



# Computational Neuroscience

## Lecture 12: Development

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# Syllabus

- Fundamental aspects of developmental biology
- Embryogenesis
- Neurogenesis
- Axon guidance and synaptogenesis

# Three fundamental aspects of developmental biology

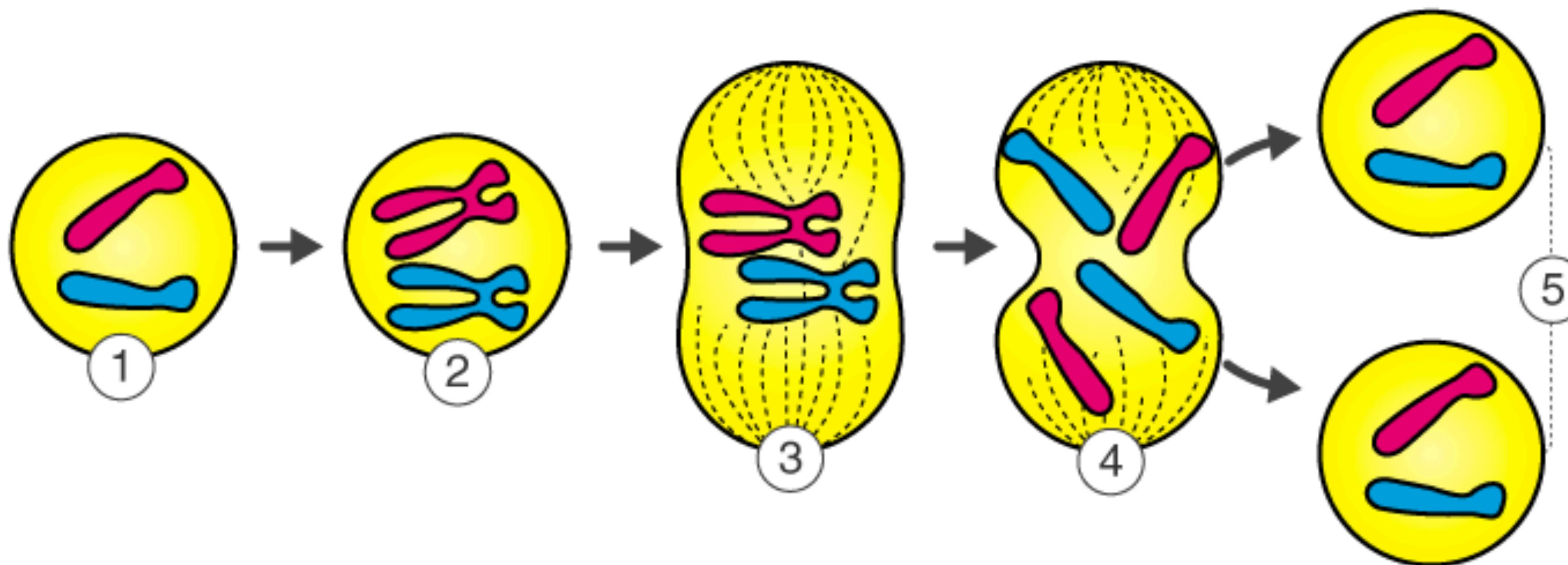
- Cell division and growth
- Cell differentiation
- Morphogenesis

# Cell Division

- Binary Fission (procaryotes, organelles)
- **Mitosis (eukaryotic somatic cells)**
- Meiosis (gametes)

# Cell Division

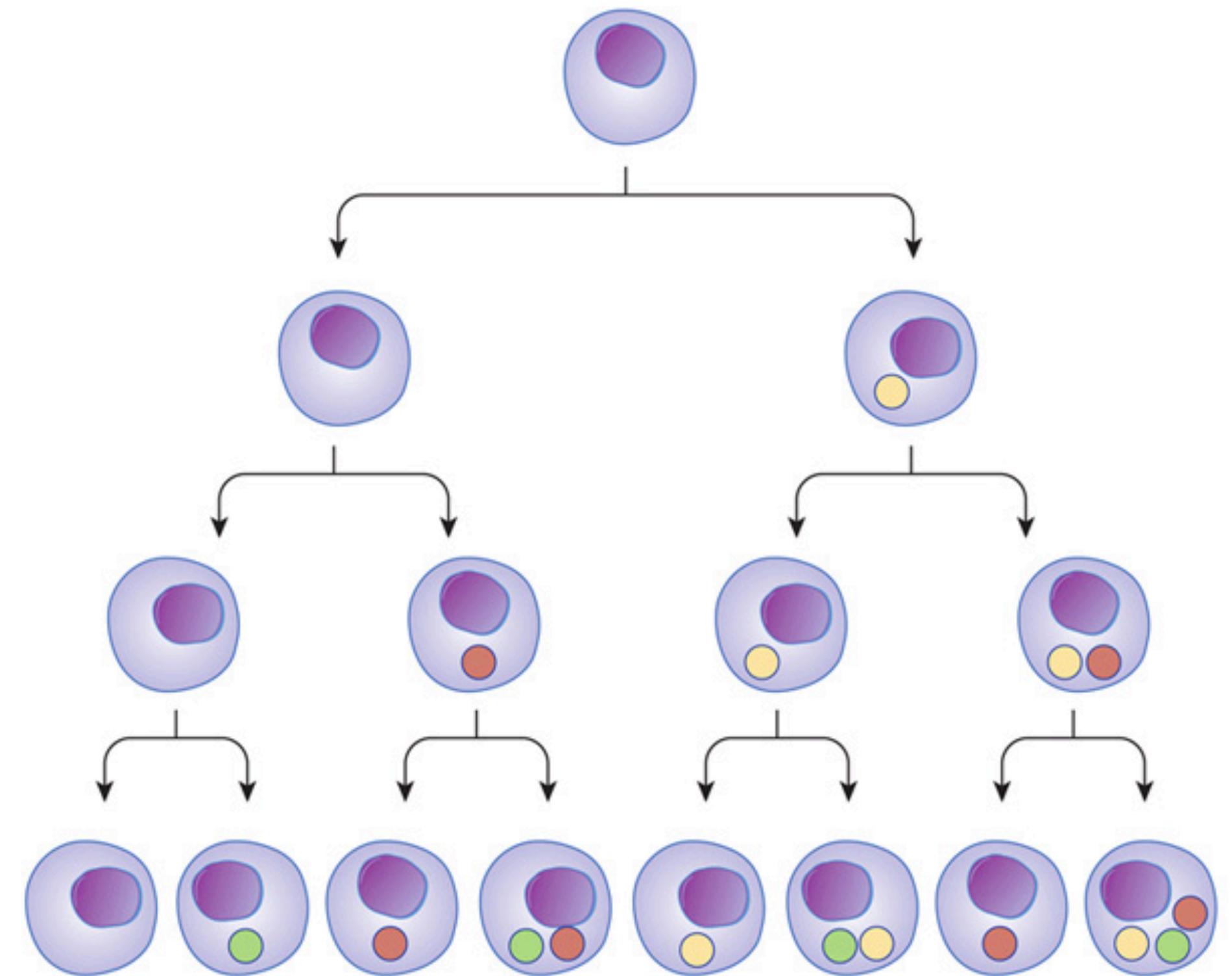
## MITOSIS : EQUATIONAL DIVISION



- 
- 1 Interphase | 2 Prophase | 3 Metaphase | 4 Anaphase | 5 Telophase

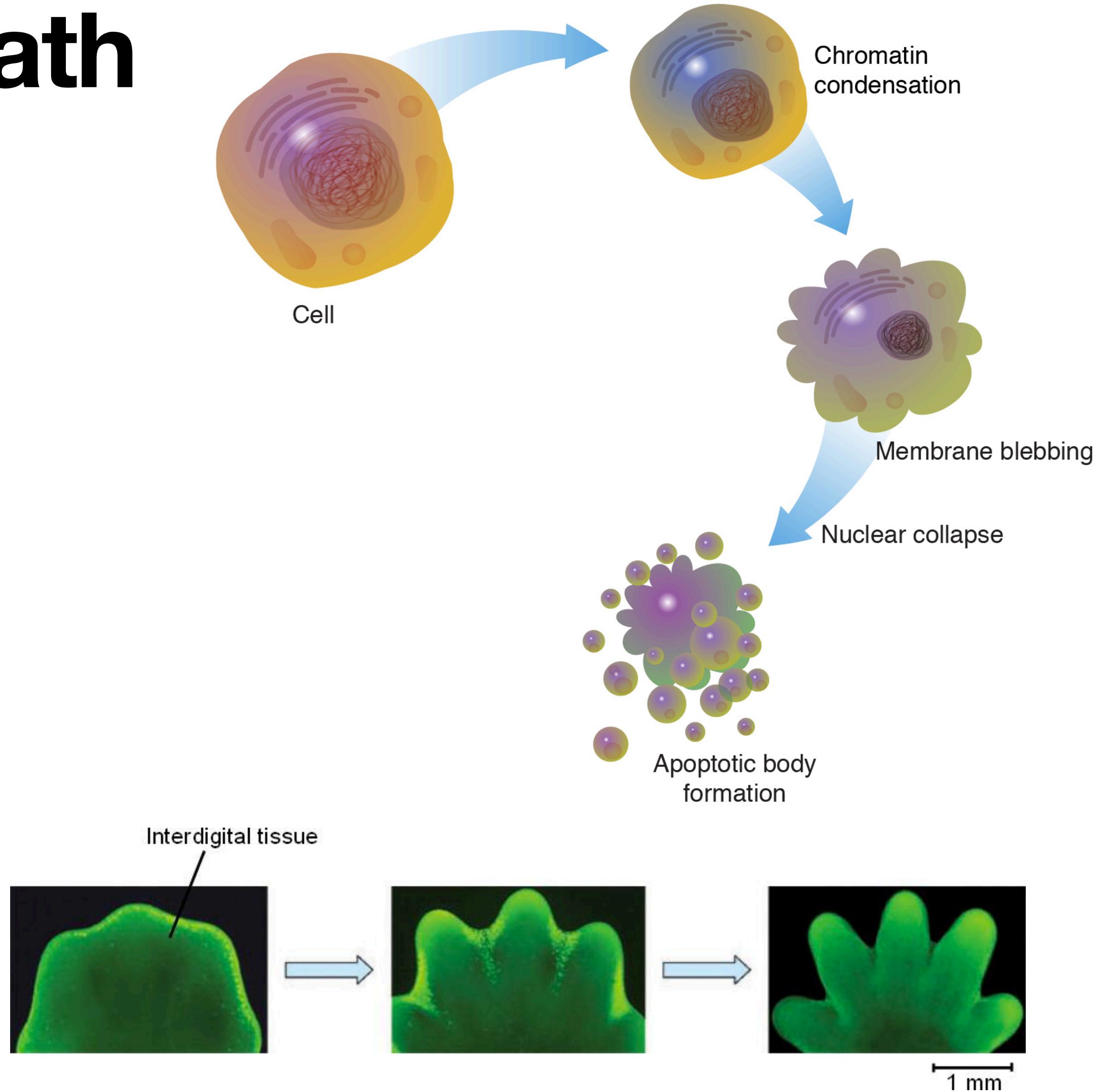
# Cell Differentiation

- All [somatic] cells in our body are genetically identical
- They differ by the sets of genes that are working (are expressed) in different types of cells
- Changes in gene expression are what drives differentiation
- Sometimes it's reversible, sometimes it isn't (or not *in vivo*)



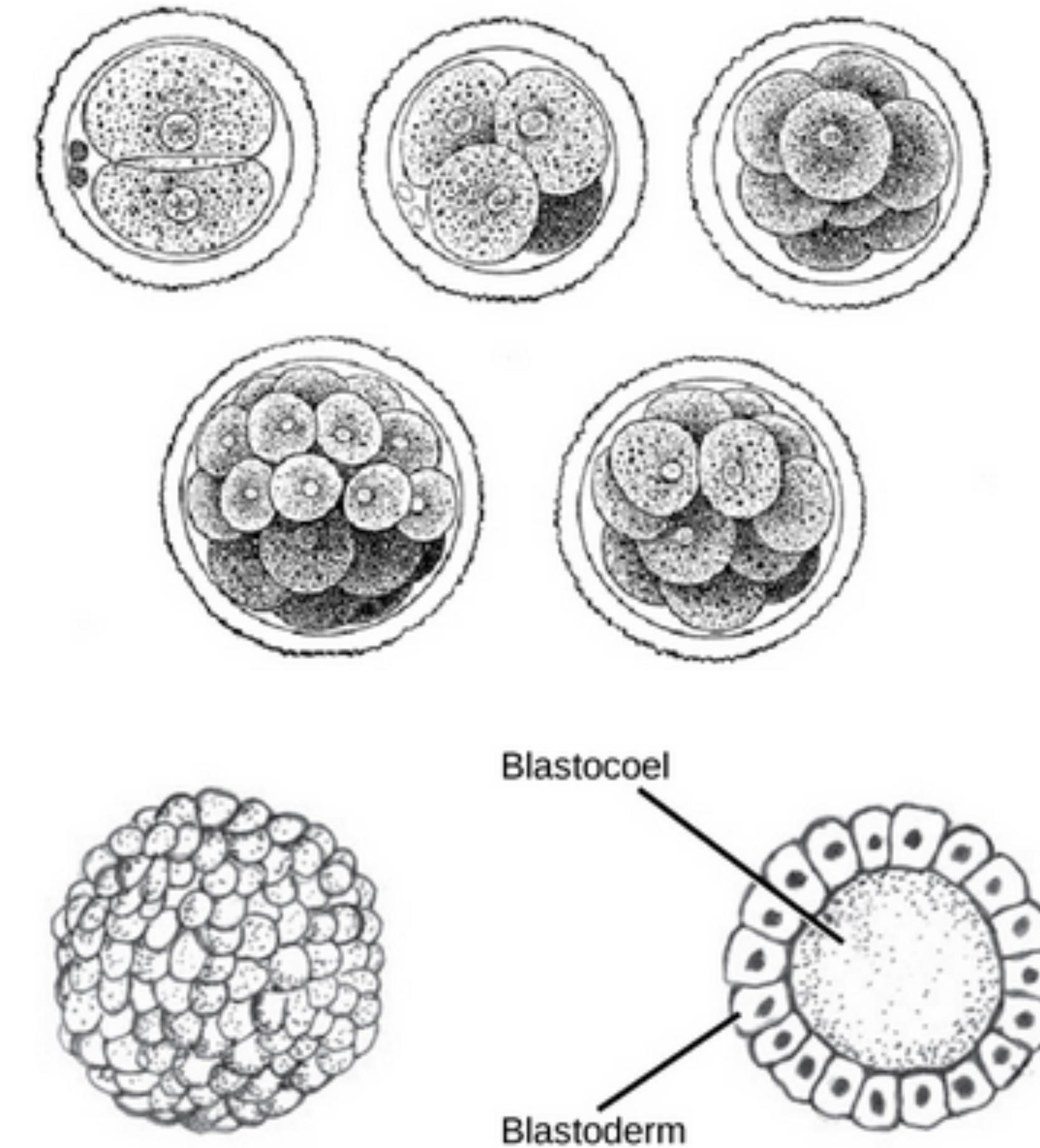
# Programmed Cell Death

- Apoptosis and other (less widespread) types
- PCD = death of a cell, mediated by an intracellular program
- PCD serves fundamental functions during both plant and animal tissue development. For example, the differentiation of fingers and toes in a developing embryo occurs because cells between the fingers apoptose. The result is that the digits get separated.
- As opposed to apoptosis, which is generally physiological, necrosis is a destructive process that occurs as a result of infection or injury

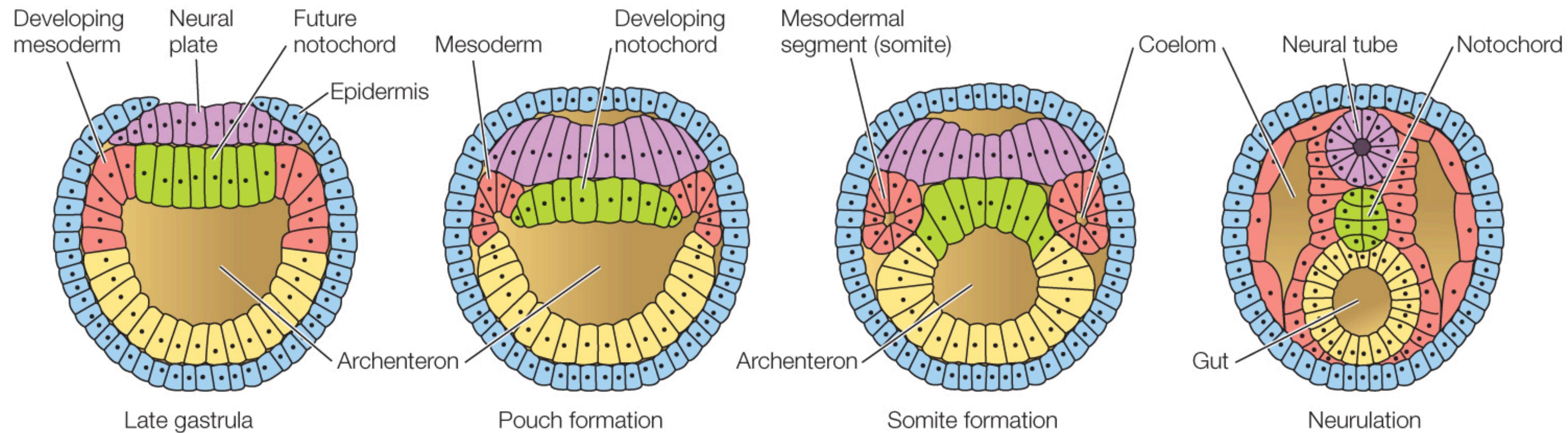
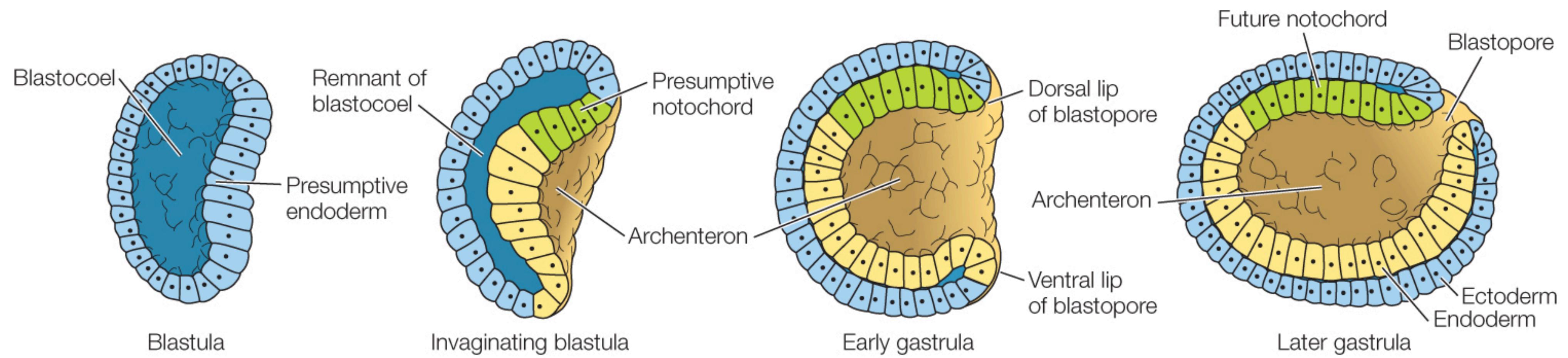


