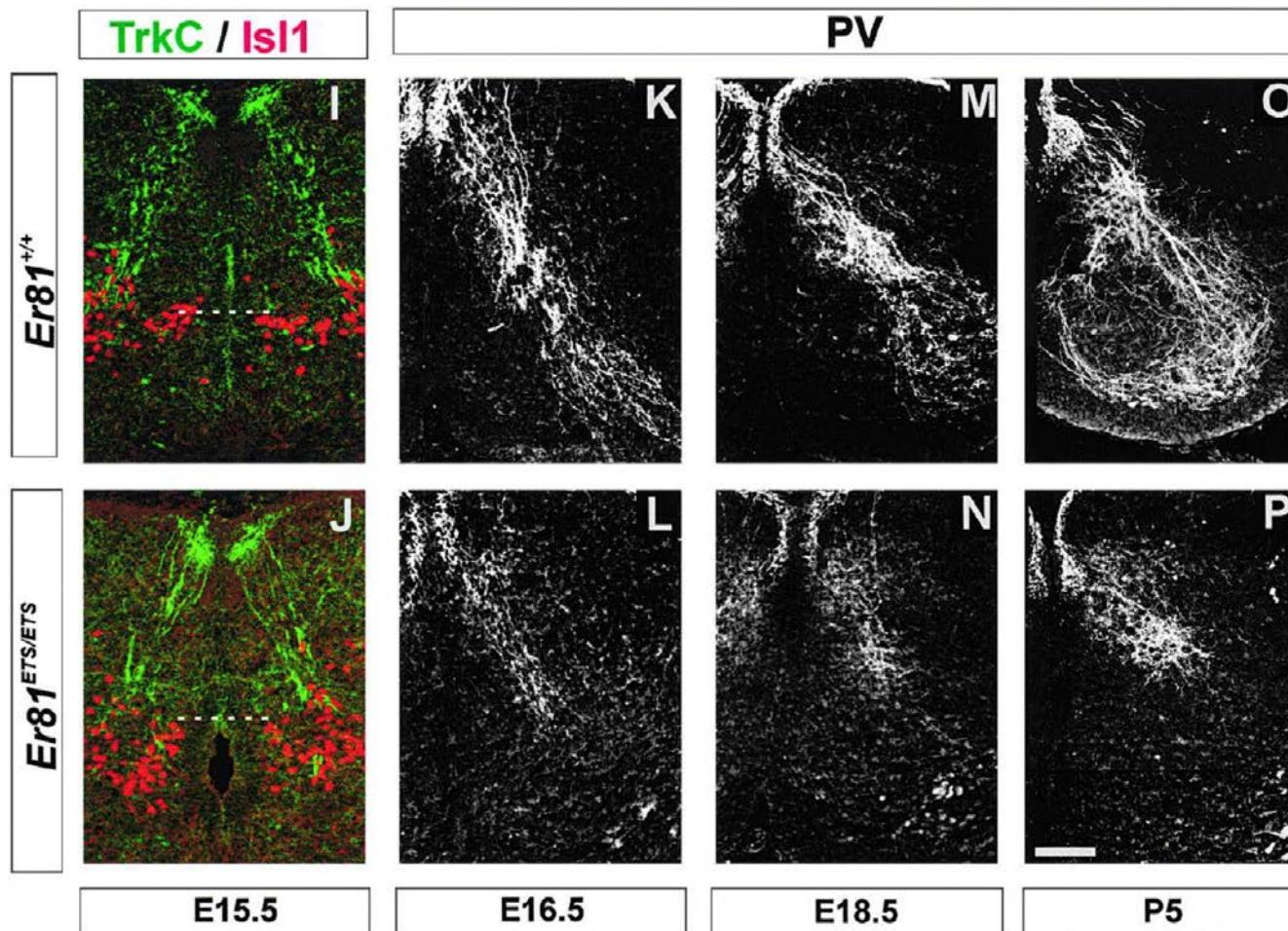


Steps in the generation of DRG sensory neurons



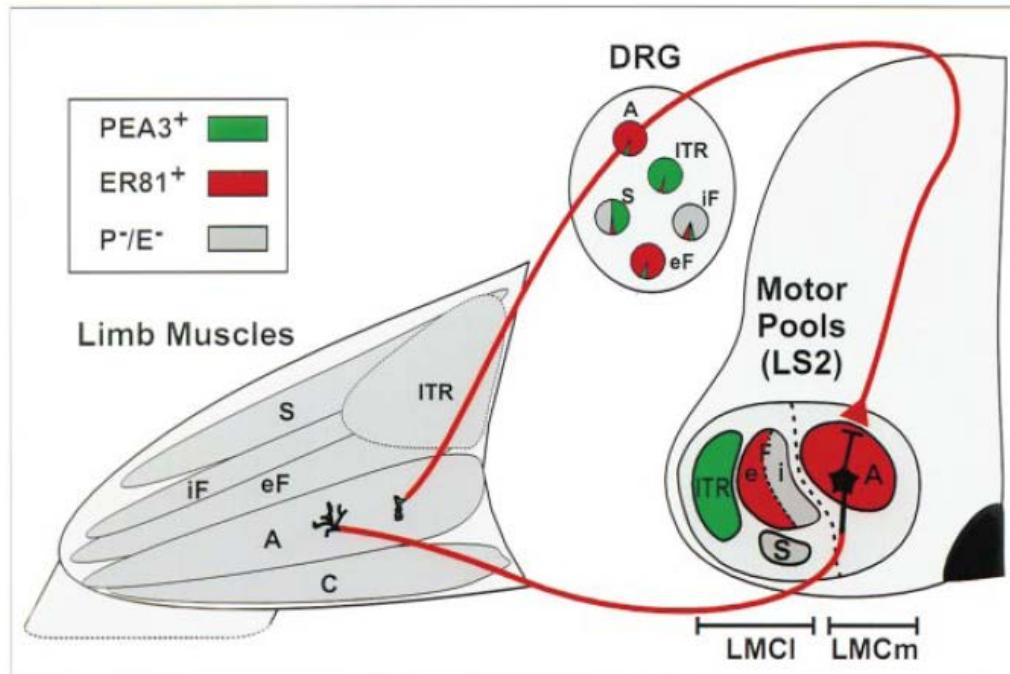
SN identity:
Peripheral connectivity?
Central connectivity?

