3. Stem Cells

Potential and Niches

- Additional (optional) textbooks:

Michal K Stachowiak & Emmanuel S Tzanakakis," *Stem Cells: From Mechanisms to Technologies"* - World Scientific, 2011. http://www.worldscientific.com/

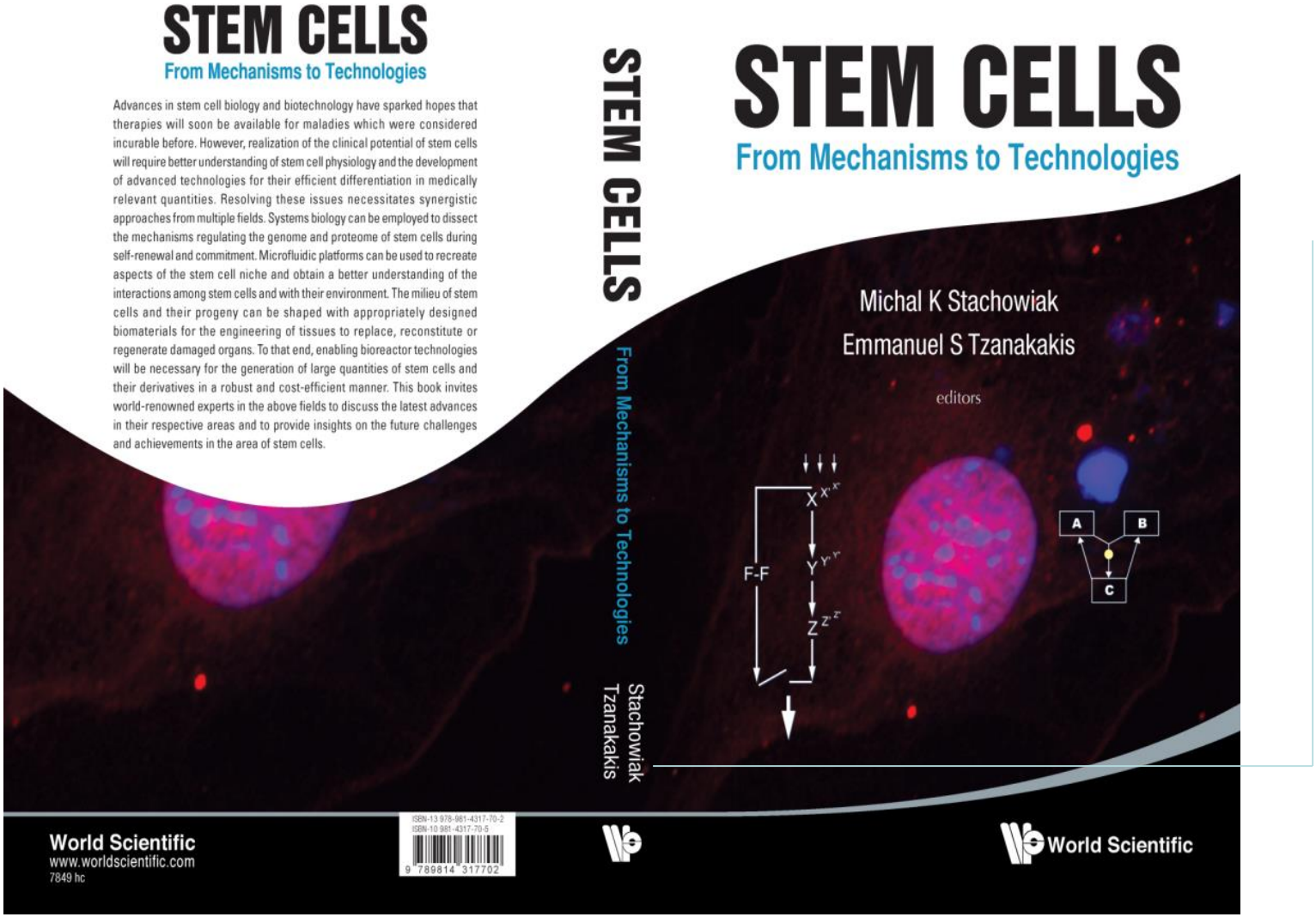
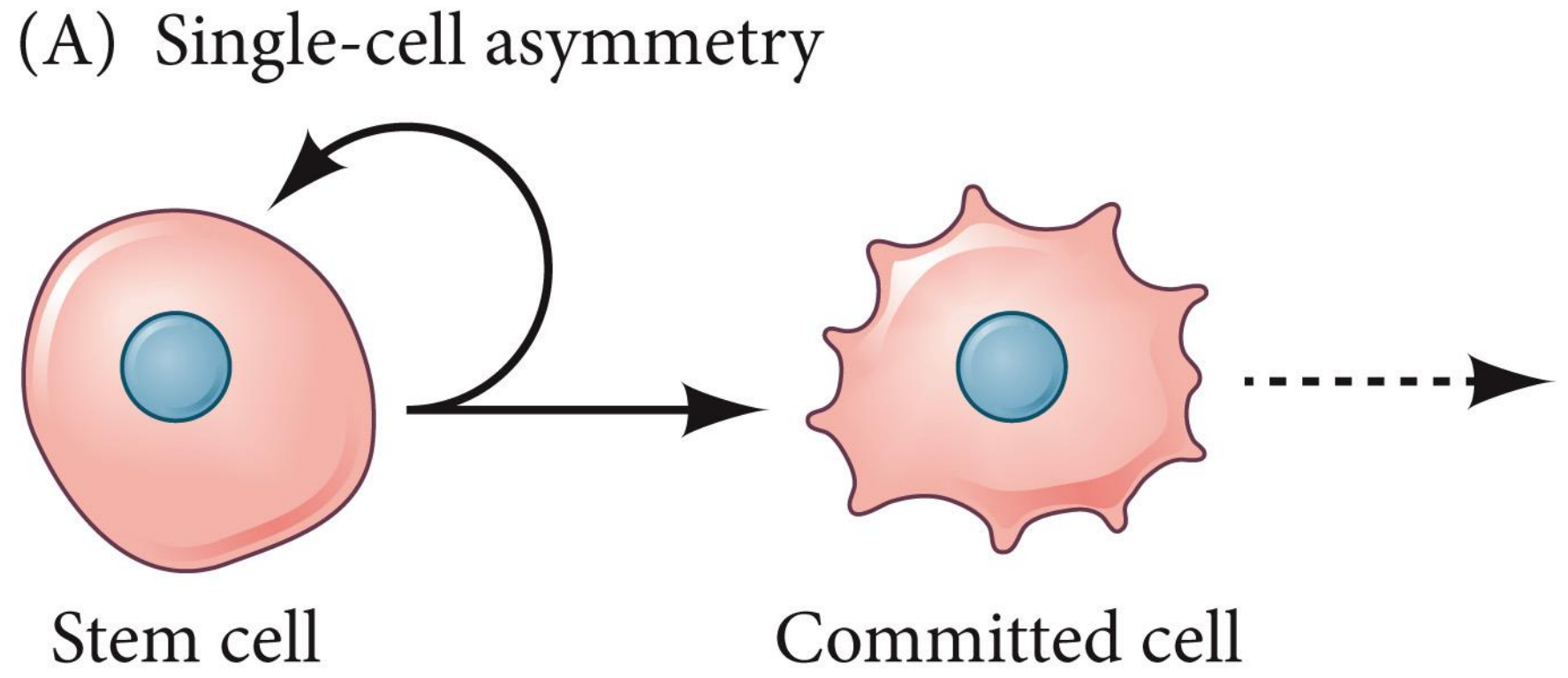
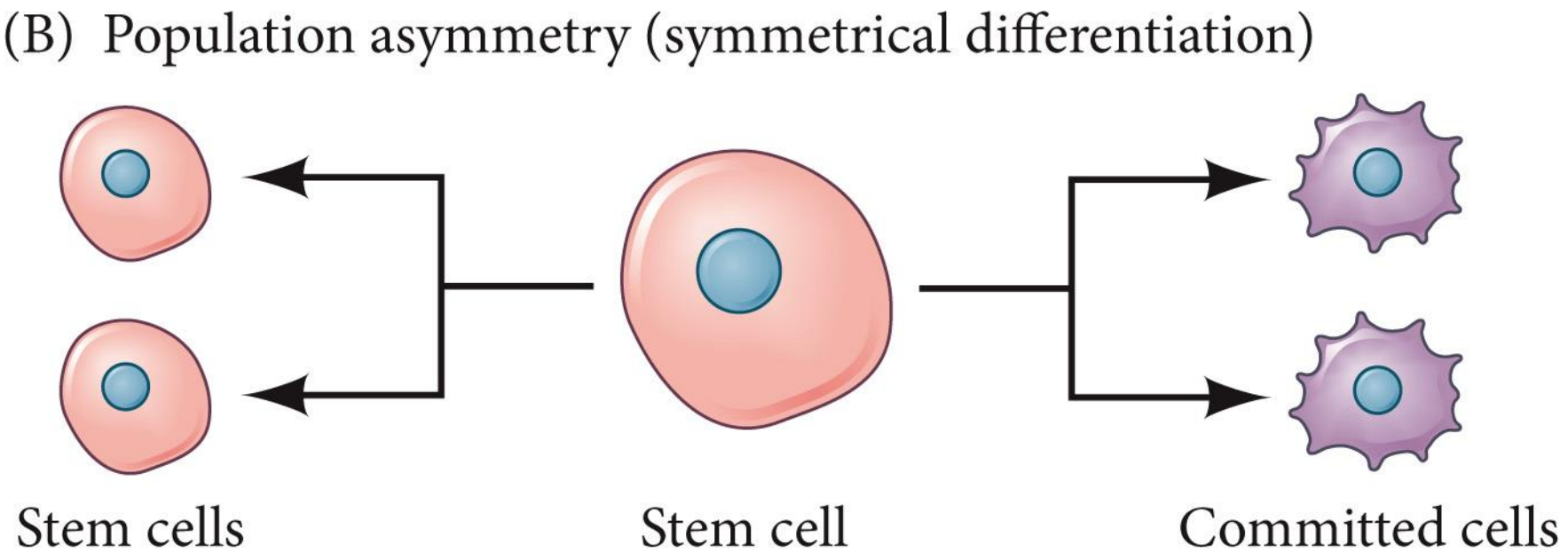