# **Embryogenesis**

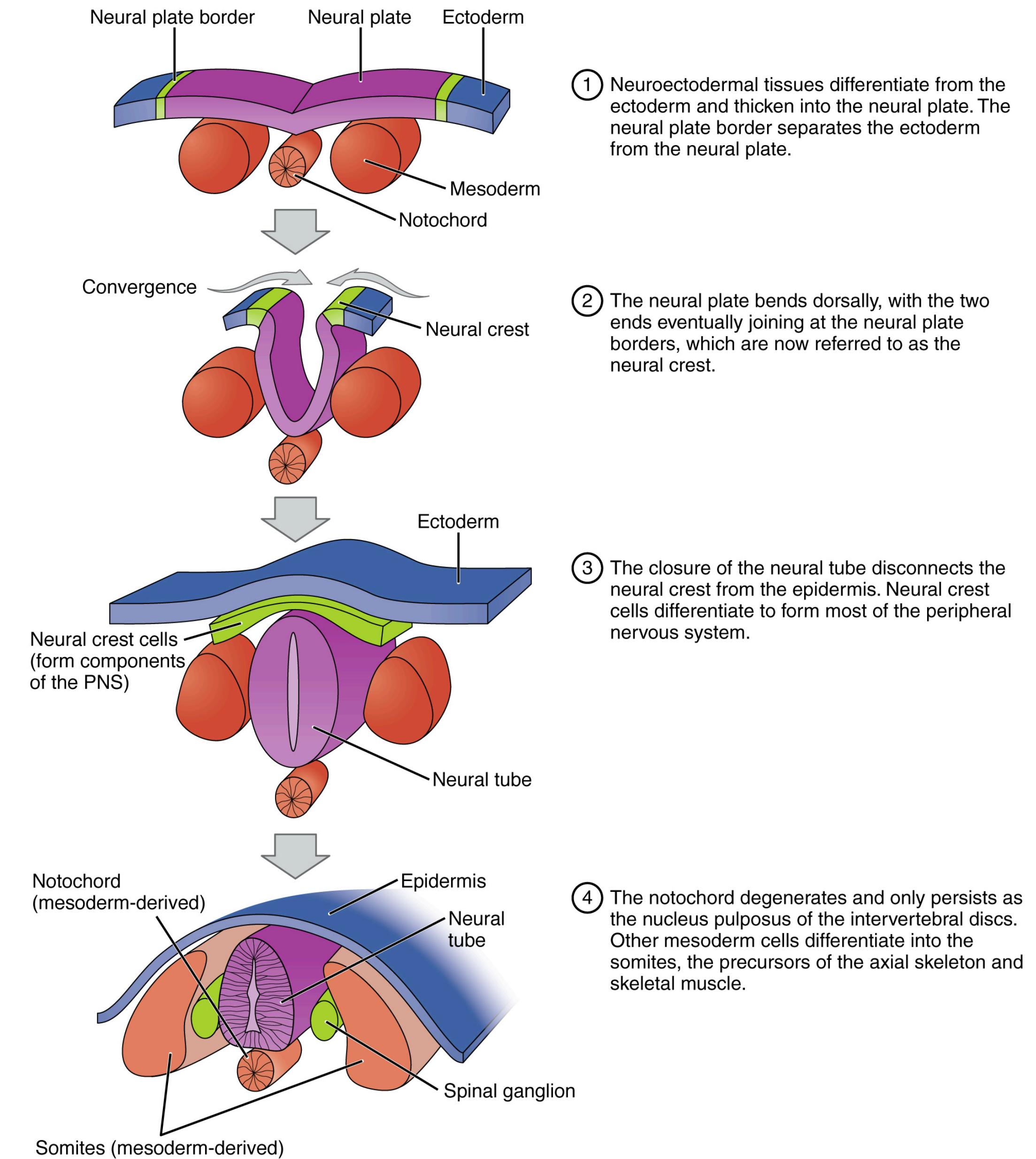
# Early development: egg cleavage



# Early development: blastula, gastrula, neurula



# Organogenesis



① Neuroectodermal tissues differentiate from the ectoderm and thicken into the neural plate. The neural plate border separates the ectoderm from the neural plate.

② The neural plate bends dorsally, with the two ends eventually joining at the neural plate borders, which are now referred to as the neural crest.

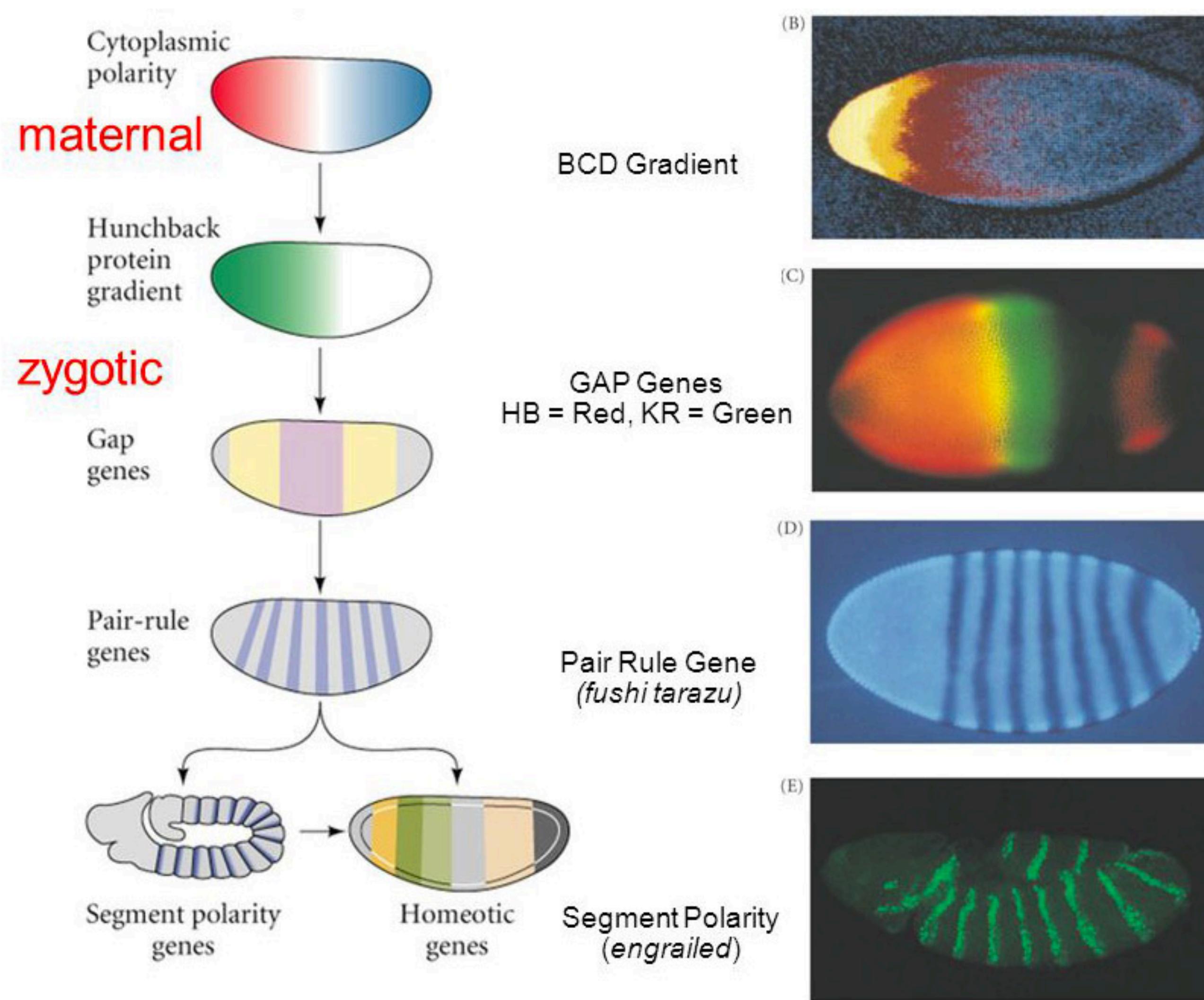
③ The closure of the neural tube disconnects the neural crest from the epidermis. Neural crest cells differentiate to form most of the peripheral nervous system.

④ The notochord degenerates and only persists as the nucleus pulposus of the intervertebral discs. Other mesoderm cells differentiate into the somites, the precursors of the axial skeleton and skeletal muscle.

NatGeo “*Becoming*”. Full video [here](#)

# Patterning

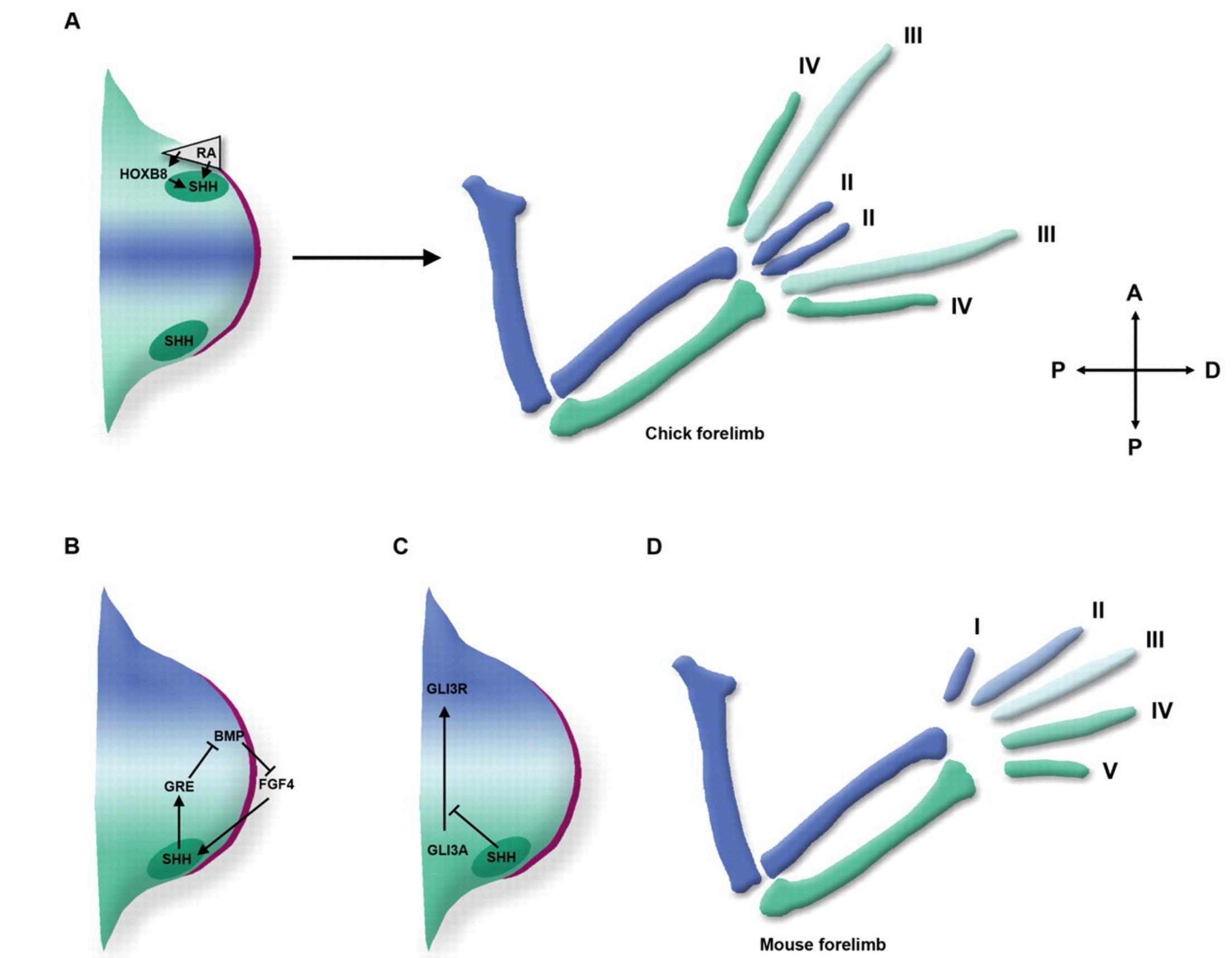
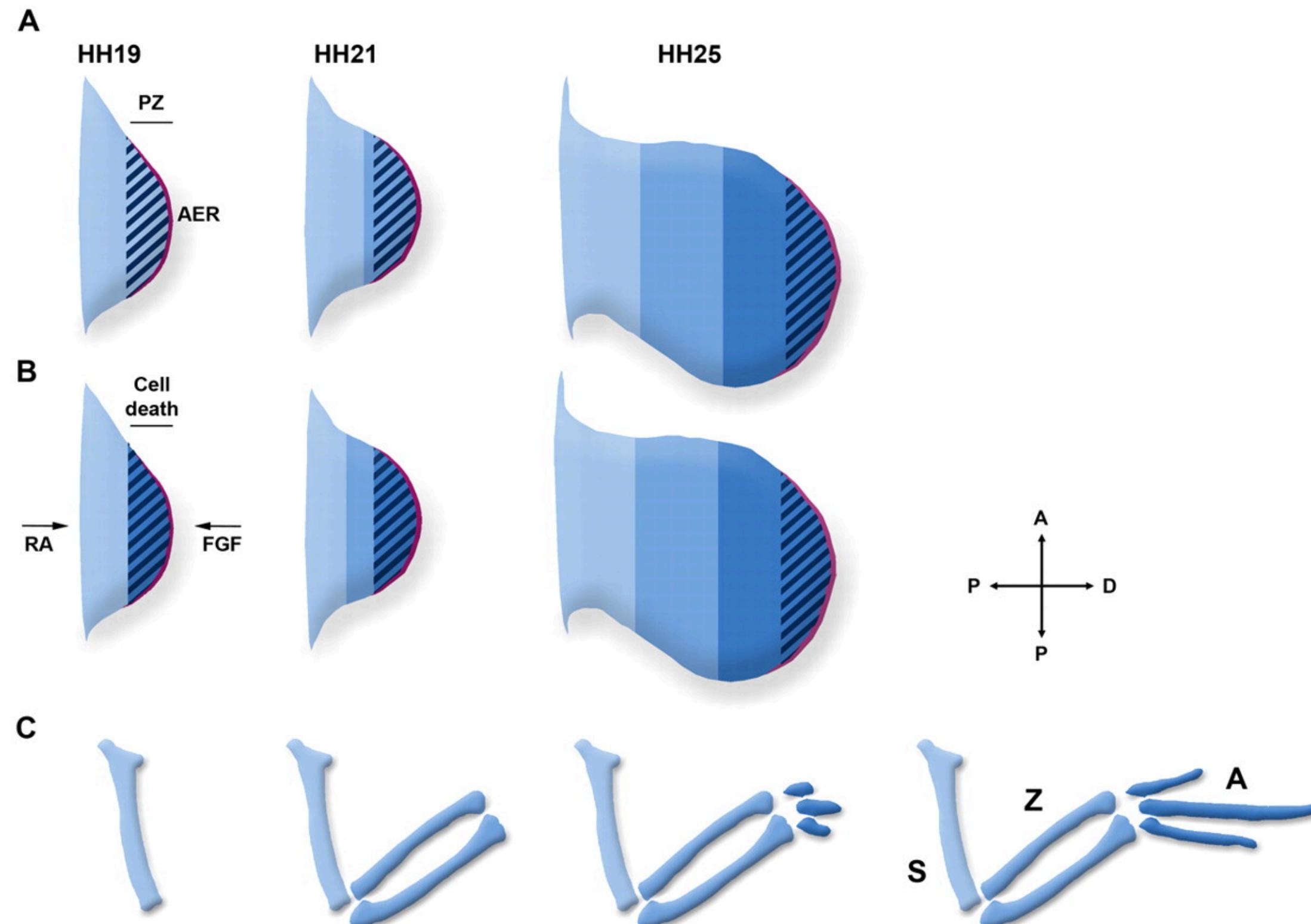
# Patterning the embryo



# Patterning the embryo: morphogens

- **Morphogen gradients** result in the differentiation of specific cell types in a distinct spatial order.
- **Expression of different target genes** is induced or maintained at distinct concentration thresholds via these gradients
- Cells **far** from the source of the morphogen will receive low levels of morphogen and express **only low-threshold target genes**. Cells **close** to the source of morphogen will receive high levels of morphogen and will express **both low- and high-threshold target genes**.
- Different combinations of target gene expression → distinct cell types
- This model is assumed to be a general mechanism by which cell type diversity can be generated in embryonic development in animals.
- Some of the earliest and best-studied morphogens are **transcription factors** that diffuse within early fruit fly embryos. However, most morphogens are secreted proteins that signal between cells.
- Most notable in vertebrates: **retinoic acid, SHH, Wnt, TGF-β**