Er81 is required for sensory-motor connectivity



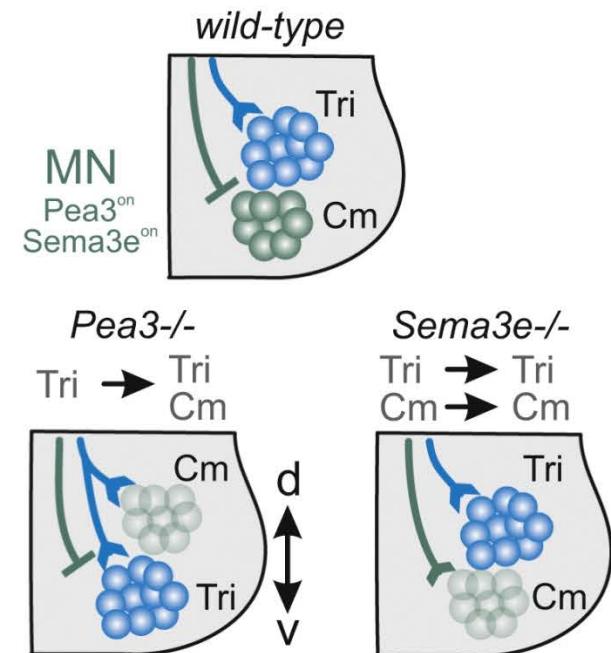
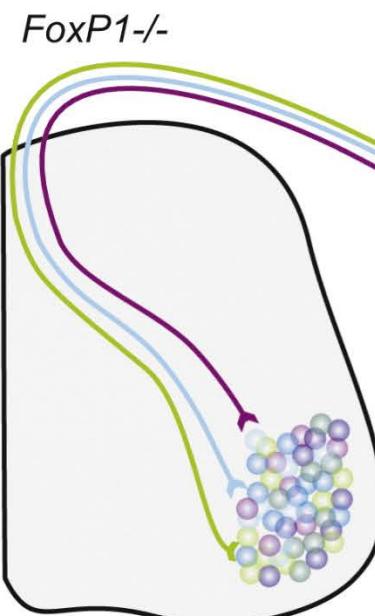
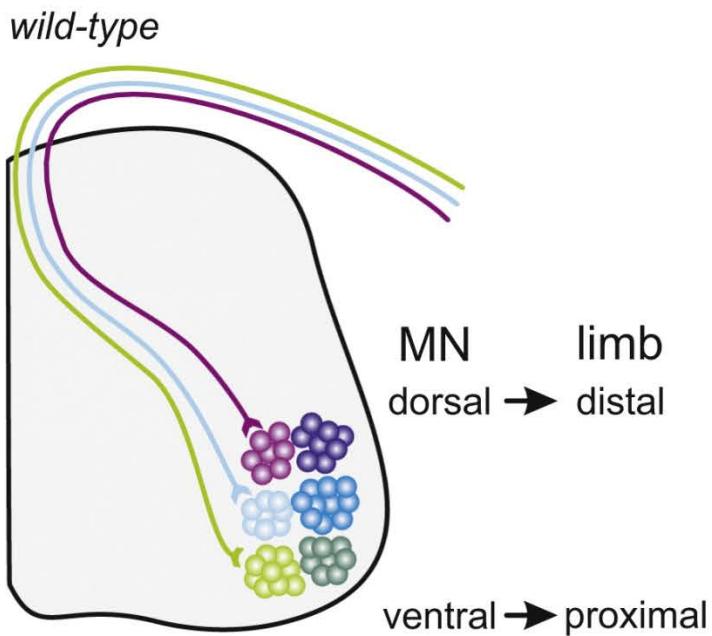
Molecular matching of neurons sensory-motor circuits