Figure 5.1 The stem cell concept (Part 1)



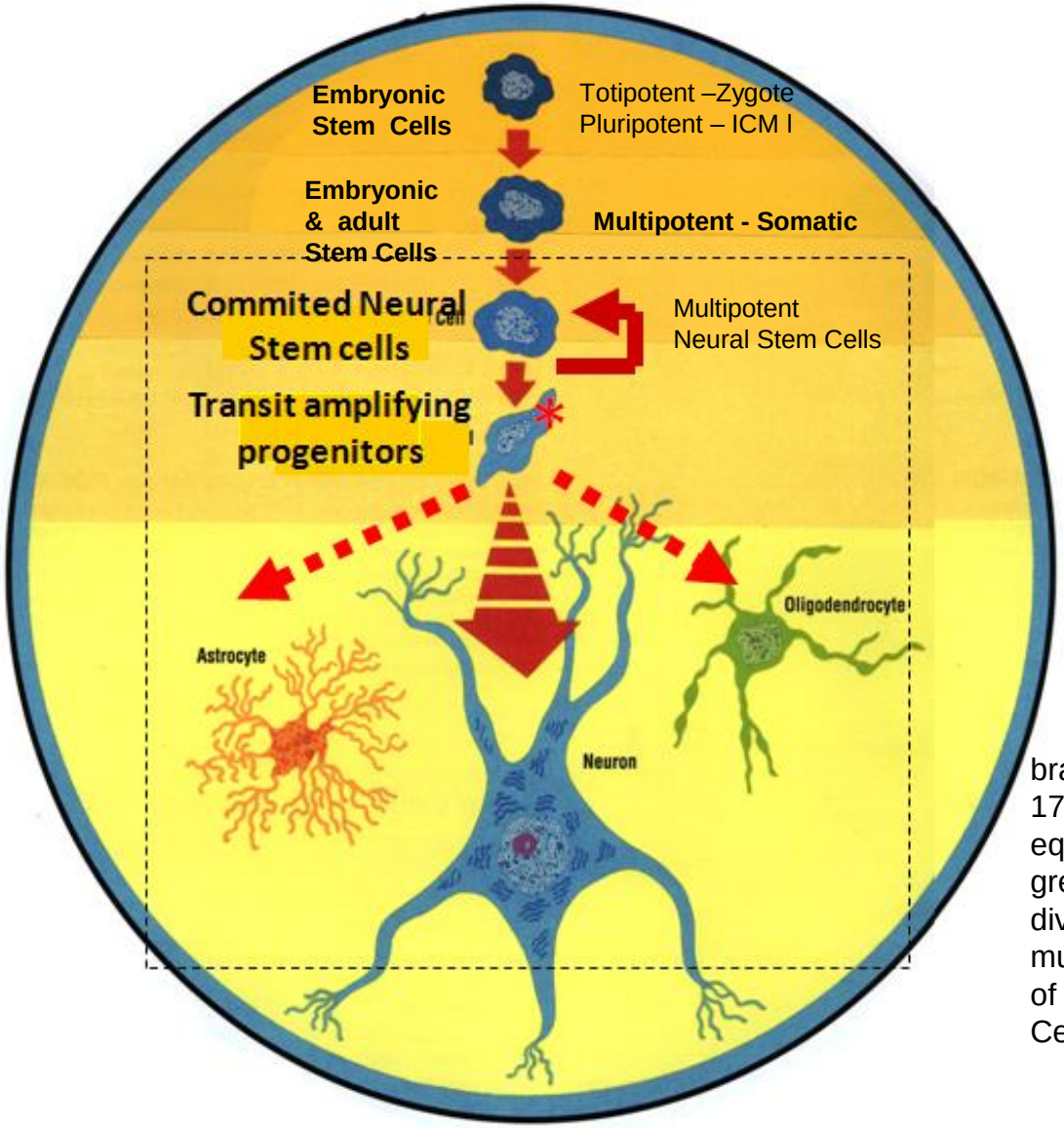
DEVELOPMENTAL BIOLOGY 11e, Figure 5.1 (Part 1)

Figure 5.1 The stem cell concept (Part 2)



DEVELOPMENTAL BIOLOGY 11e, Figure 5.1 (Part 2)

Unfolding Developmental Potential of Stem Cells



brain contains approximately 170 billion cells (neurons an equal number of glial cells of of great variety of types). This diversity begins with the multipotent neuroepithelial cells of the neural tube Neural Stem Cells.

Adult stem cells (typically multipotent):
create restricted array of cells in culture and have a finite number of generations for self-renewal (contributes to aging)