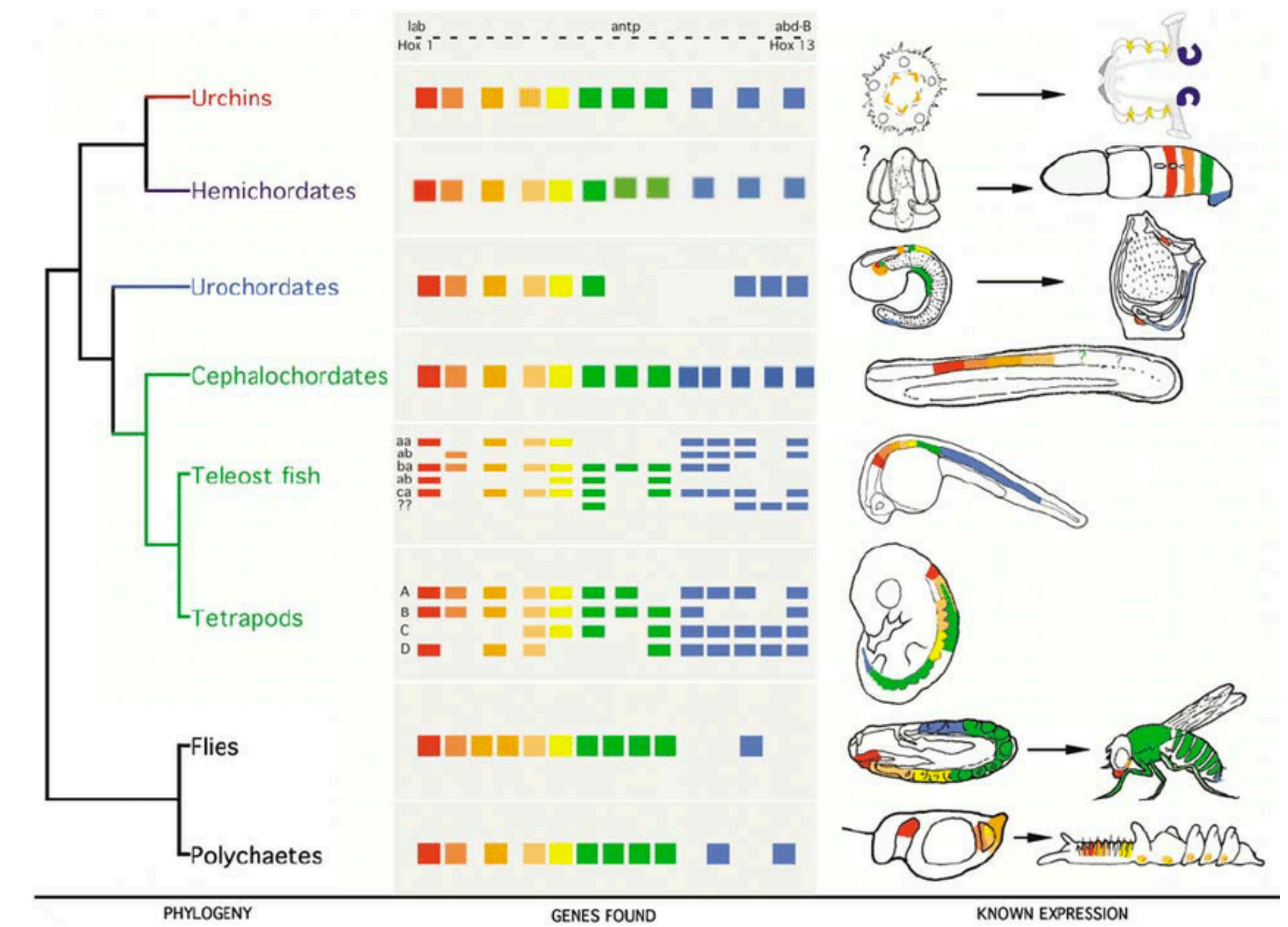
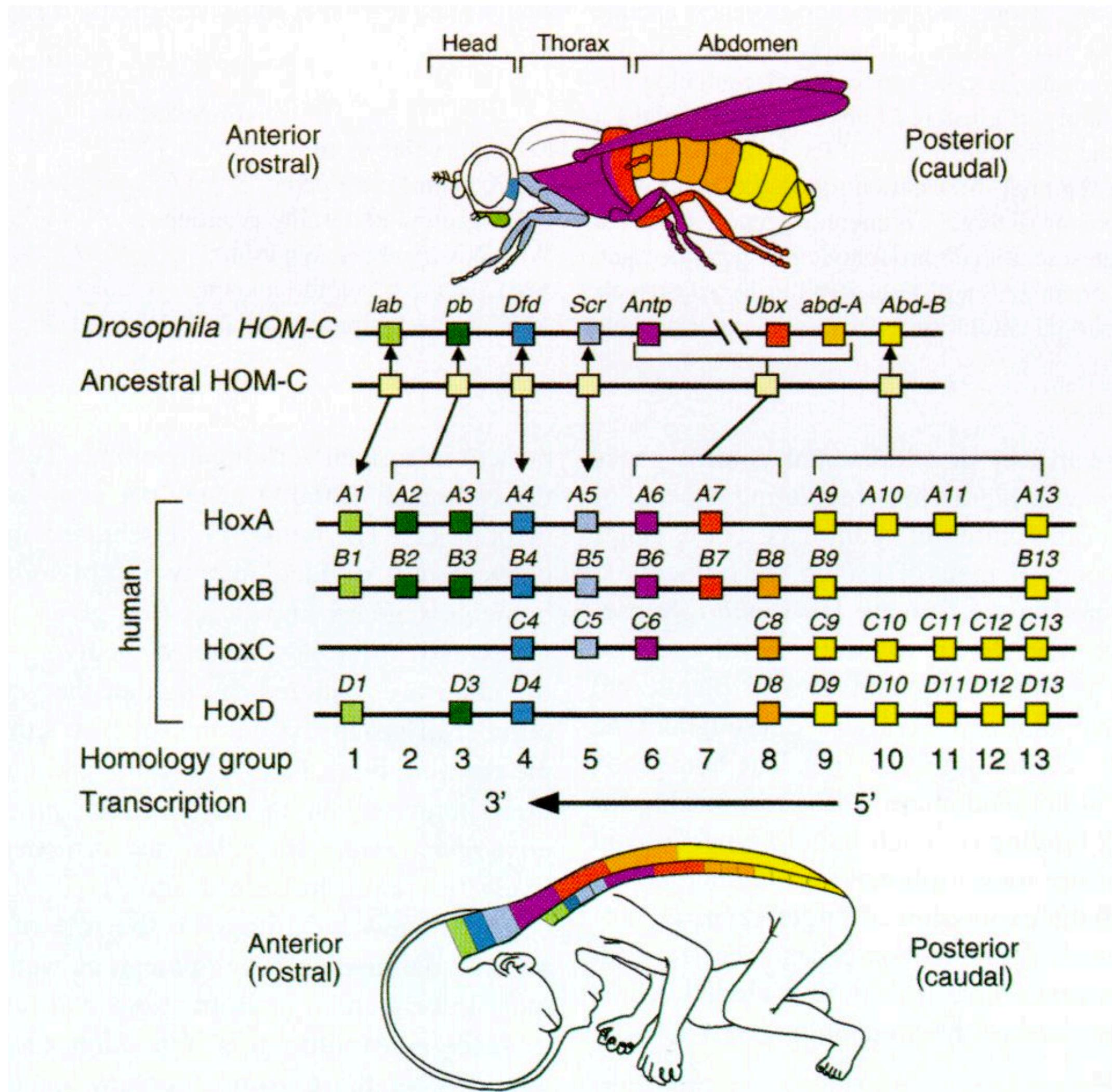
# Morphogens case study: Retinoic Acid, SHH and limbs patterning



# Patterning the embryo: HOX genes

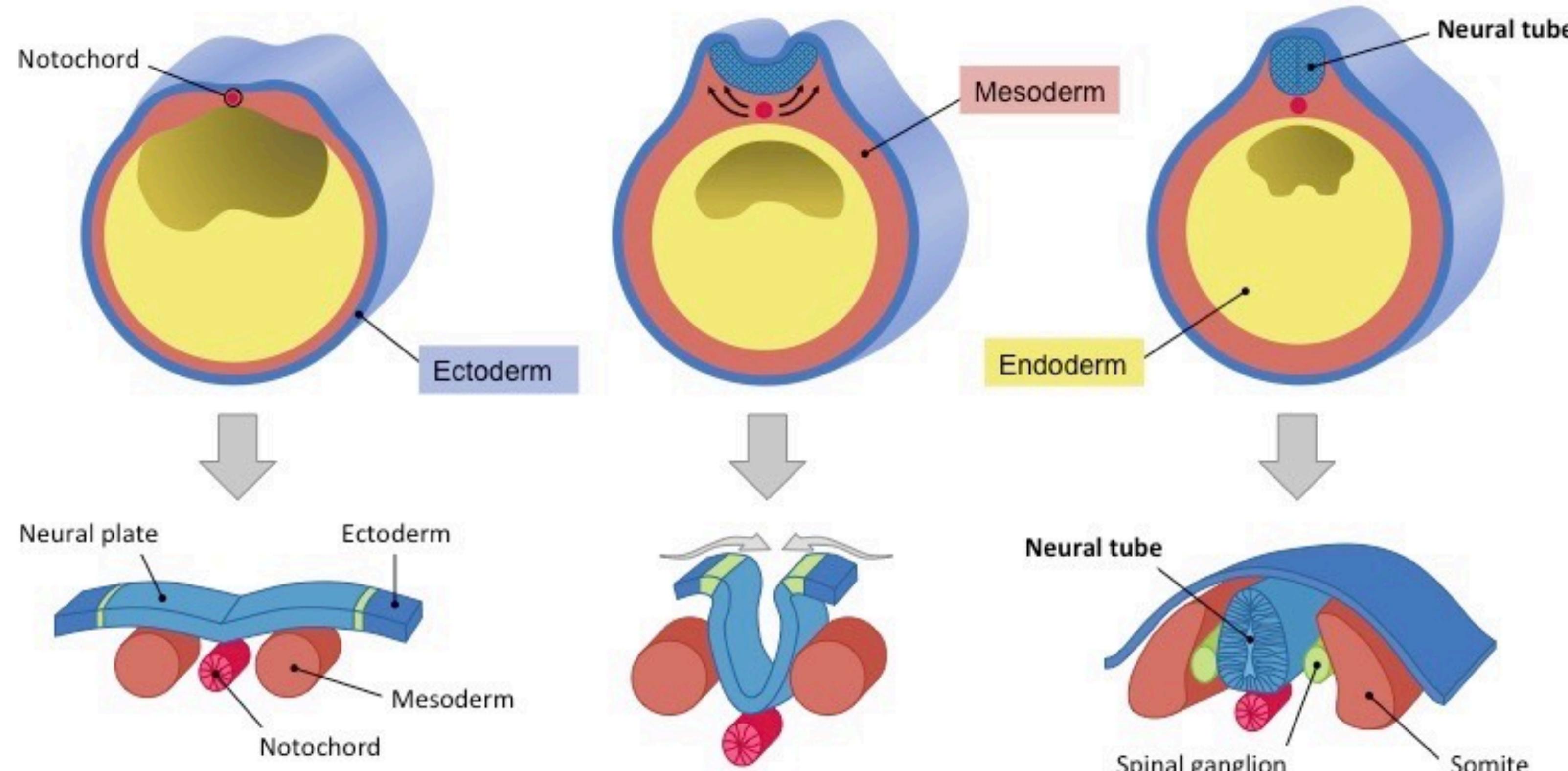
- Hox genes are a subset of **homeobox genes**
- A homeobox is a DNA sequence, around 180 base pairs long, found within genes that are involved in the regulation of patterns of anatomical development (**morphogenesis**)
- Homeobox genes encode homeodomain protein products that are **transcription factors** sharing a characteristic protein fold structure that binds DNA to regulate expression of target genes.
- Homeodomain proteins regulate gene expression and cell differentiation during early embryonic development, thus mutations in homeobox genes can cause **developmental disorders**.

# Patterning the embryo: HOX genes



# **Development of the nervous system**

# Neurulation

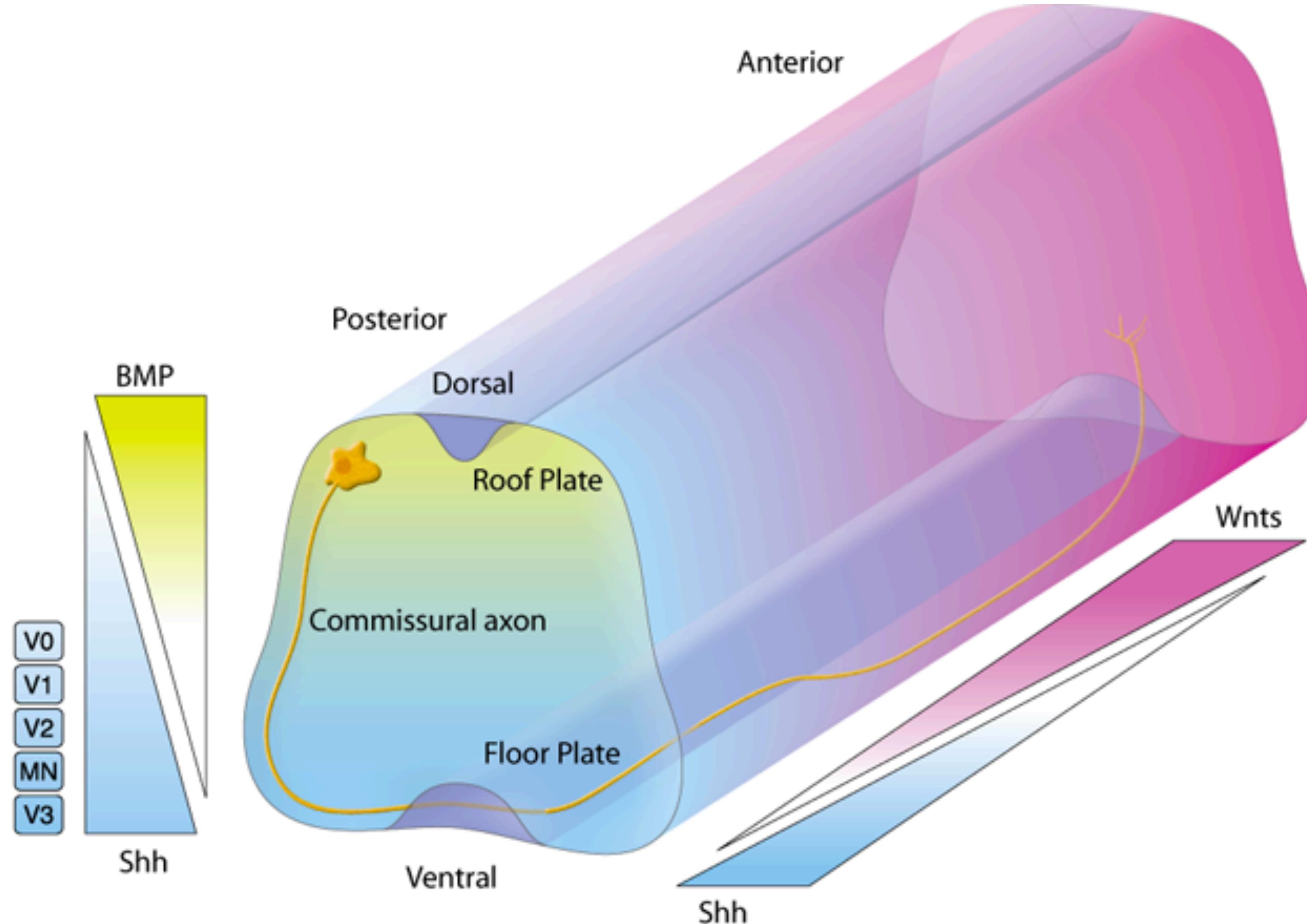


**1.** Notochord forms from mesoderm cells soon after gastrulation is complete

**2.** Signals from notochord cause inward folding of ectoderm at the neural plate

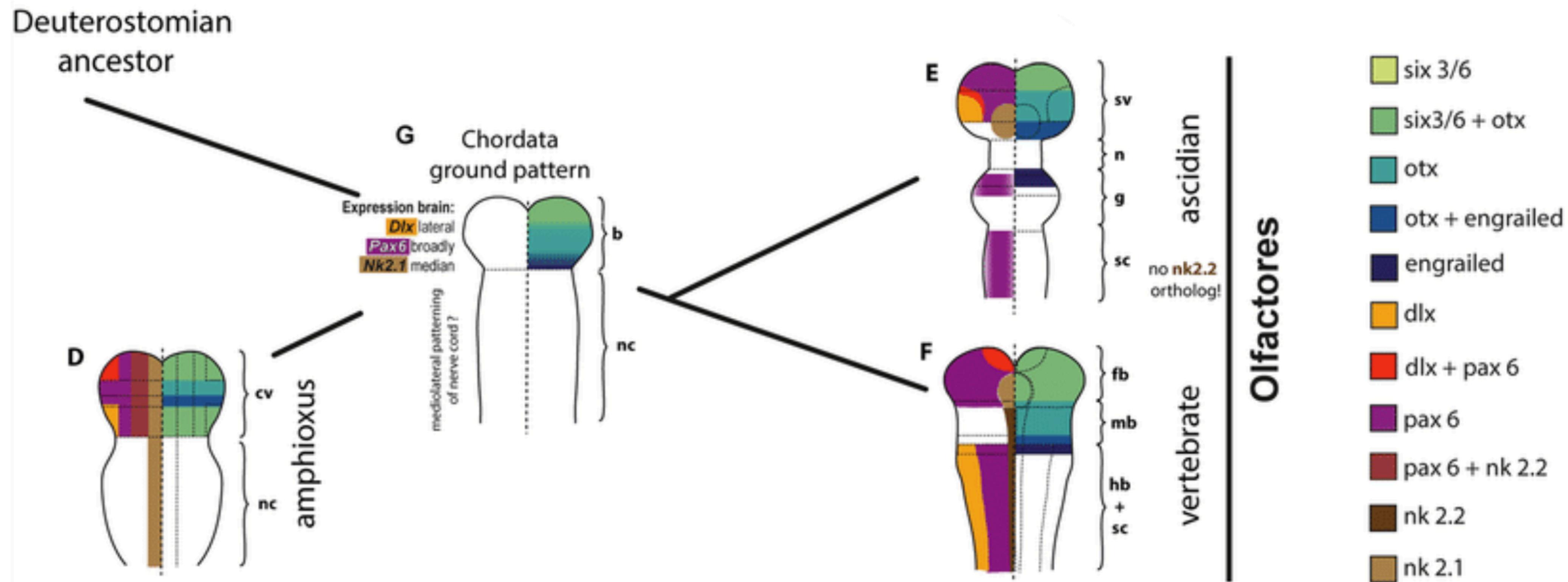
**3.** Ends of neural plate fuse and disconnect to form an autonomous neural tube

# Neural tube patterning



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# Brain patterning



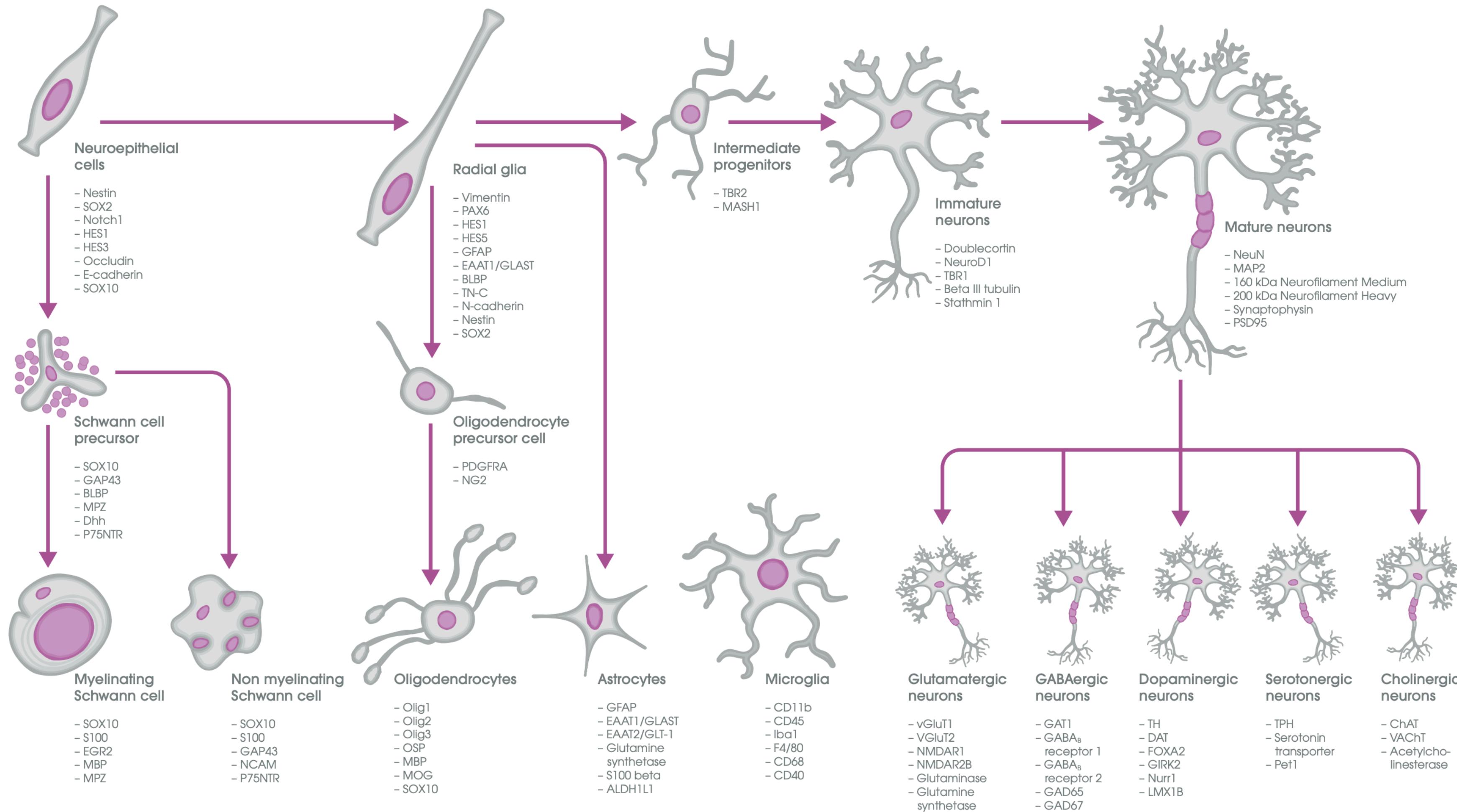
# Neurogenesis

Neurogenesis is the process by which new neurons are formed.