ETS transcription factors

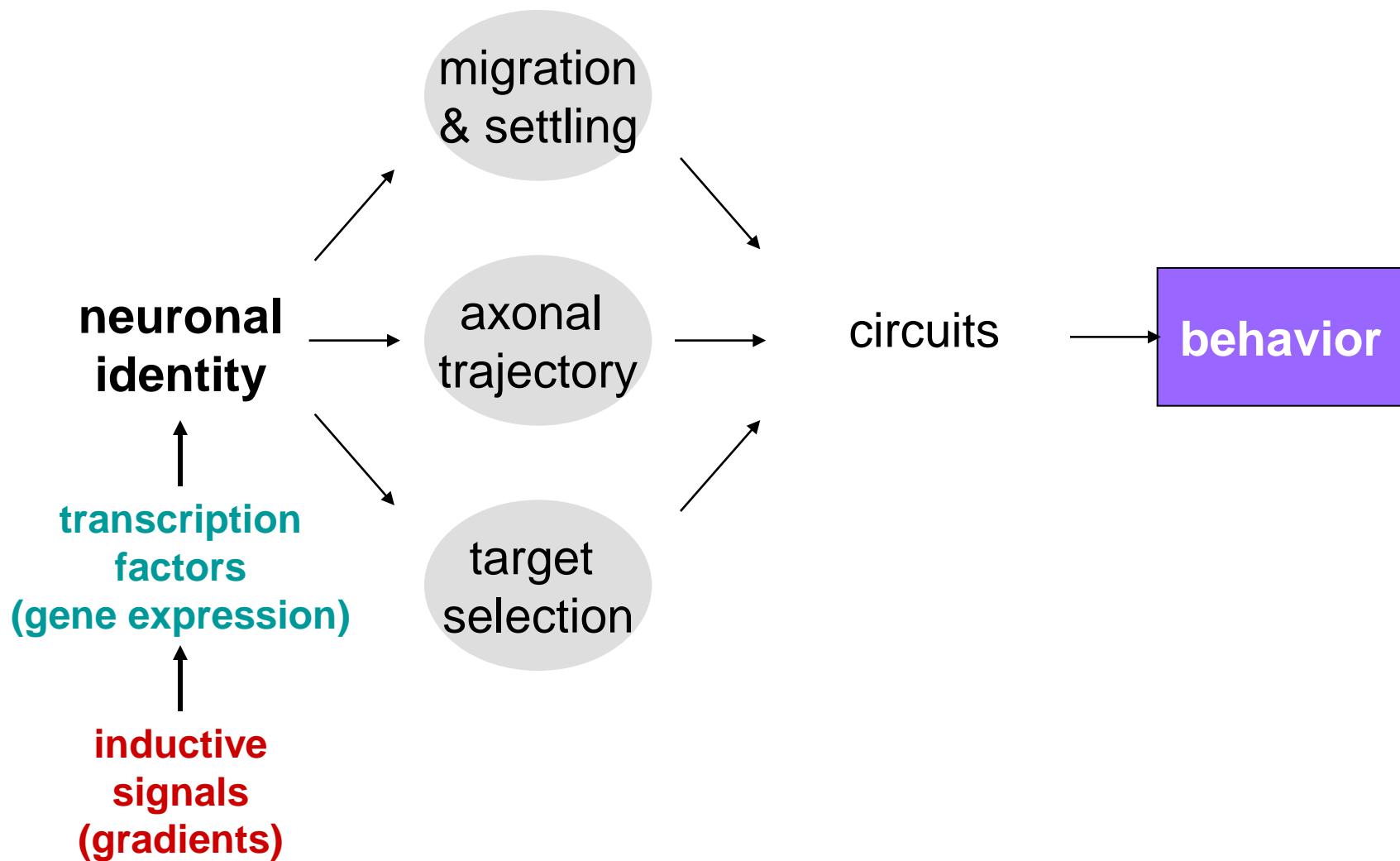


Cell body position as a determinant of synaptic specificity

sensory-motor connectivity



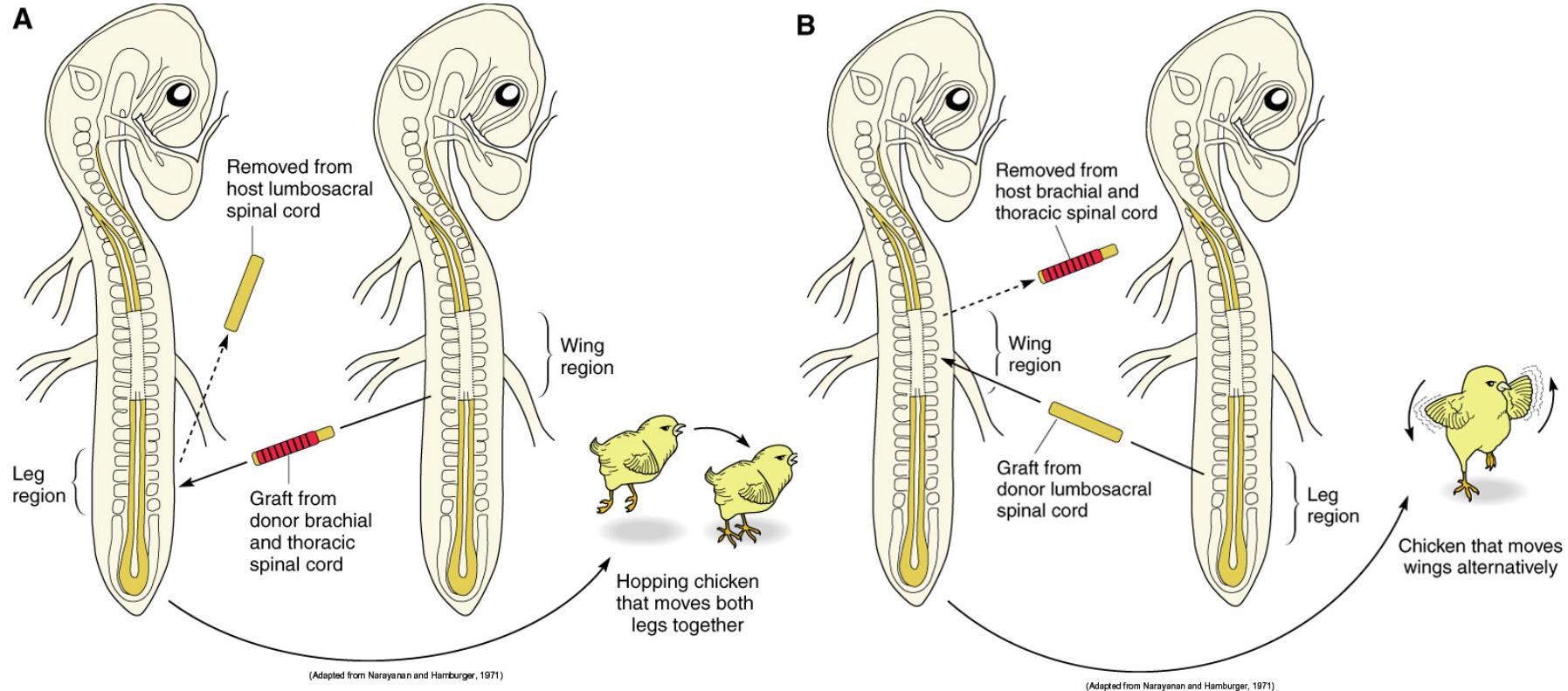