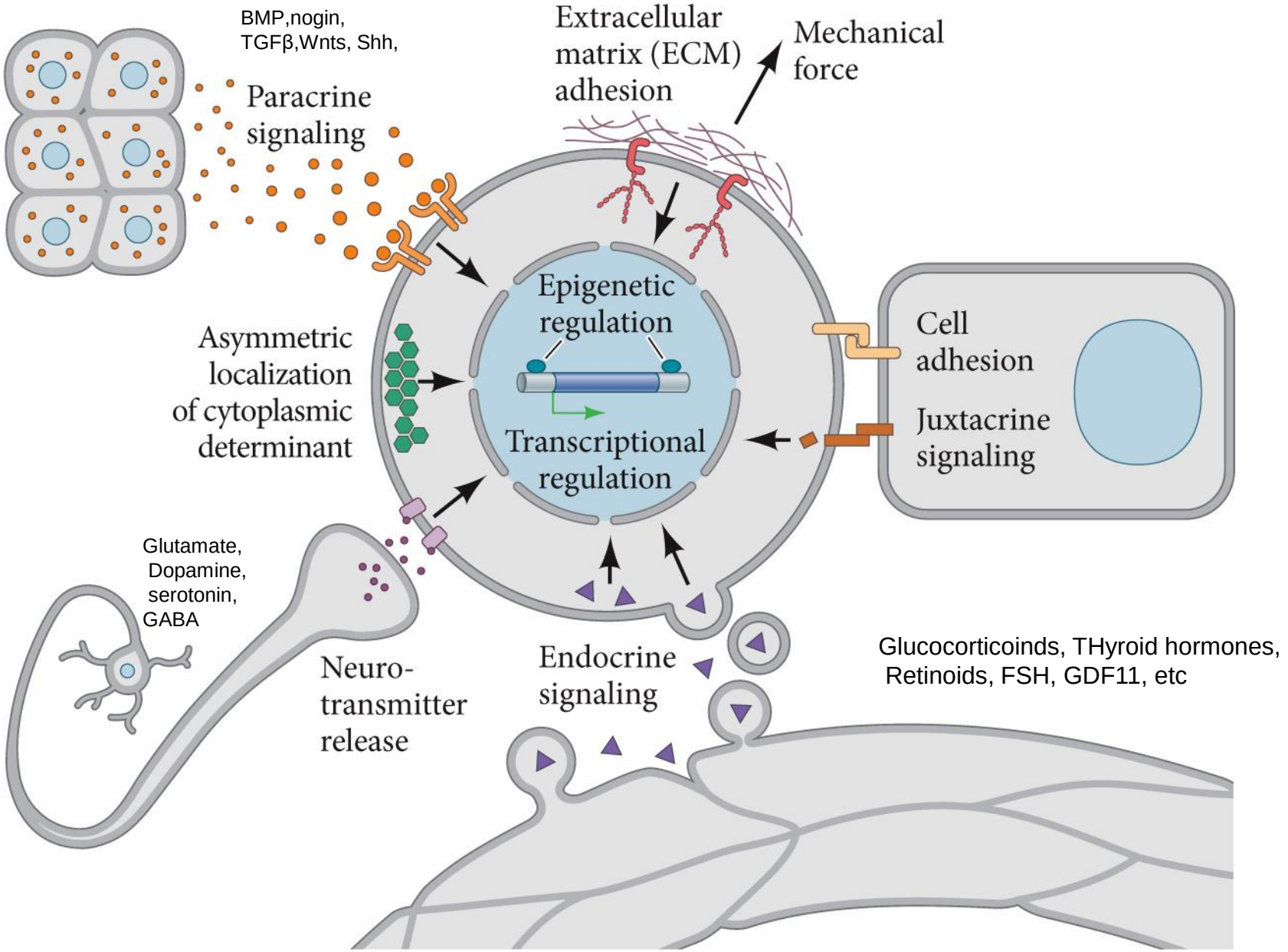
- hematopoietic stem cells that function to generate all the cells of the blood,

- Germinal stem Cells (testes, ovarian)