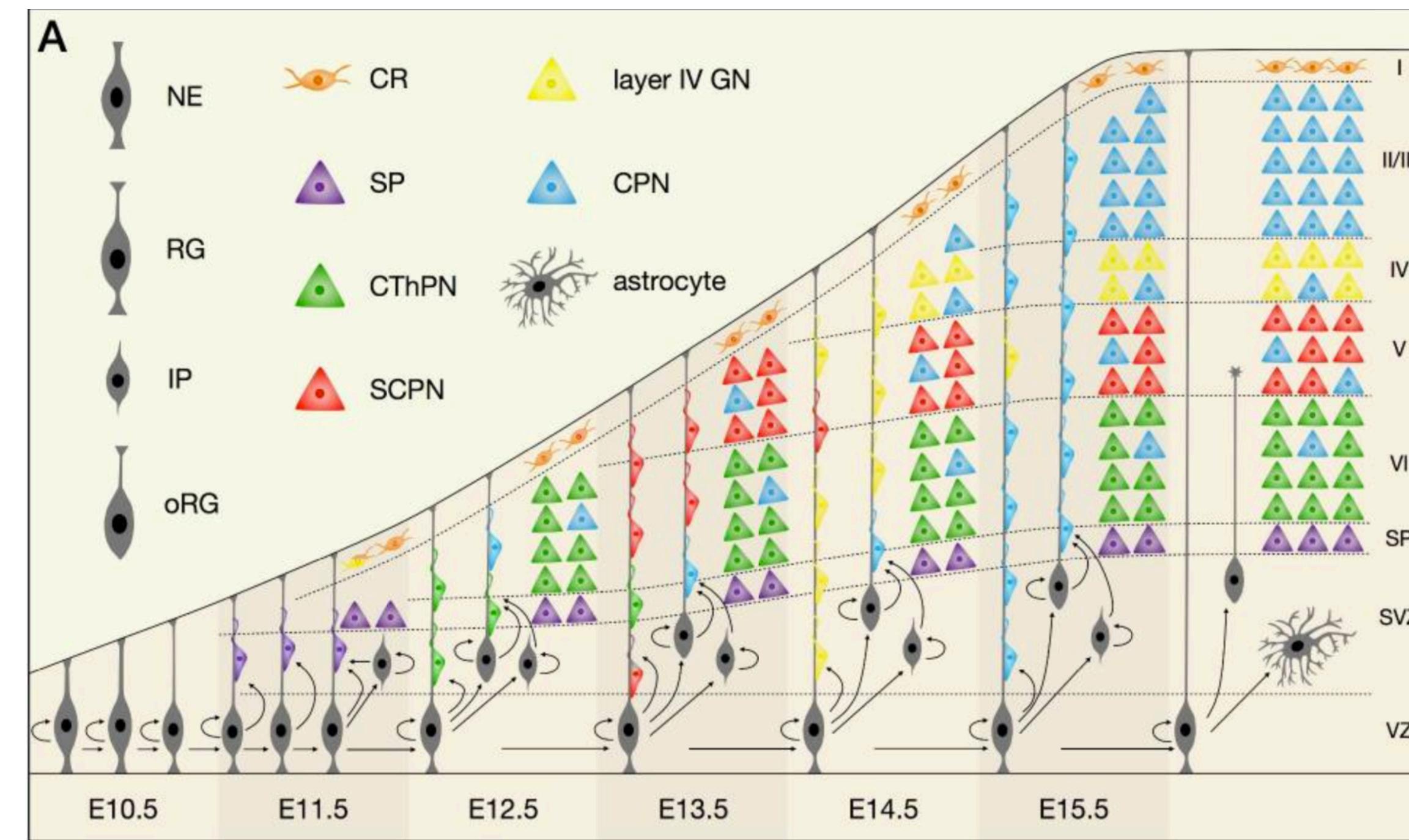
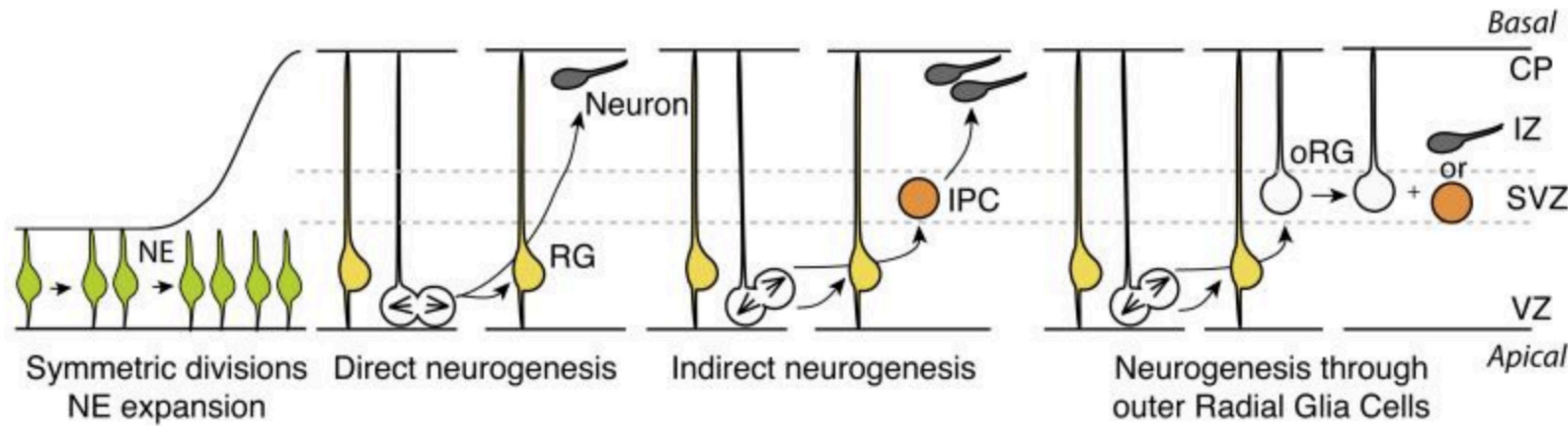
Neurogenesis is crucial when an embryo is developing, but also continues in certain brain regions after birth and throughout our lifespan.

# Neurogenesis

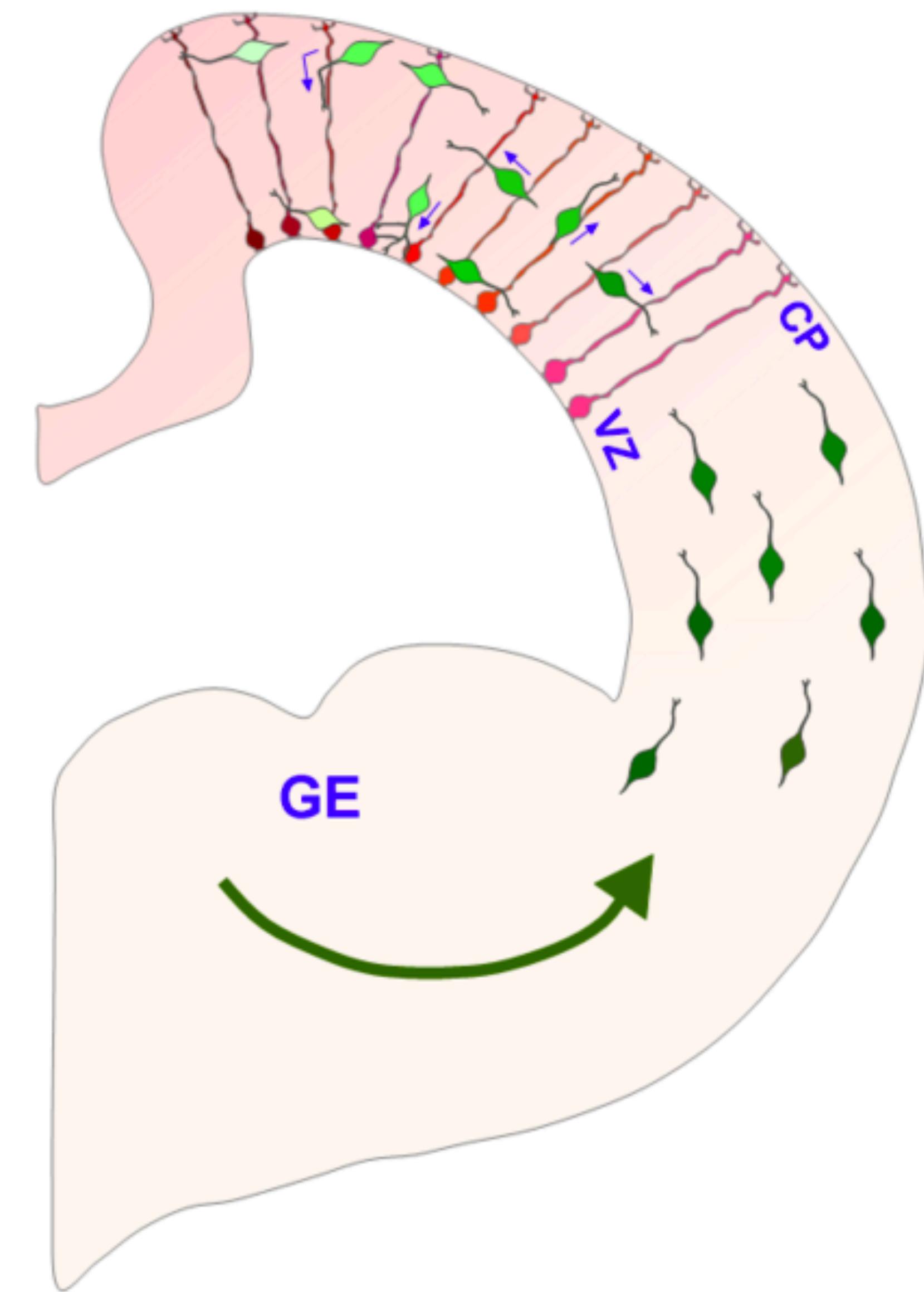
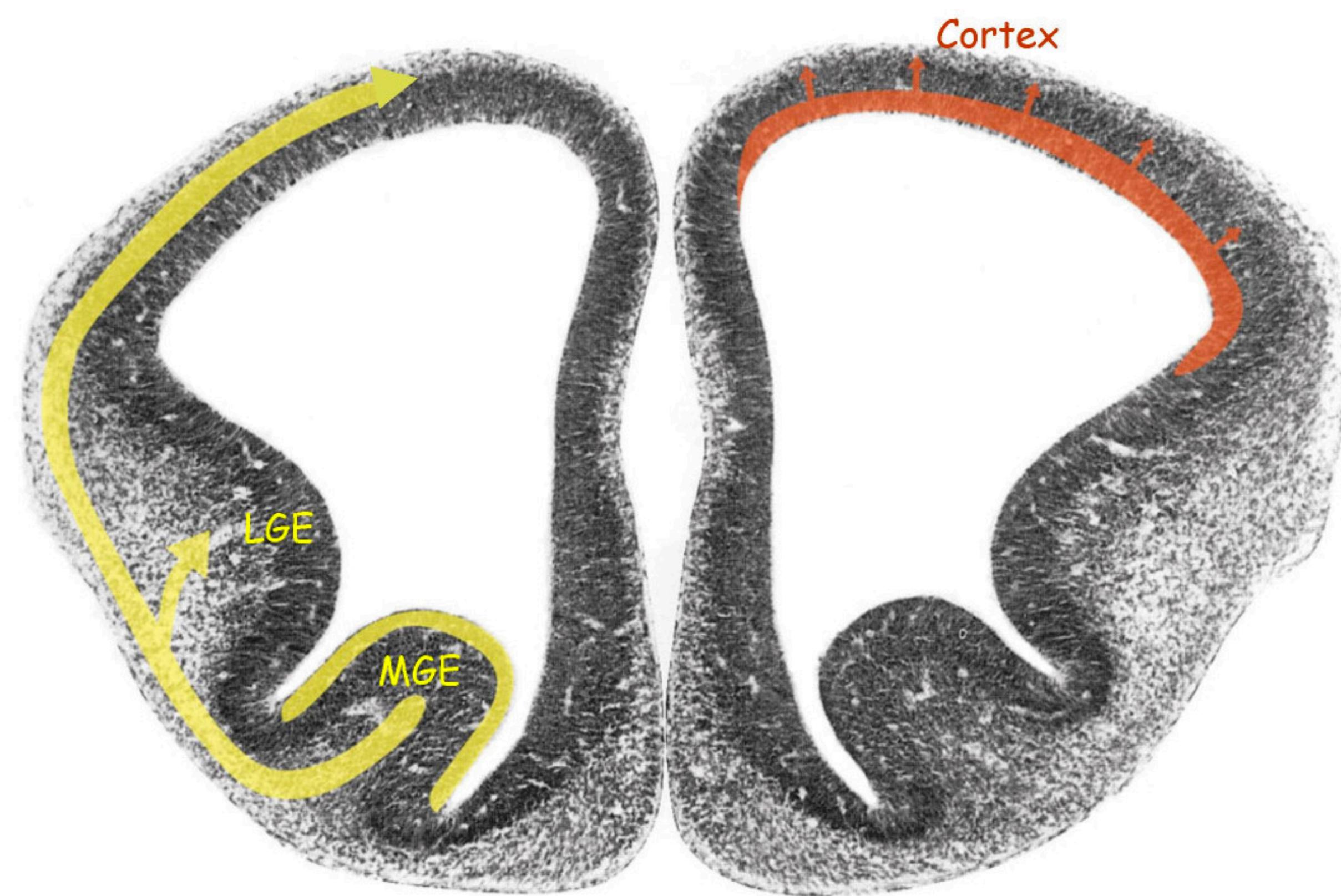
## Neural cell lineage