Neuronal identity as a determinant of circuit assembly



How does positional identity affect locomotor behaviors?



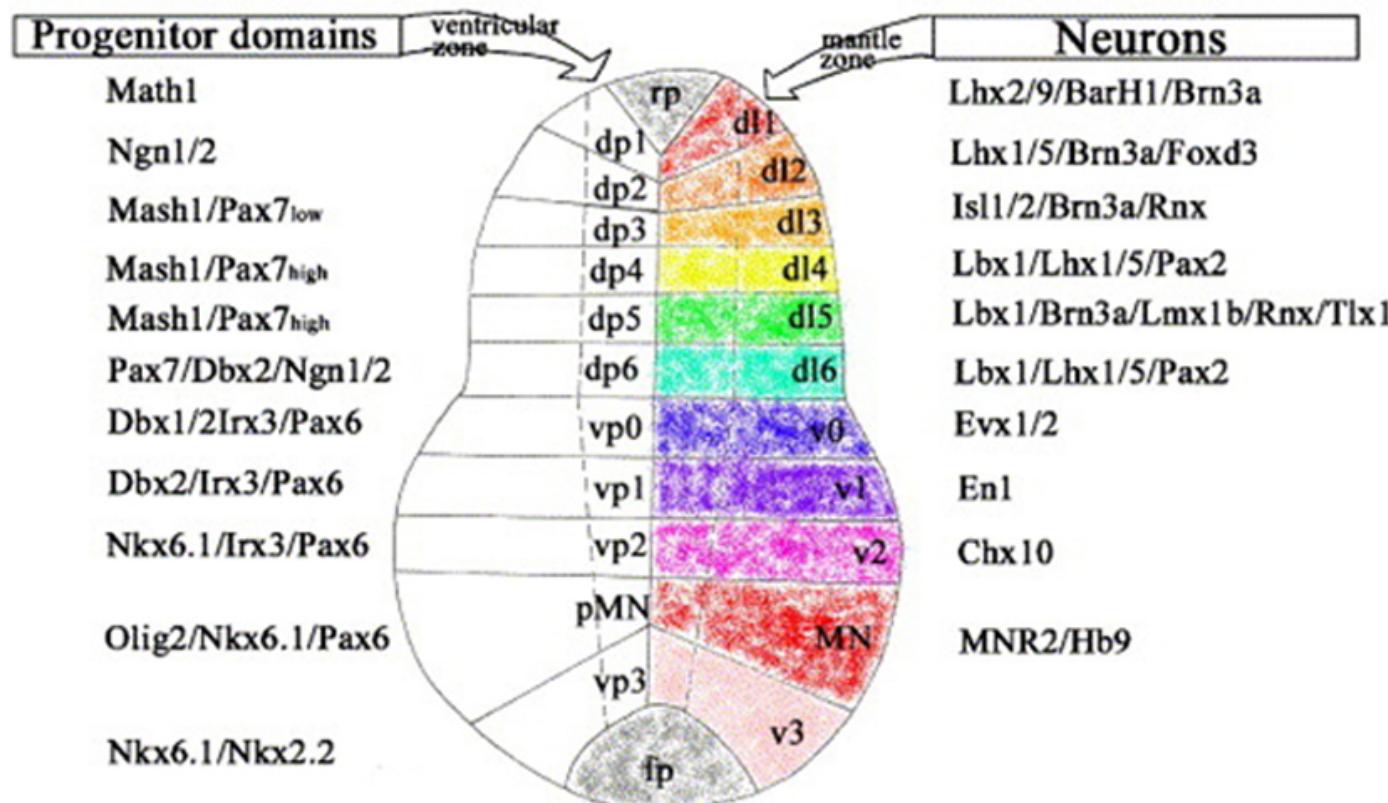
Positional information in the spinal cord can dictate locomotor behaviors in the chick