- brain

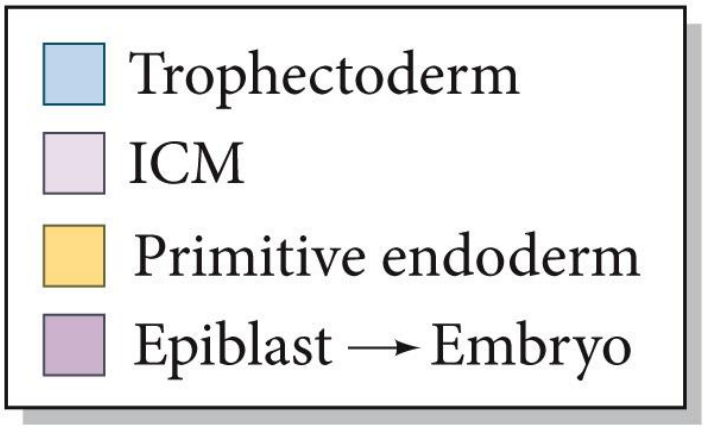
- epidermis,
- muscle,
- teeth,
- gut,
- lung,
- cornea,
- etc.,

Figure 5.4 To divide or not to divide: overview of stem cell regulatory mechanisms – Niche Factors



DEVELOPMENTAL BIOLOGY 11e, Figure 5.4