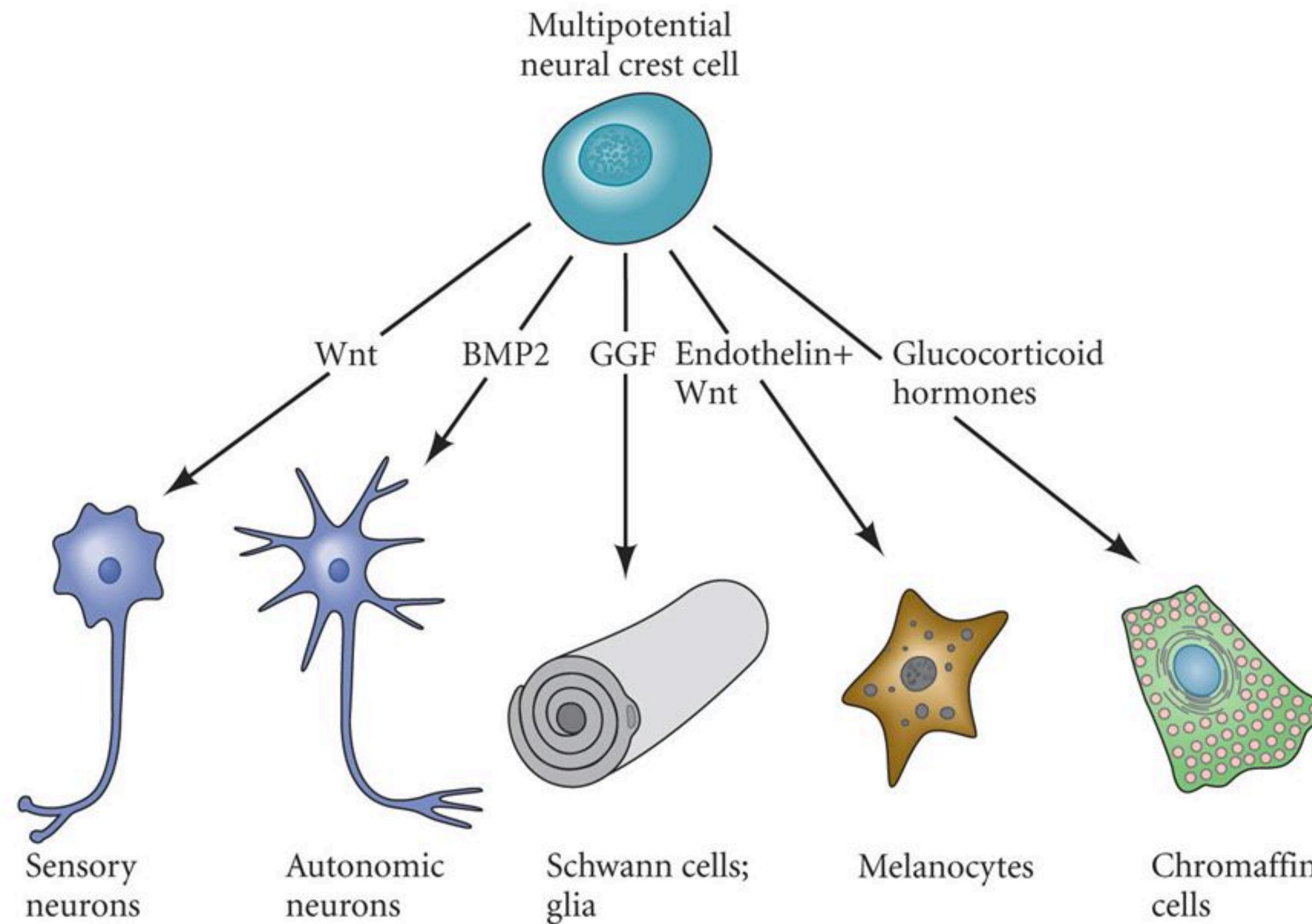
# Corticogenesis



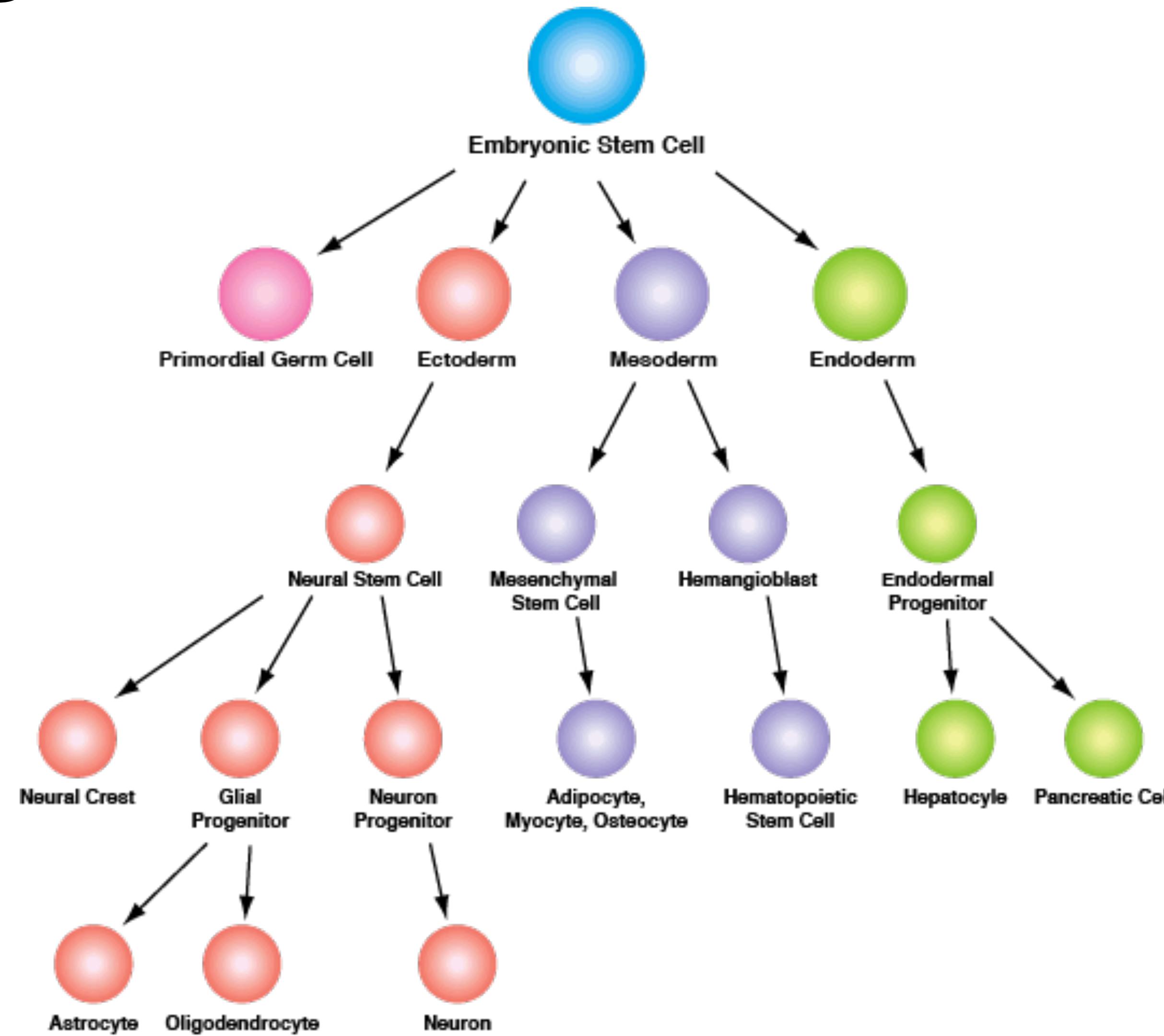
# Corticogenesis



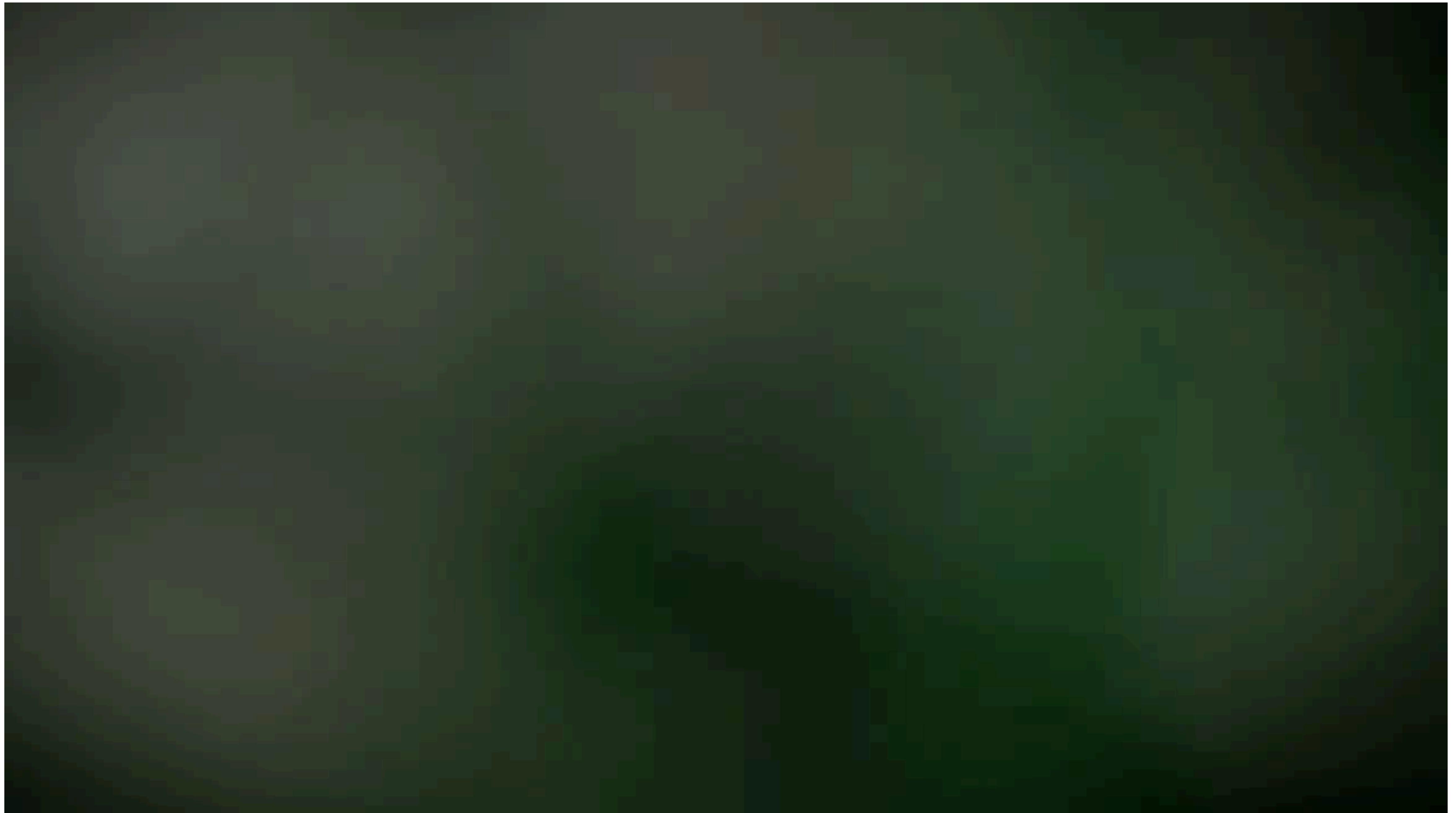
# Cell Lineage



# Cell Lineage

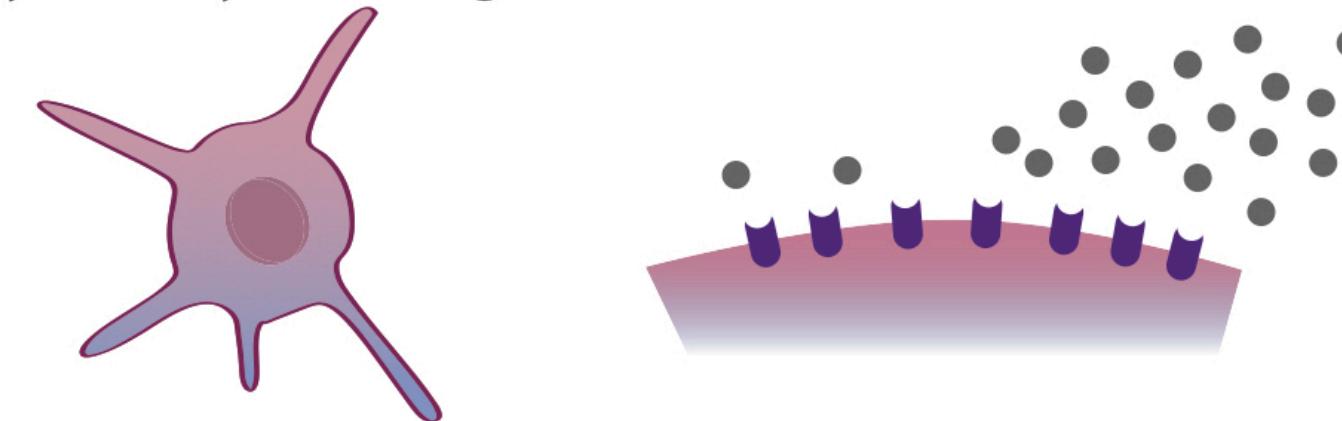


# **Axon guidance and synaptogenesis**

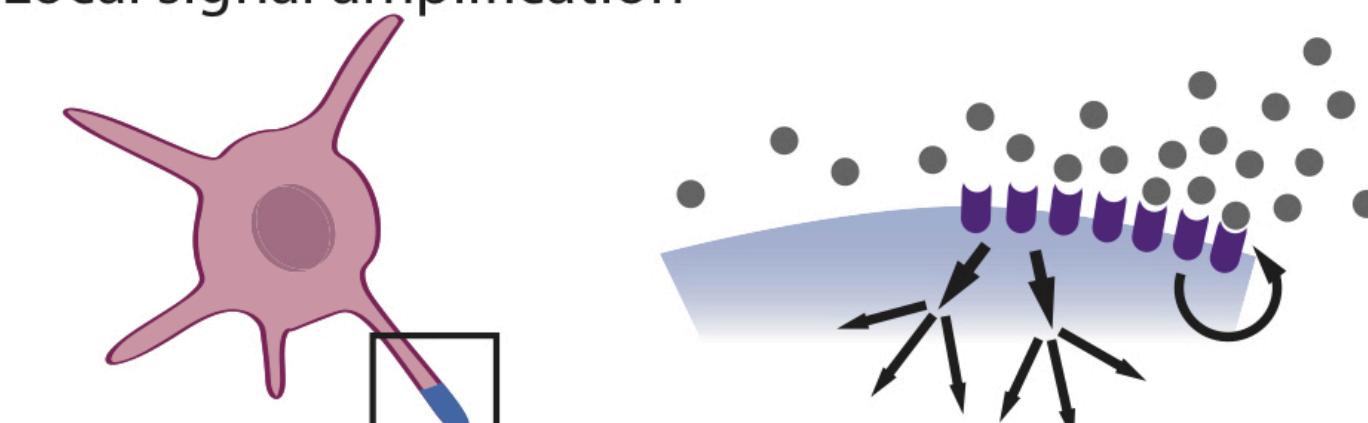


# Formation of neurites and polarity establishment

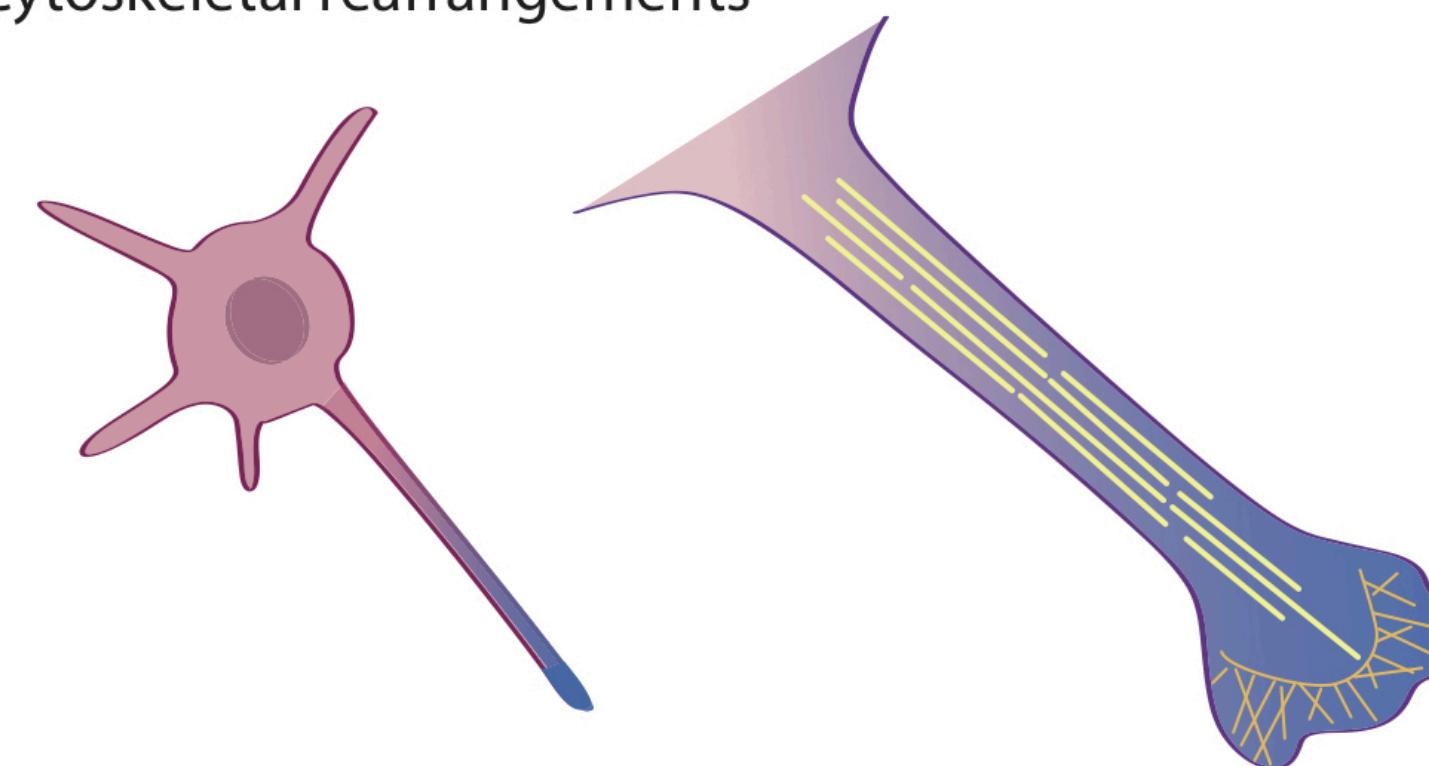
1. Symmetry breaking cue



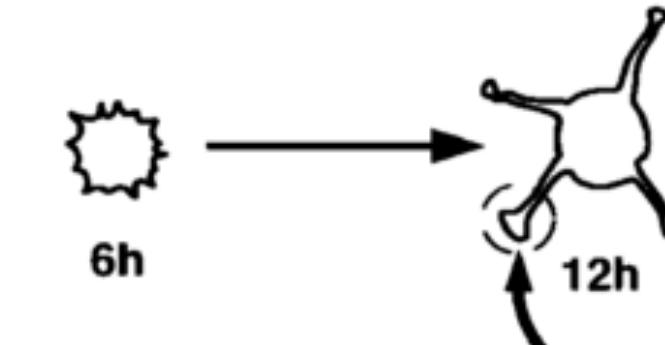
2. Local signal amplification



3. Cytoskeletal rearrangements



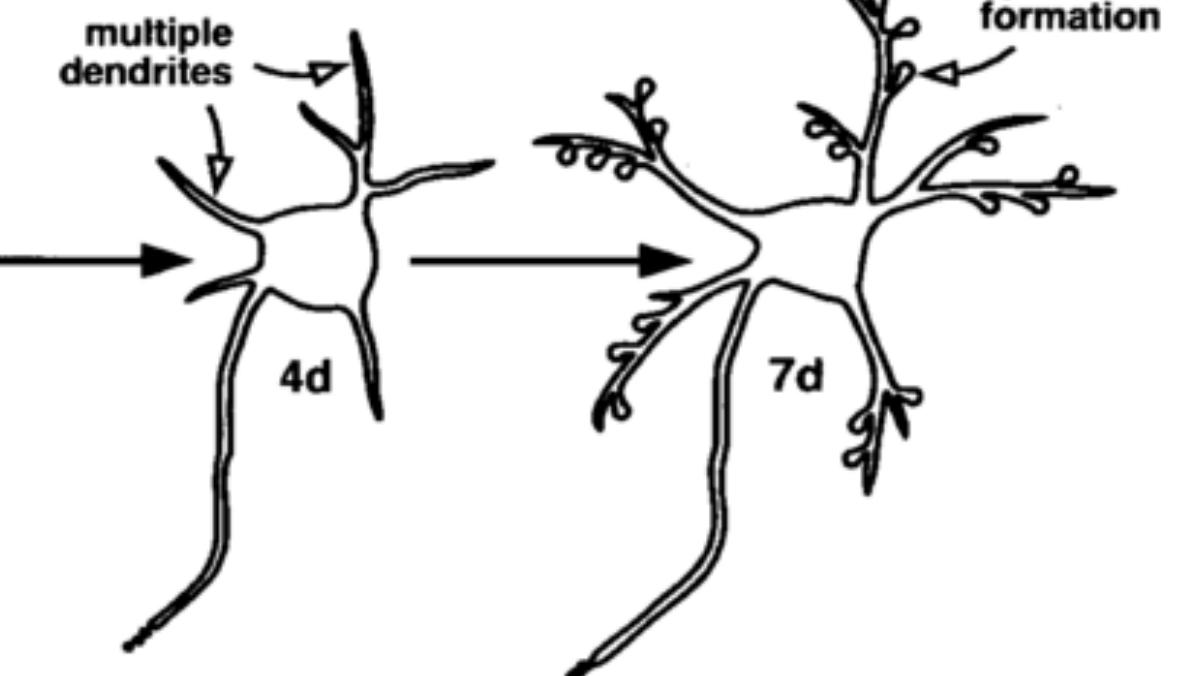
Stage 1  
Lamellipodia



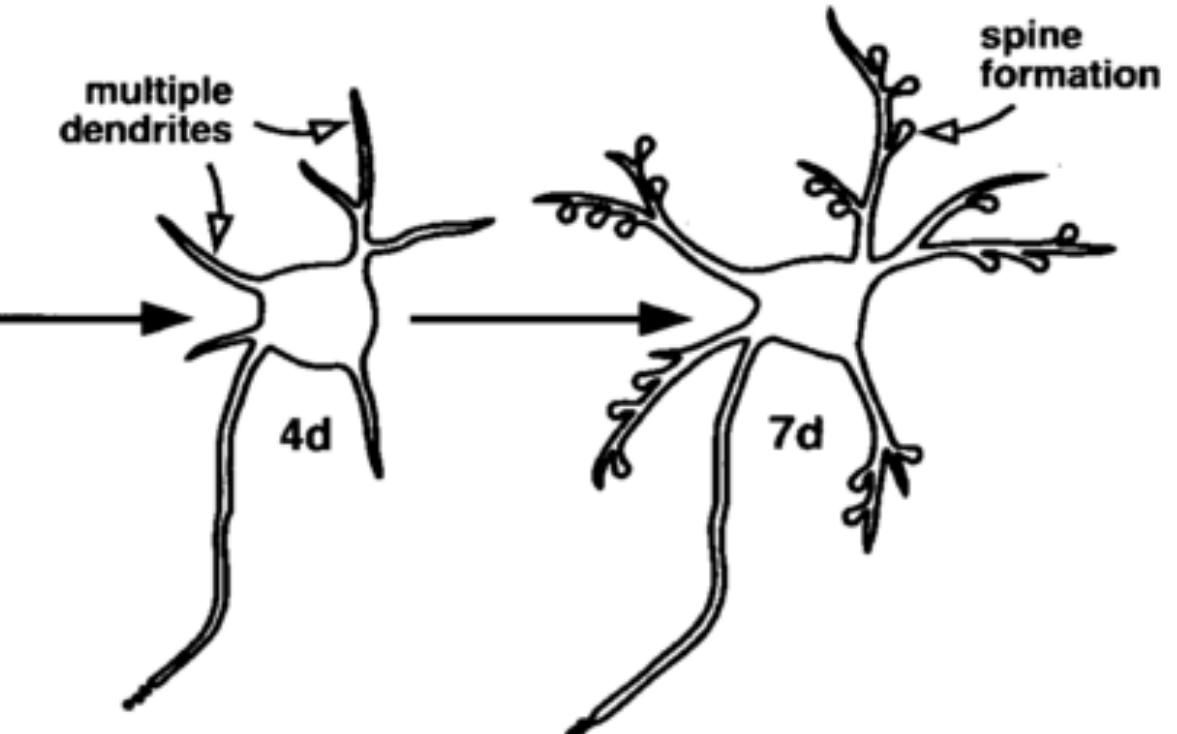
Stage 2  