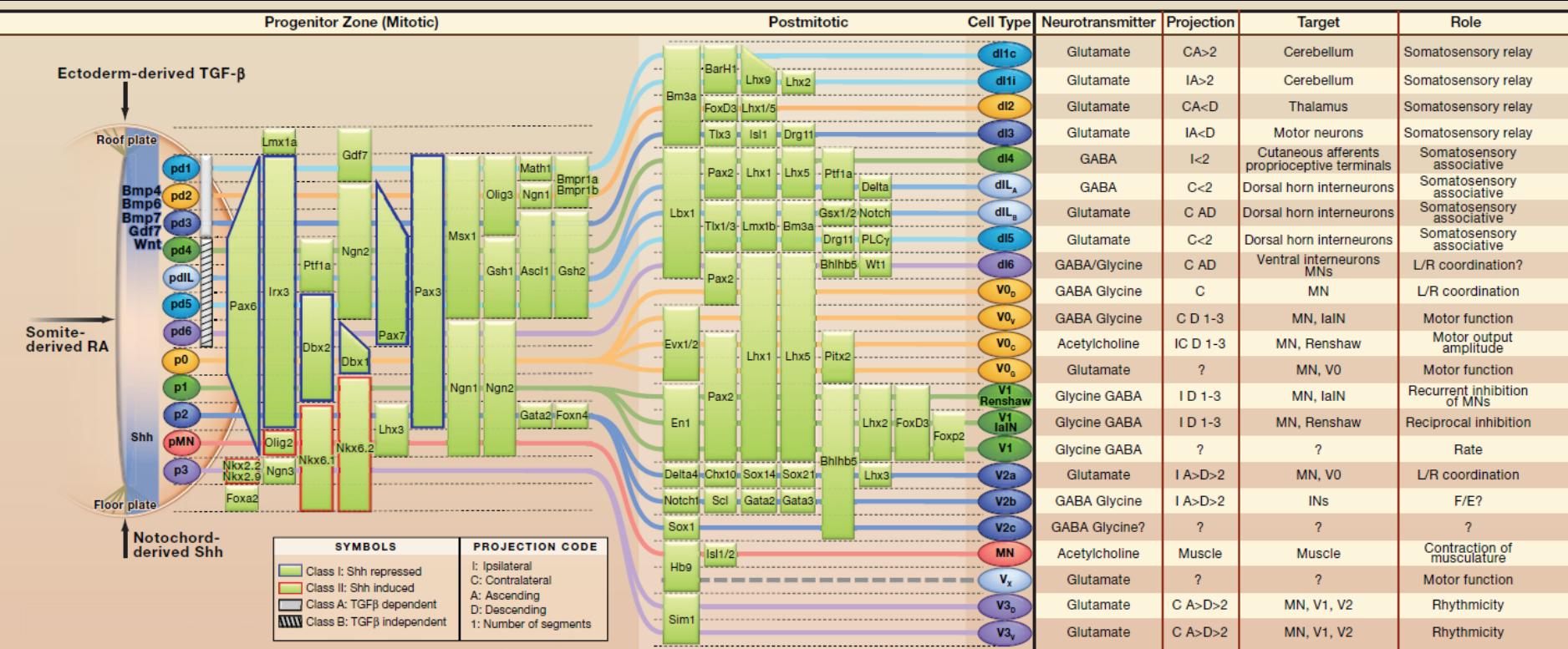
Narayanan and Hamburger 1971

Progenitor and post-mitotic transcription codes in the cord

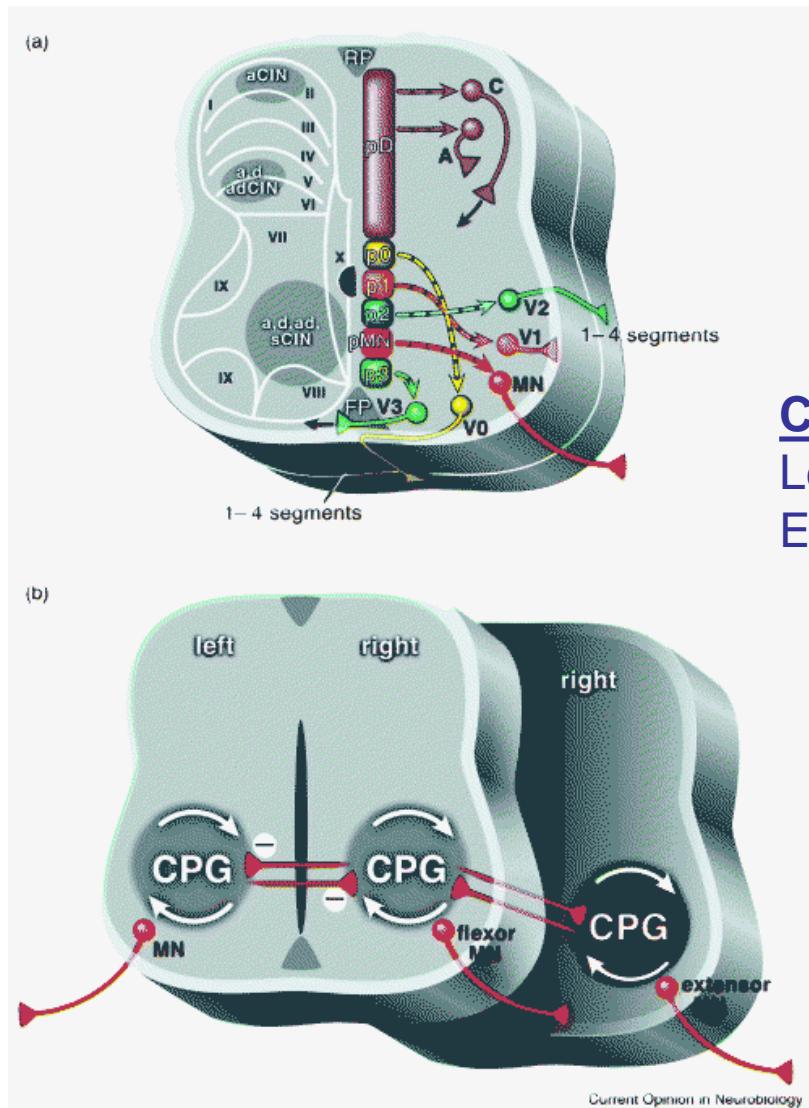
Do individual neuronal classes contribute to specific aspects of “behavior”?