Immature neurites



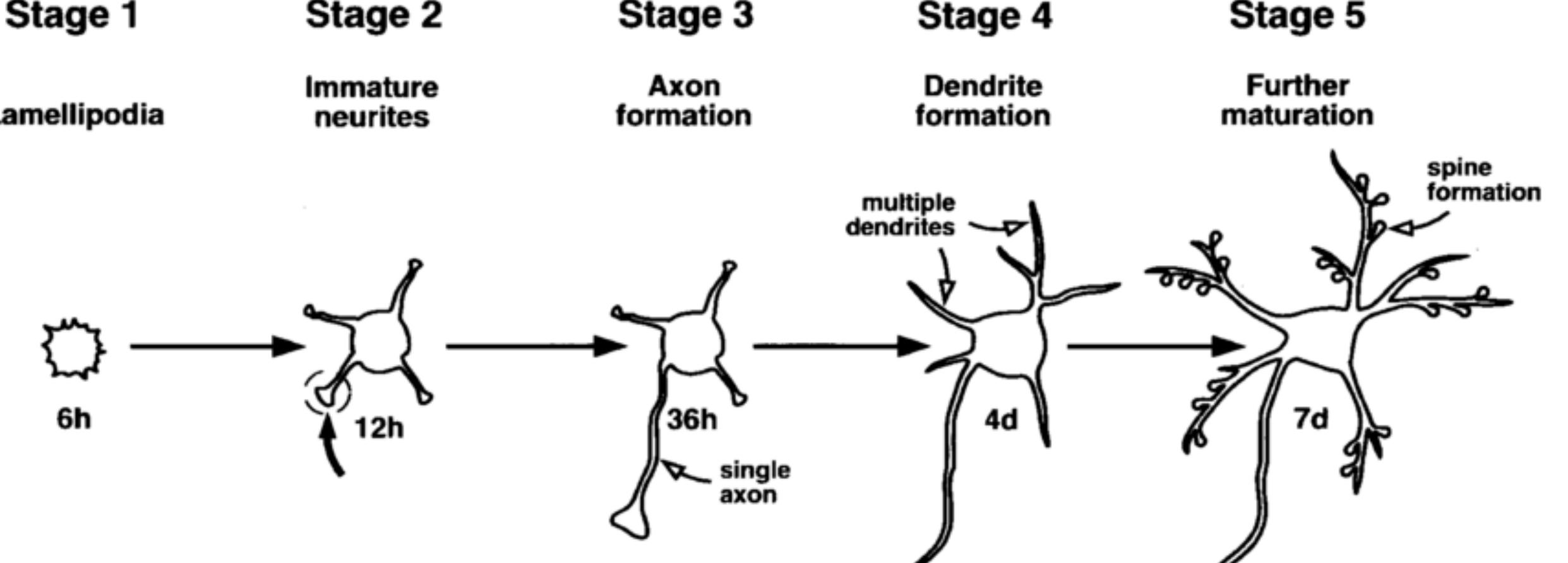
Stage 3  
Axon formation



Stage 4  
Dendrite formation

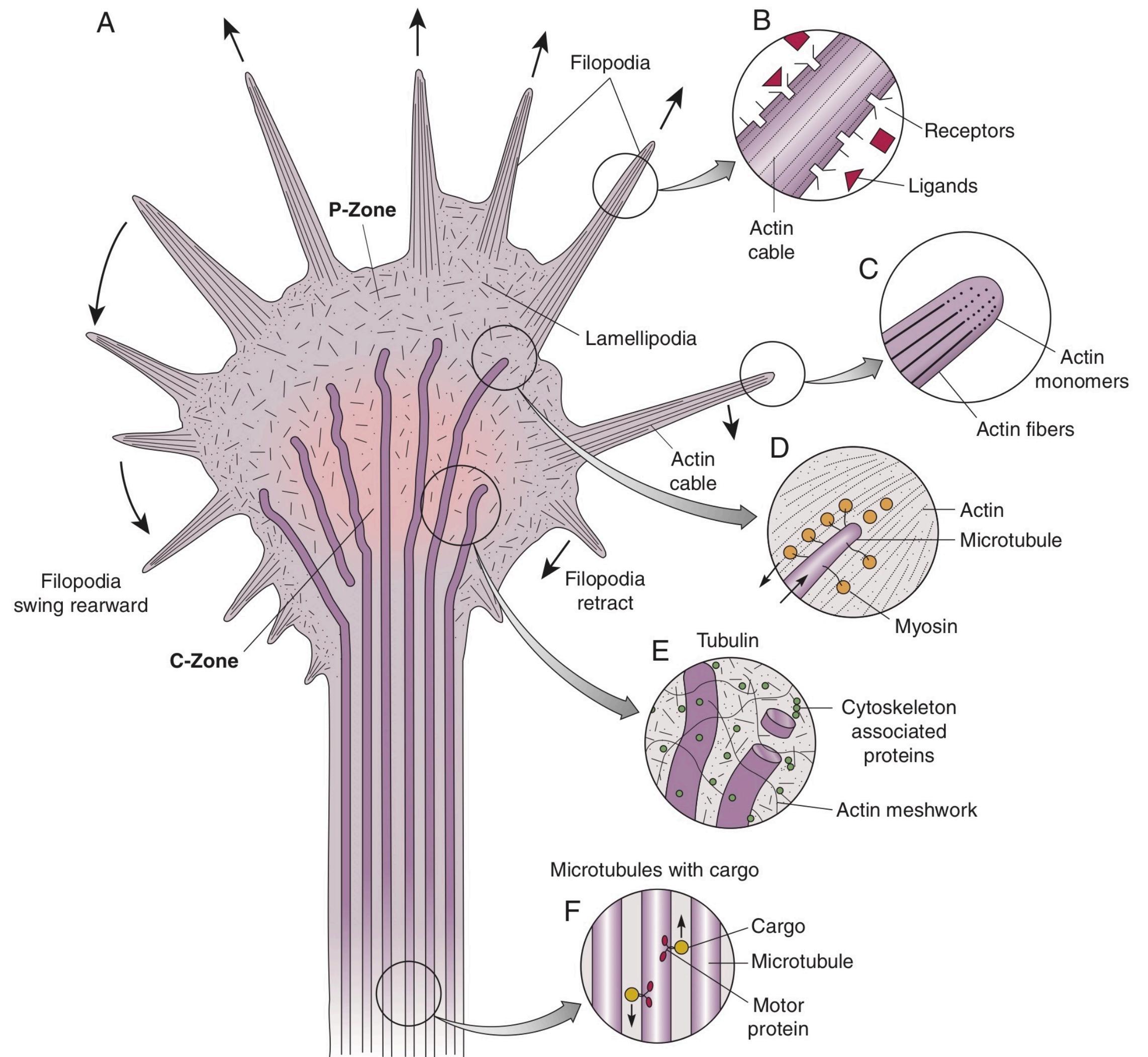


Stage 5  
Further maturation

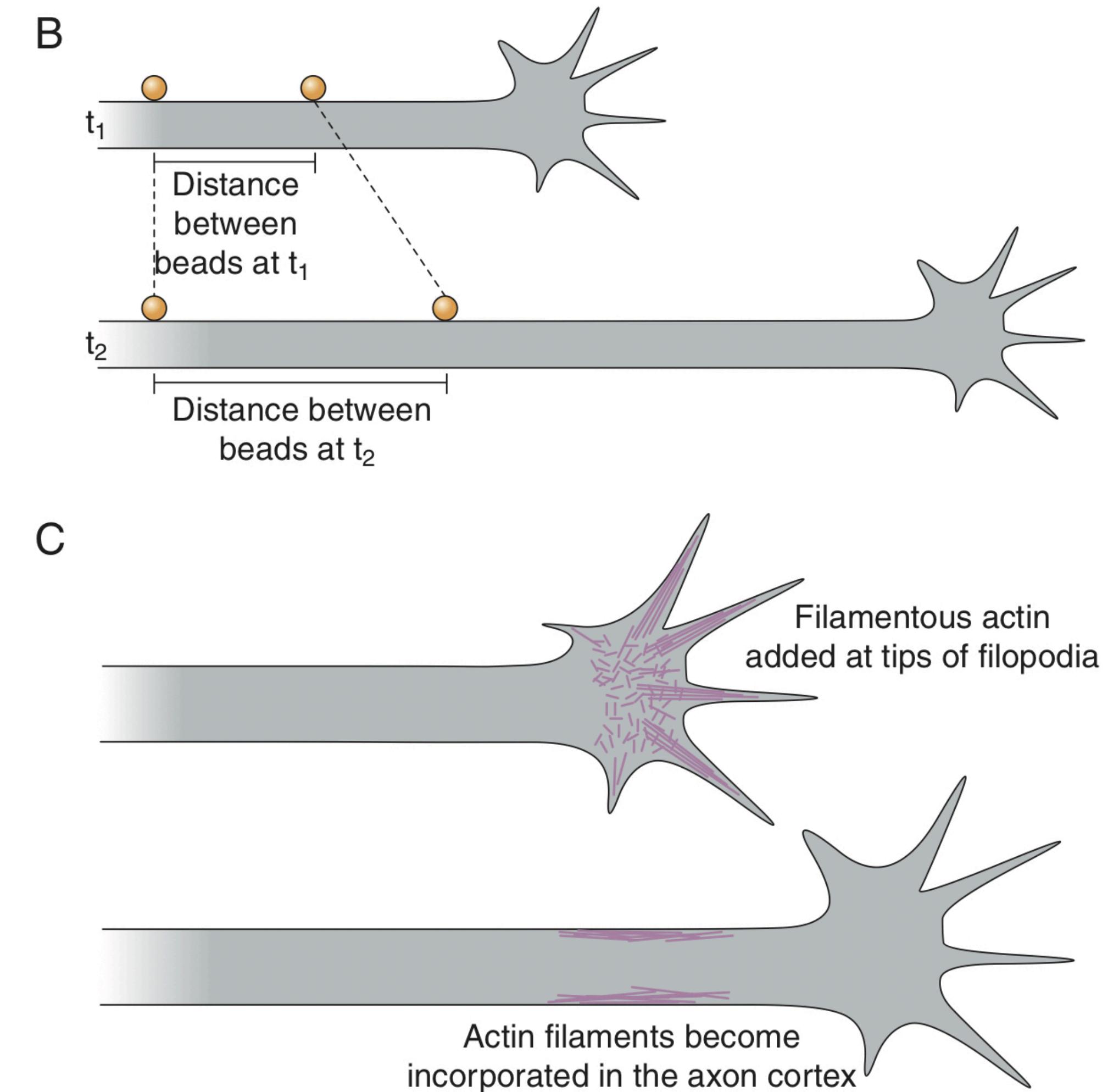
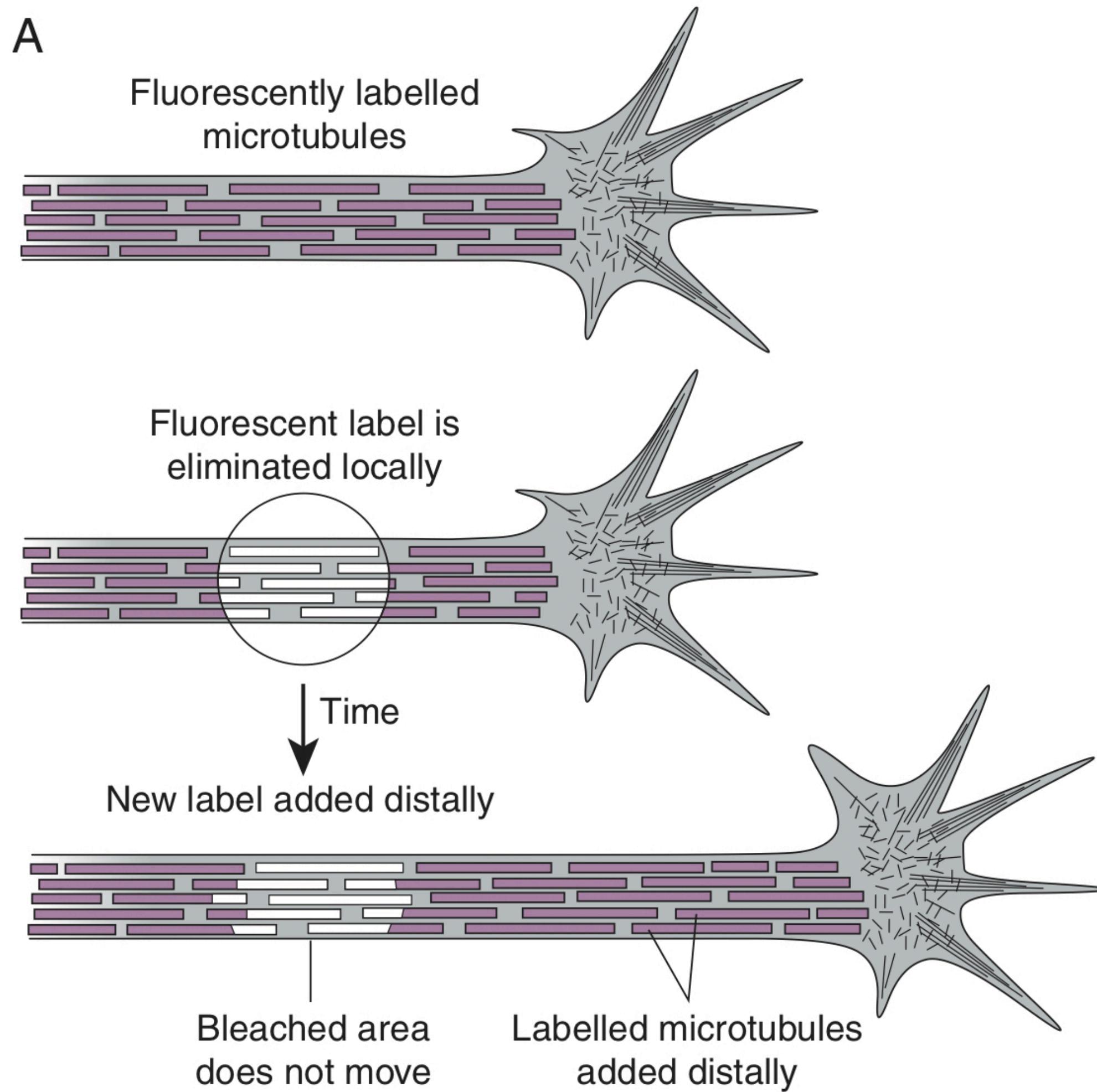


# Growth cone

- Actin bundles fill dynamic filopodia, which are bounded by membranes with cell adhesion molecules and various receptors
- Between the filopodia are sheets of lamellipodia that extend forward. They are filled with an actin meshwork.
- Microtubules push forward and carry cargo to and from the cell body along the axon shaft as they enter the growth cone and fan out toward the filopodia

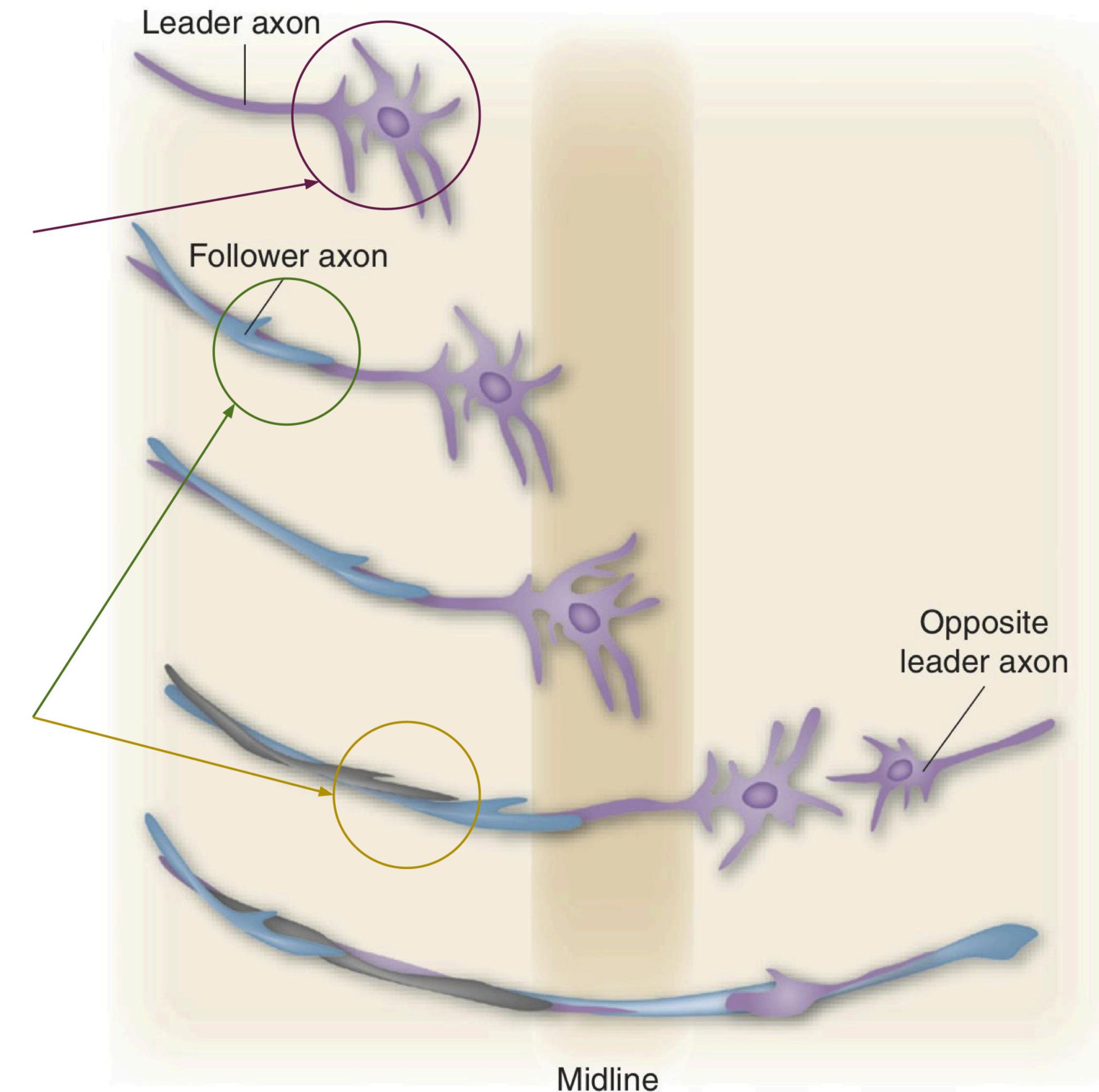


# Axon guidance: cytoskeleton dynamics



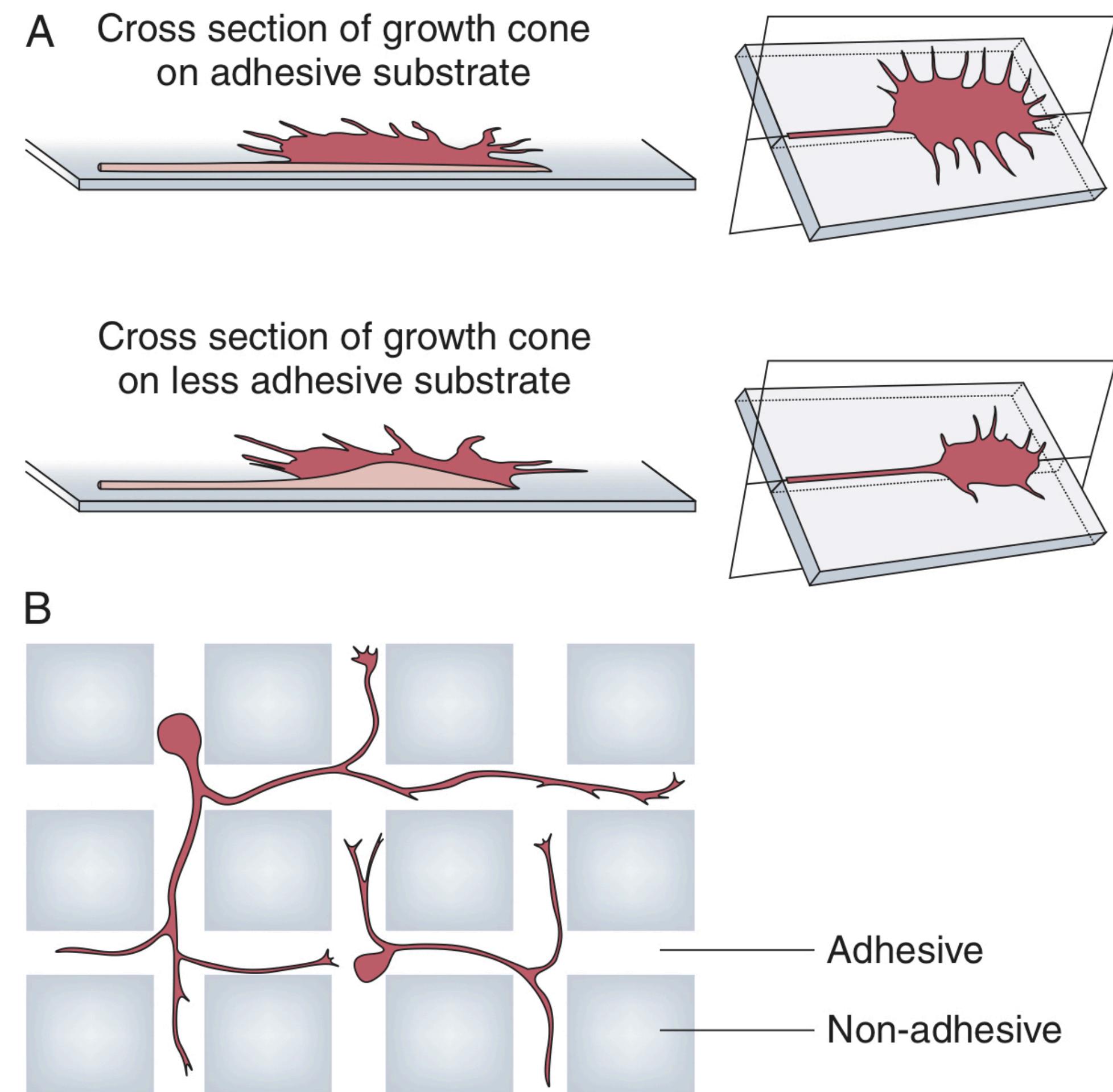
# Axon guidance: leader and follower

- The growth cones of pioneer axons that are growing straight ahead have several active filopodia and a few lamellipodia
- The growth cones of follower axons tend to be more simple, bullet-shaped with few filopodia. Growth cones get particularly complex when they arrive at choice points along the pathway such as the midline

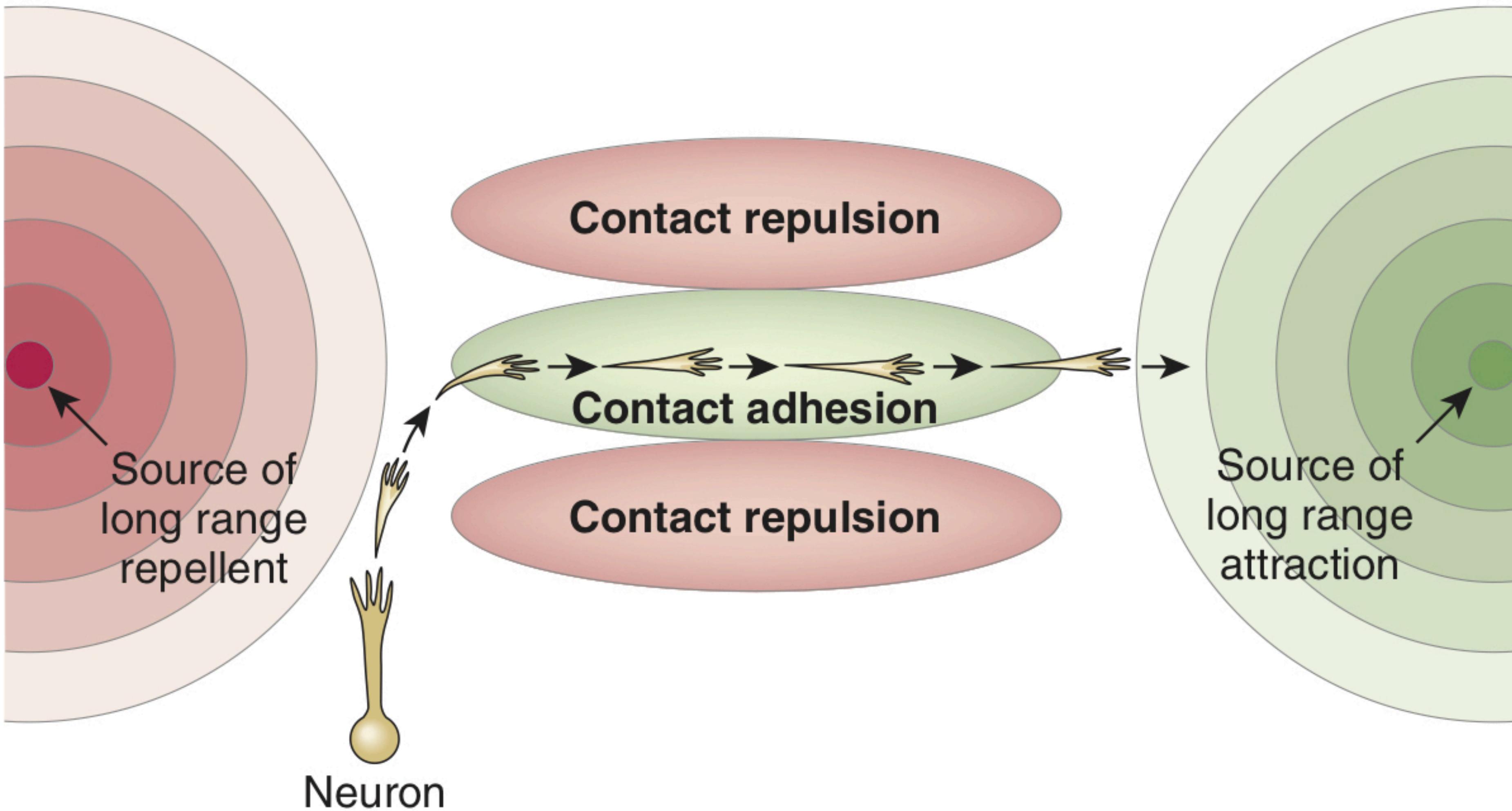


# Axon guidance: adhesion and repulsion

- Growth cones form also changes depends on substrate adhesivity:
- On a very adhesive substrate growth cones are flattened, have lots of filopodia, and do not move rapidly (top)
- On a less adhesive substrate, growth cones are more compact, rounded, have fewer processes, and often move more quickly
- Neurites in culture given a choice between an adhesive and a non-adhesive substrate will tend to follow the adhesive trails

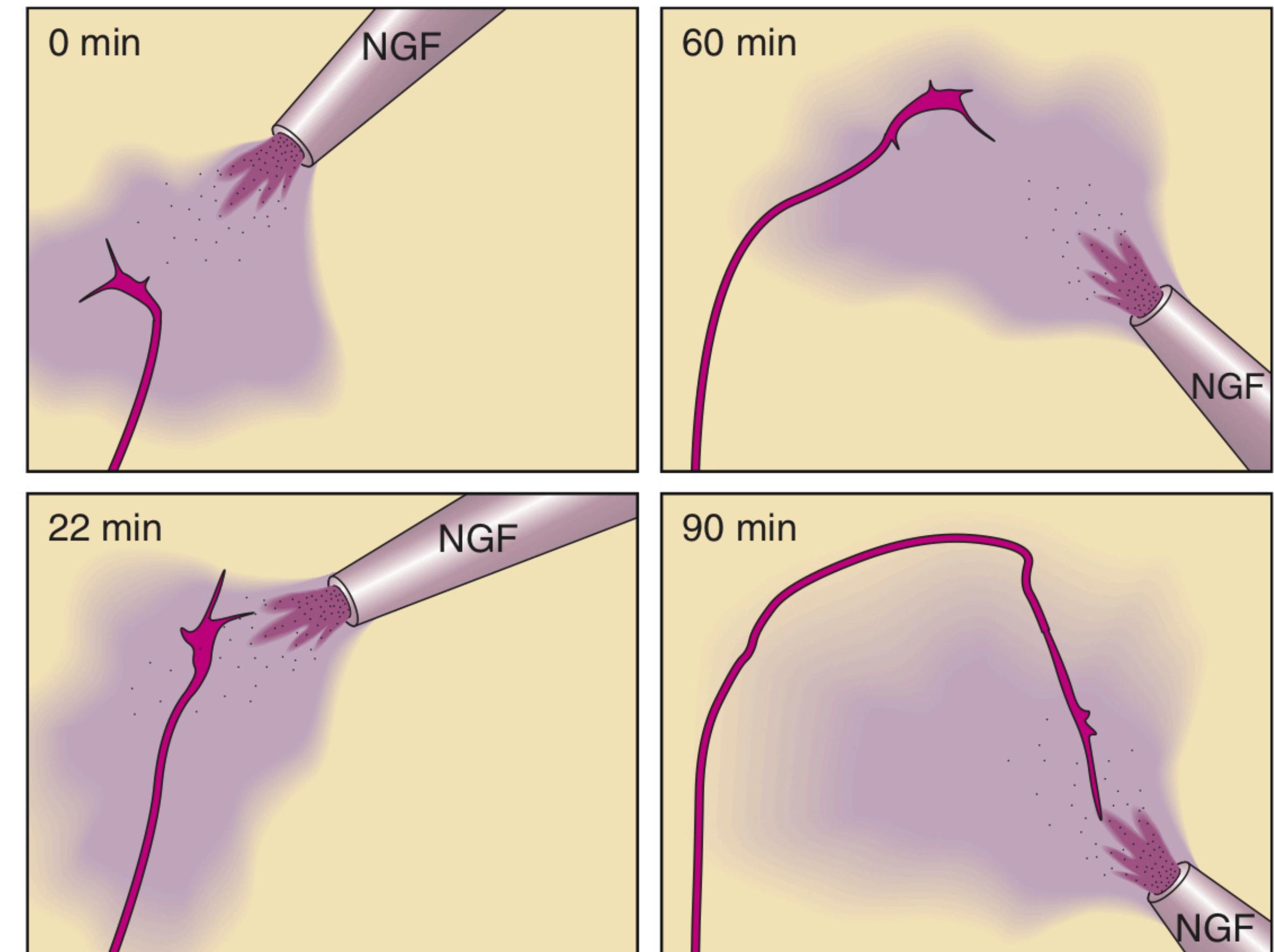


# Axon guidance: adhesion and repulsion

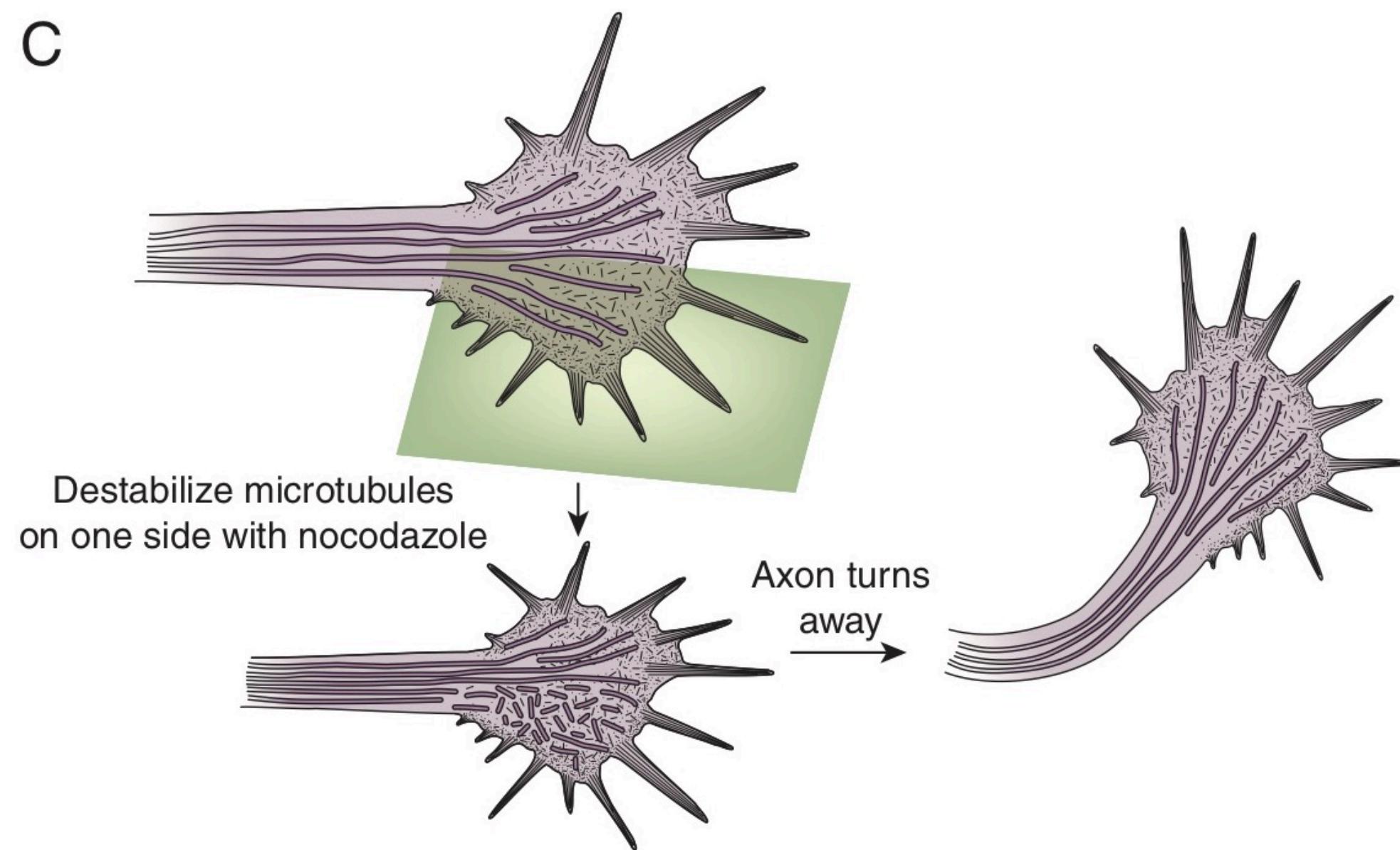
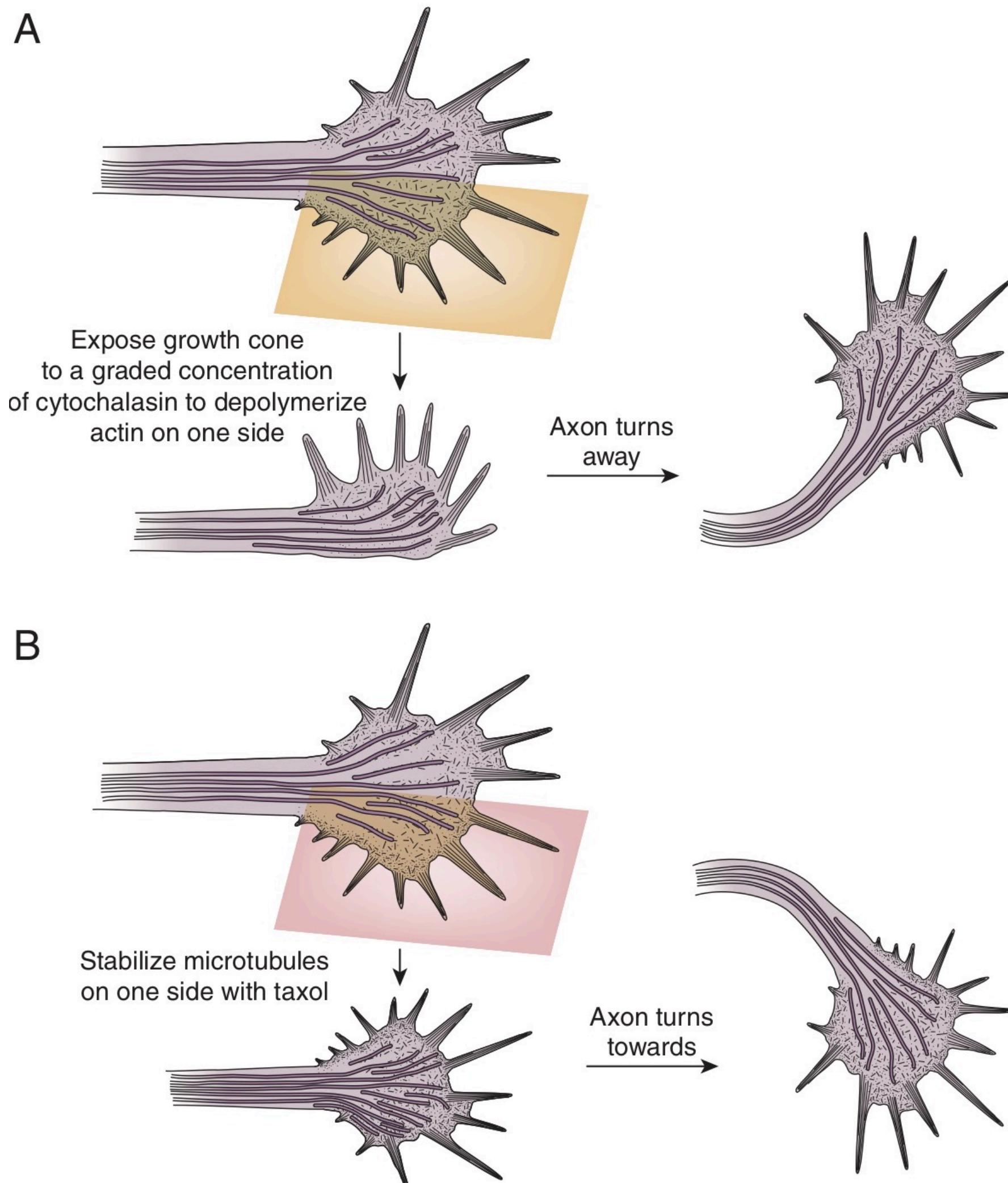