Functional diversity of spinal neuronal classes



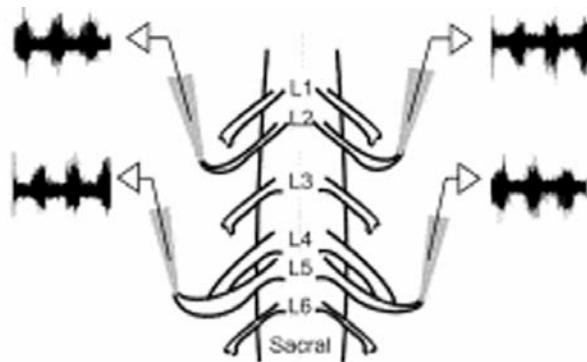
Linking identity to behavior : interneurons and locomotor circuits



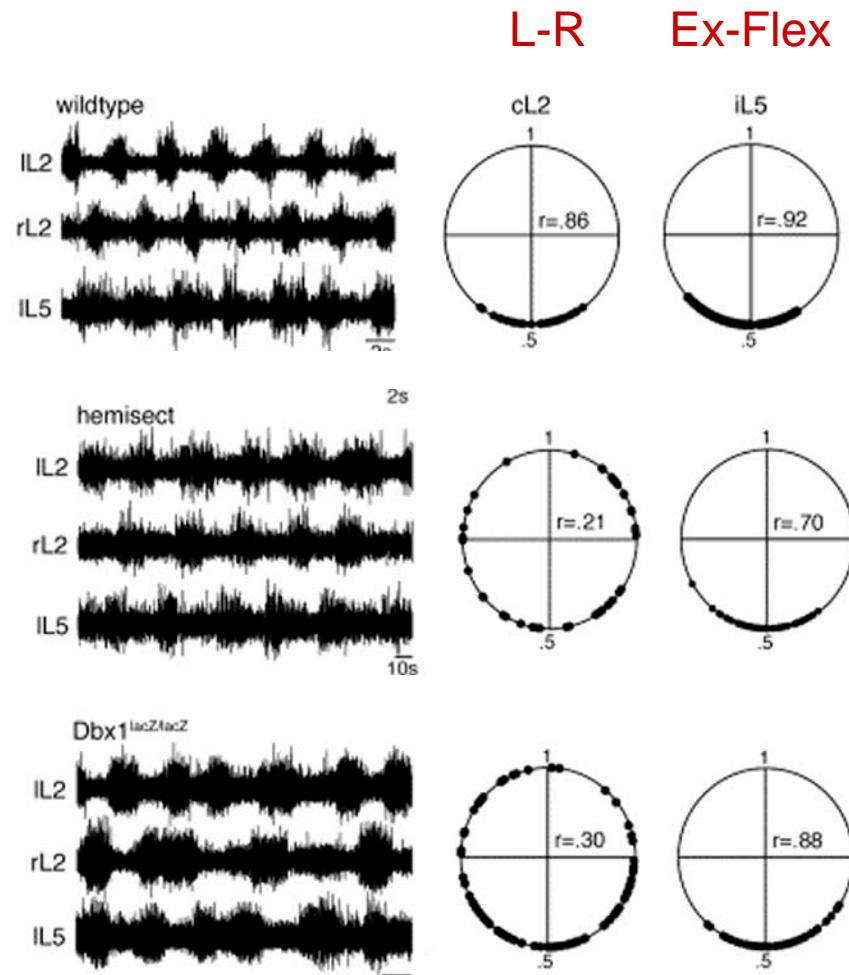
Central pattern generators (CPGs):
Left-right alternation
Extensor-Flexor coordination