# Axon guidance: chemotaxis and gradients

- Growth cones can rely on chemotaxis to orient their growth
- “A sensory neuron turns toward a pipette that is ejecting nerve growth factor (NGF) and thus producing a diffusible gradient. Each time the pipette is moved, the axon reorients its growth.”
- (After Gundersen and Barrett, 1979)



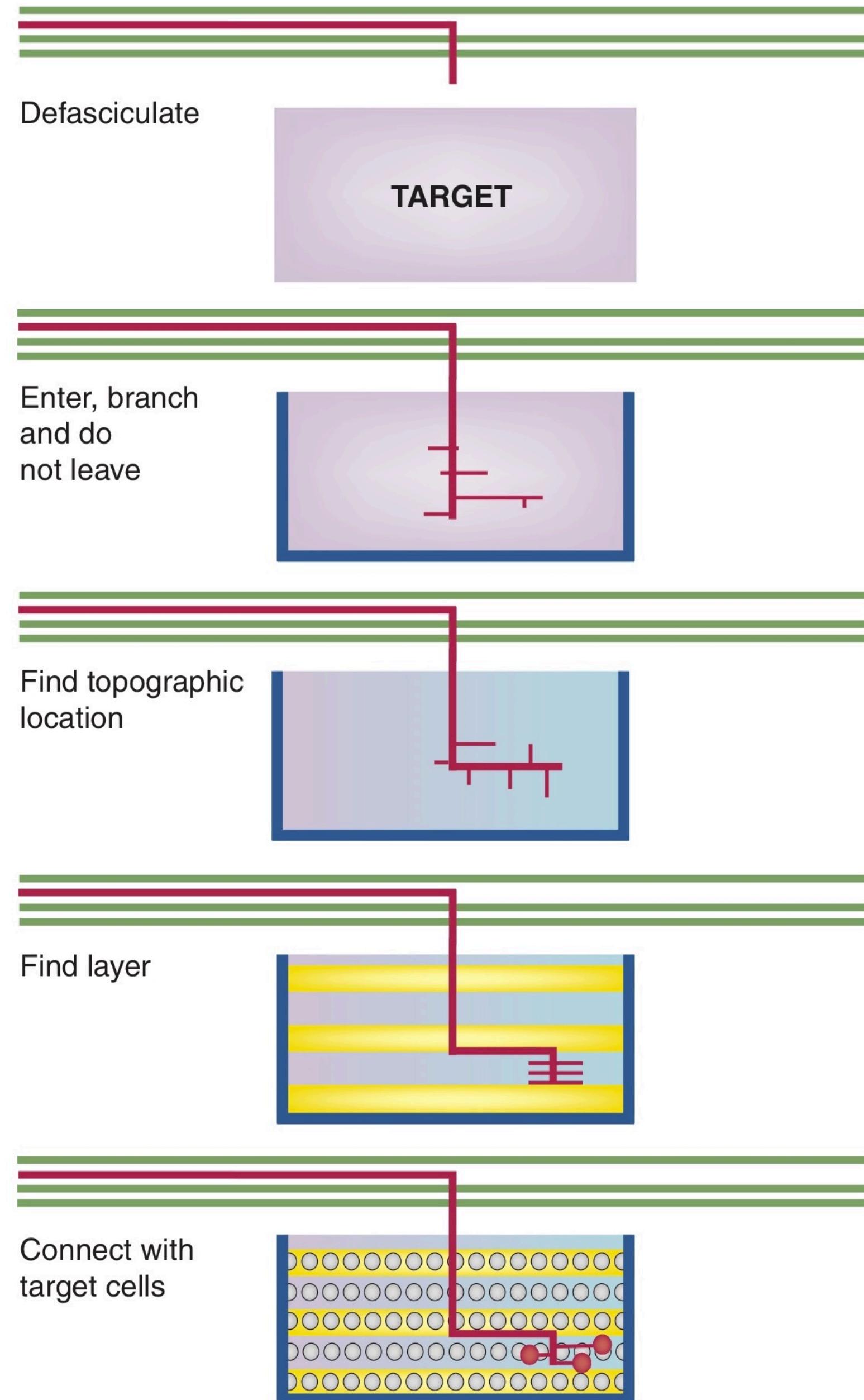
# Axon guidance: steering the growth cone



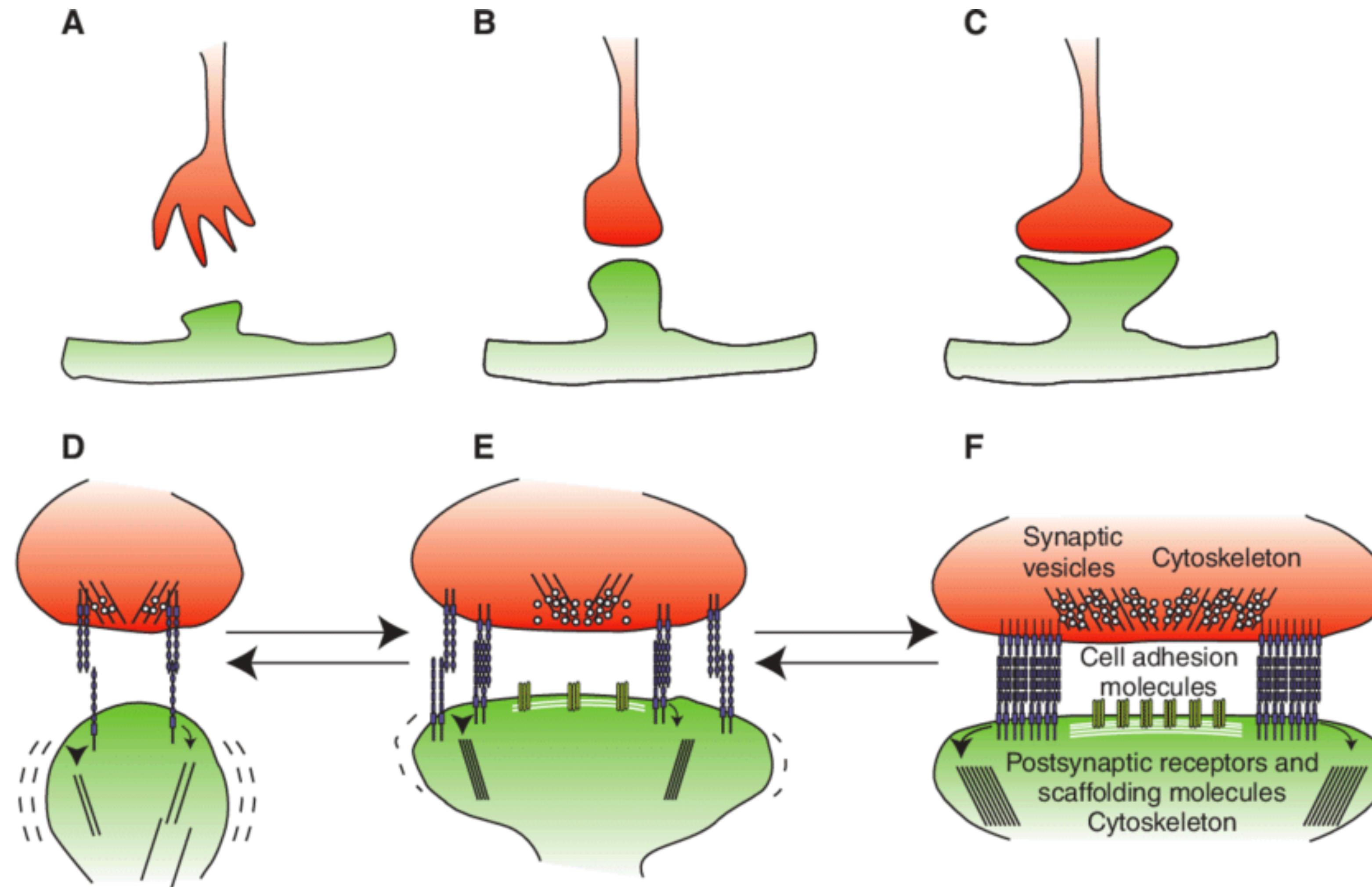
The growth cone is driven by a dynamic microtubule apparatus

# Stages of targeting

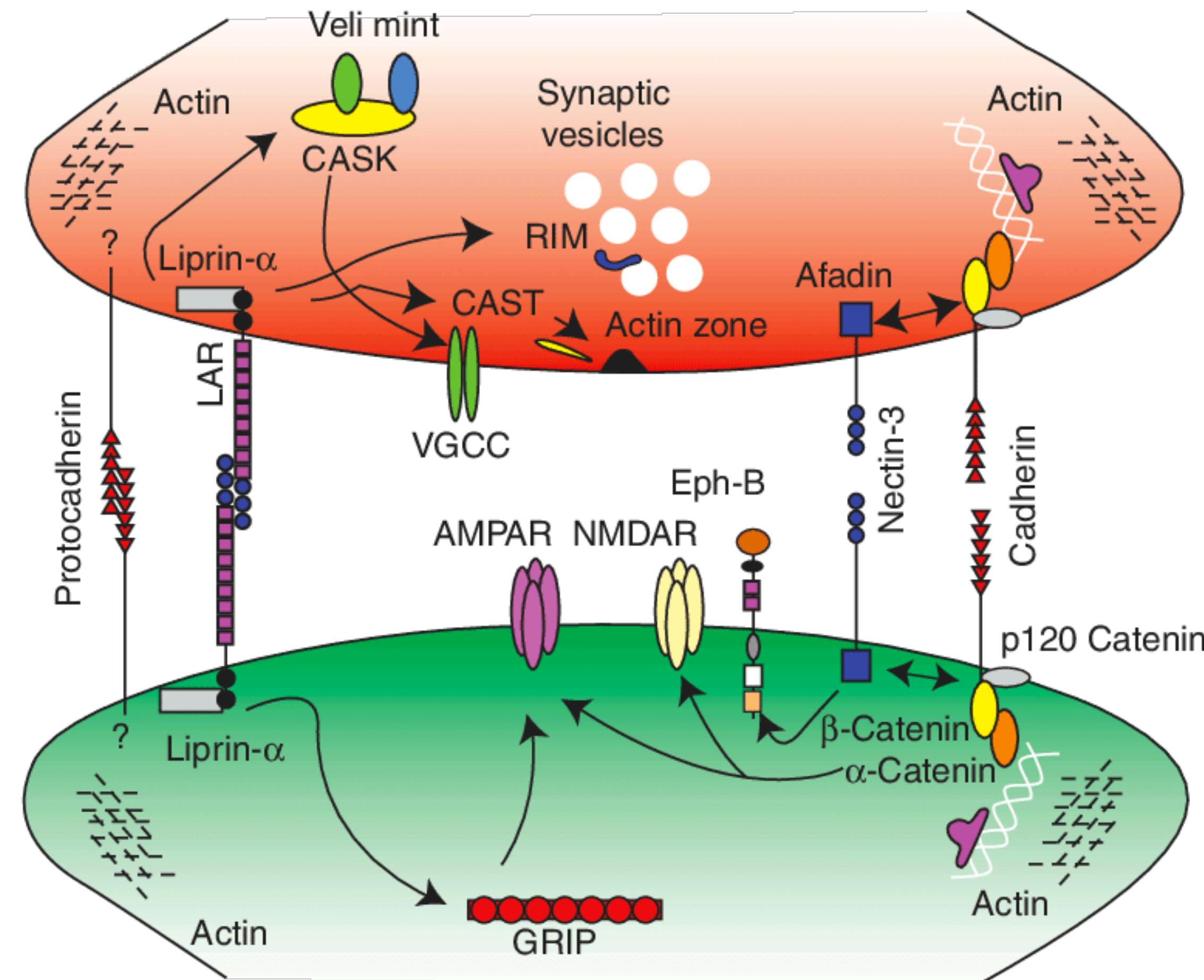
- An axon defasciculates in the region of the target
- It enters the target zone and begins to branch
- Then the axon responds to a topographic gradient that promotes branching at the current location
- It then selects one particular layer and finally homes in on particular target cells



# Stages of synapse formation

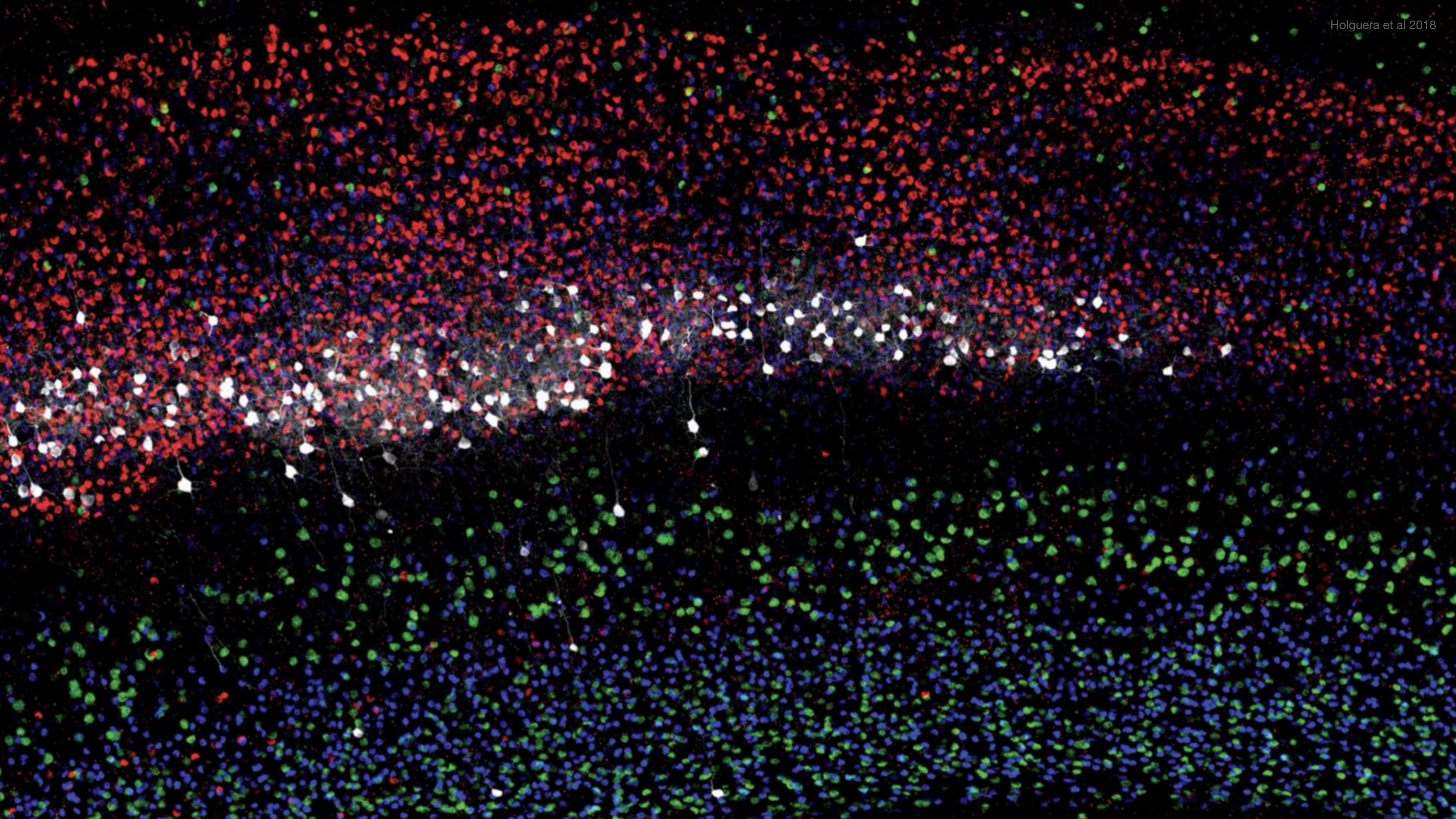


# Synapse formation



# Modeling

- Mechanical Forces in Neurulation and Cortical Folding
- Specifying Regions and Areas
- Neurogenesis and Building the Cerebral Cortex
- Neuronal Migration and Polarization
- Axon and Dendrite Growth, Guidance, and Branching
- Retinotectal Map Formation
- Activity-Dependent Development



# Links

- Goodhill GJ. Theoretical Models of Neural Development. *iScience*. 2018;8:183–199. doi:10.1016/j.isci.2018.09.017
- The physics of organoids: a biophysical approach to understanding organogenesis. Svend Dahl-Jensen, Anne Grapin-Botton. *Development* 2017 144: 946-951; doi: 10.1242/dev.143693
- Ziebell Frederik, Martin-Villalba Ana and Marciniak-Czochra Anna. Mathematical modelling of adult hippocampal neurogenesis: effects of altered stem cell dynamics on cell counts and bromodeoxyuridine-labelled cells. *J. R. Soc. Interface* <http://doi.org/10.1098/rsif.2014.0144>
- Julia M. Gohlke, William C. Griffith, Elaine M. Faustman, Computational Models of Neocortical Neuronogenesis and Programmed Cell Death in the Developing Mouse, Monkey, and Human, *Cerebral Cortex*, Volume 17, Issue 10, October 2007, Pages 2433–2442, <https://doi.org/10.1093/cercor/bhl151>
- Nie J, Li G, Guo L, Liu T. A computational model of cerebral cortex folding. *Med Image Comput Comput Assist Interv.* 2009;12(Pt 2):458–465. doi:10.1007/978-3-642-04271-3\_56