Genetic analysis of central pattern generators (CPGs)

Ventral root recordings



Rhythmic bursts of activity
Alterations : left (IL2) & right (rL2)
: flex (L2) & ext (L5)

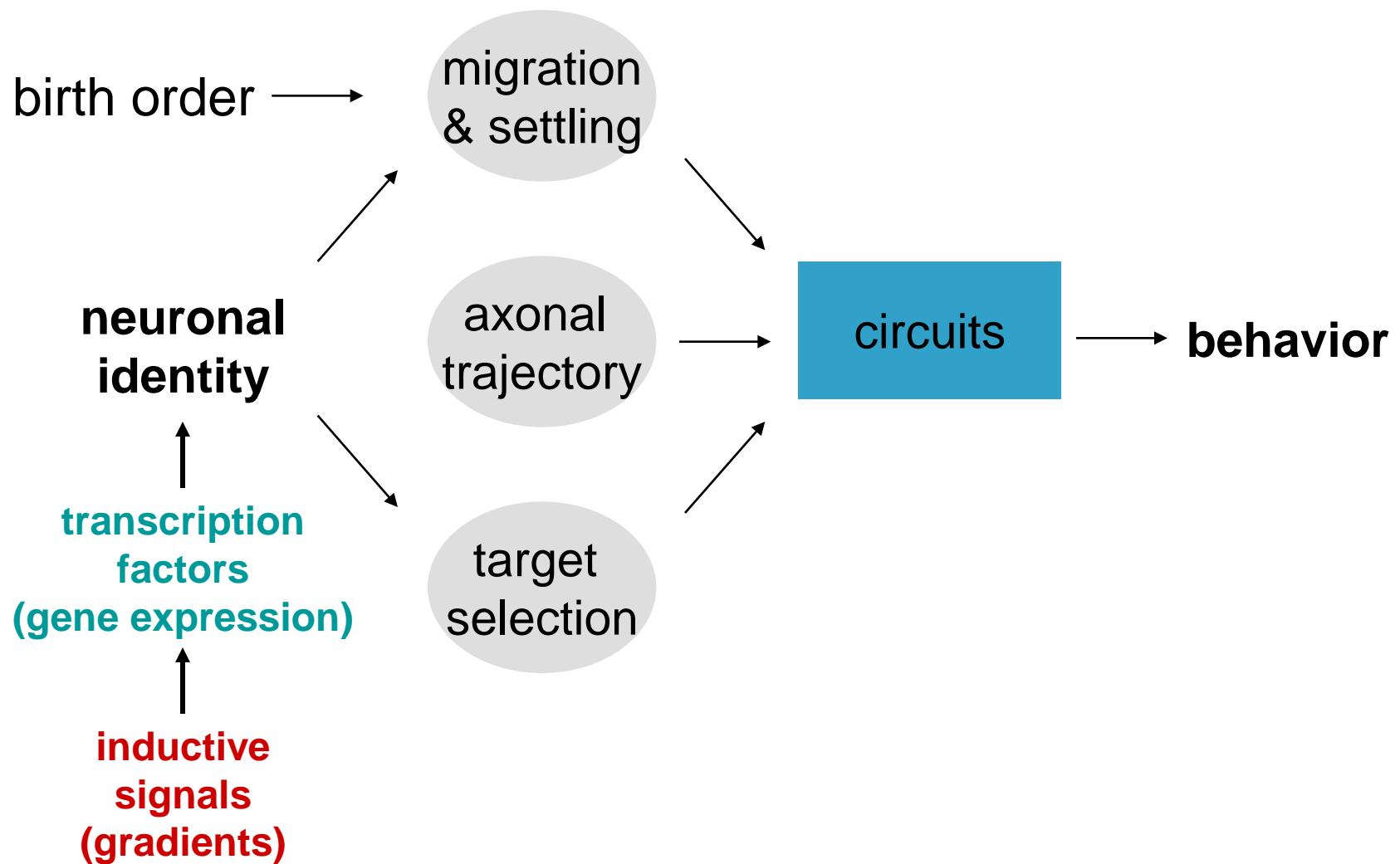


Role of DV patterning in locomotor circuit assembly

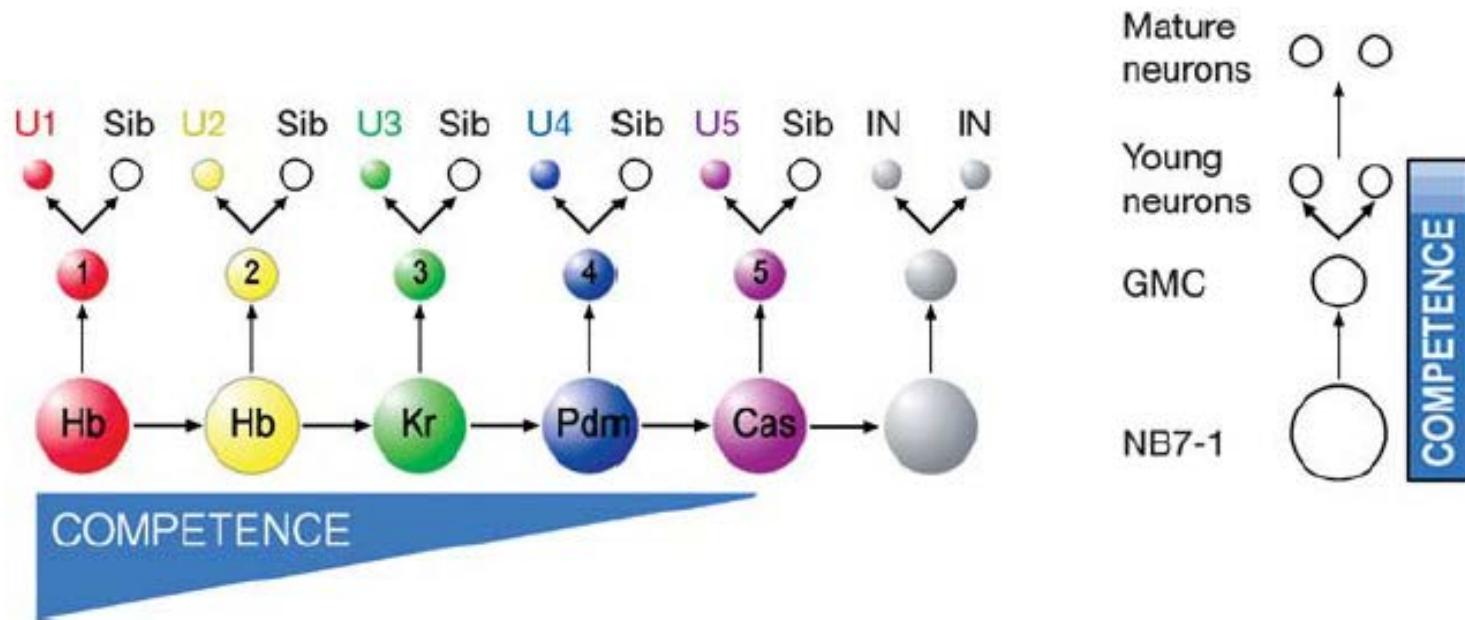
4 IN
progenitor
domains
defined by
Shh

B	classes/markers	known projections	functions
V0 Dbx1	V0d V0v Evx1/2 GABA/Glu ?	contralateral MN	<ul style="list-style-type: none"> left-right alternation <i>Lanuza et al., 2004</i>
V1 En1	RC IaIN Calb Parv GABA/Gly ?	ipsilateral MN IaIN MN RC	<ul style="list-style-type: none"> locomotor cycle speed <i>Gosgnach et al., 2006</i>
V2 Lhx3	Glu V2a V2b Chx10 Sox14 (EphA4) GATA2 GATA3 (EphA4) Gly/GABA ?		<ul style="list-style-type: none"> burst robustness left-right alternation <i>Crone et al., 2008</i>
V3 Sim1	?		?
		contralateral 85% MN V2 RC IaIN	<ul style="list-style-type: none"> burst robustness <i>Zhang et al., 2008</i>

Neuronal identity as a determinant of circuit assembly

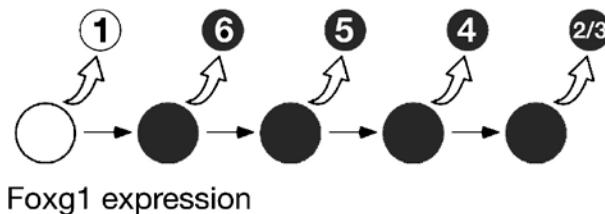


“Temporal cascade” specification in the fly embryonic CNS



Temporal specification in the vertebrate CNS

**Foxg1 represses
early-born temporal identity**



**Hb promotes
early-born temporal identity**