Figure 5.5 Establishment of the inner cell mass Niche in blastocyst

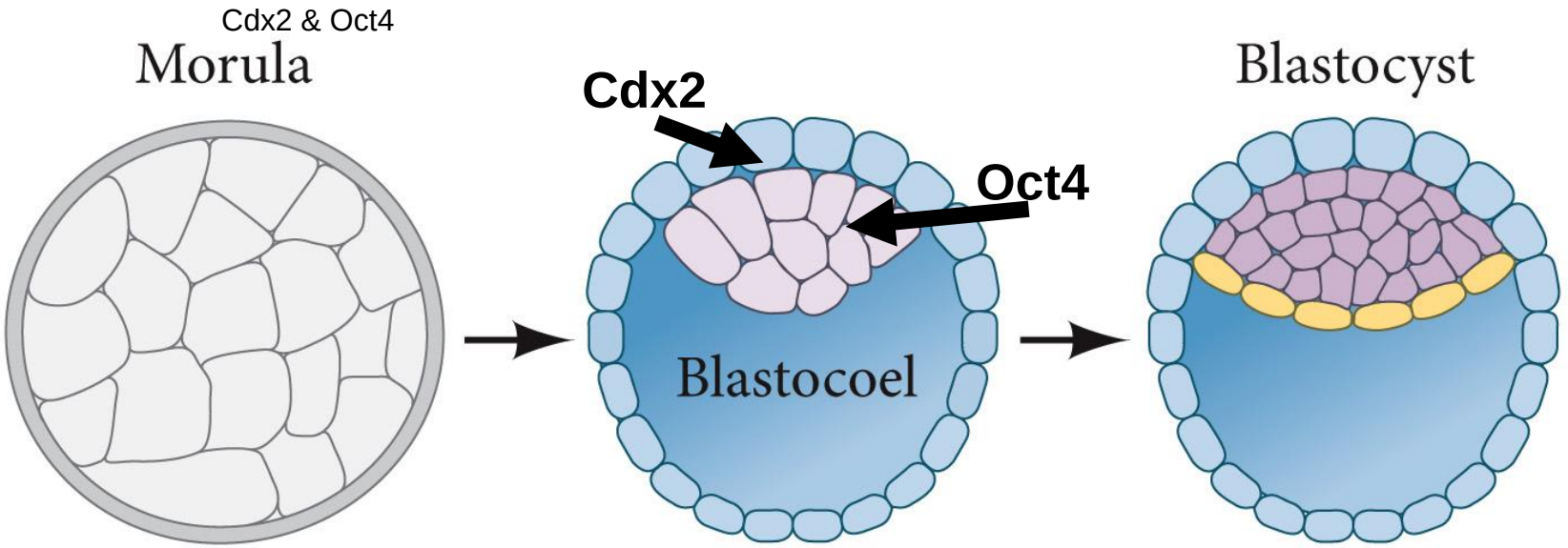


Embryonic placenta, chorion

Epiblast, hypoblast

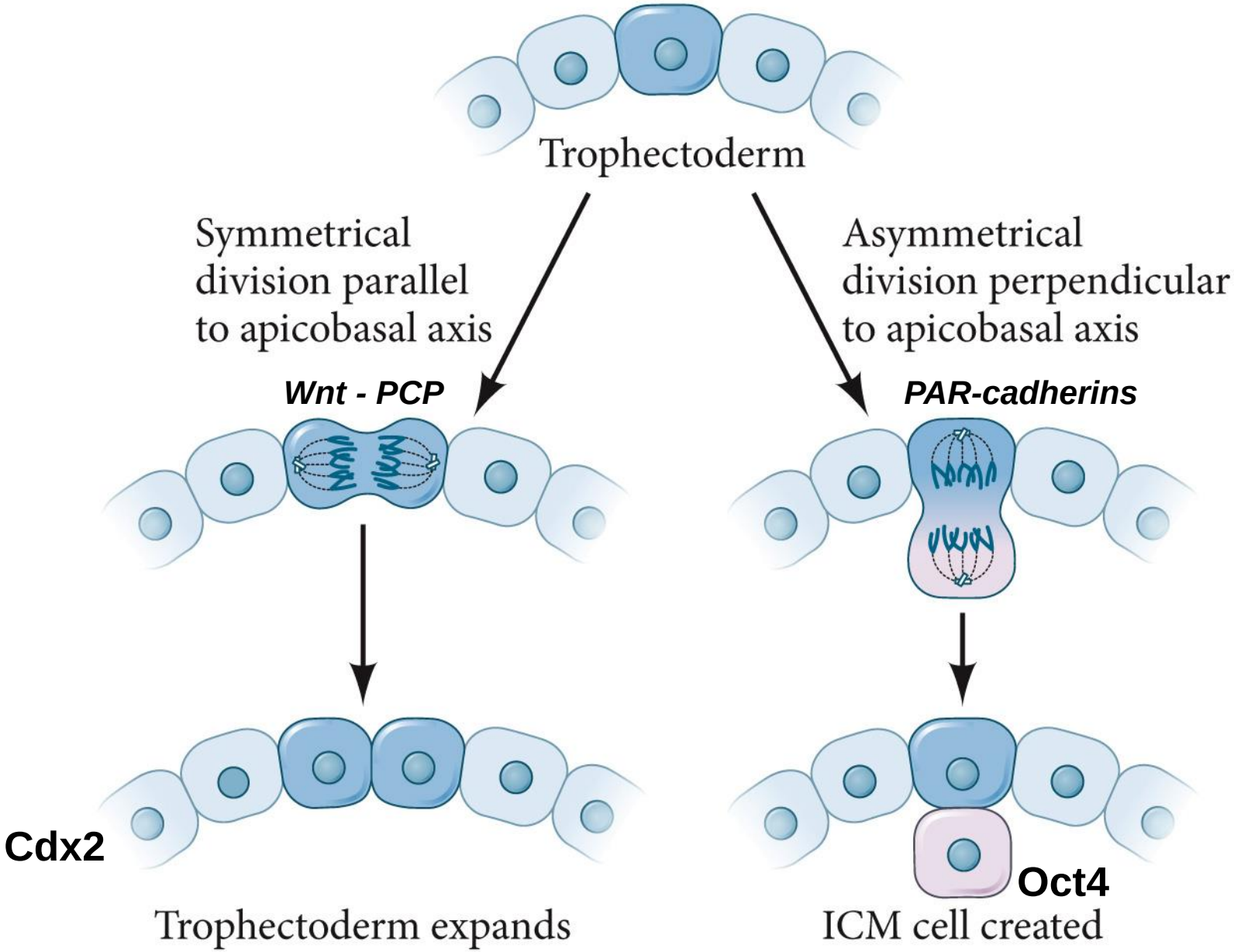
Hypoblast > primitive endoderm, yolk sac

Epiblast > 200 cell types



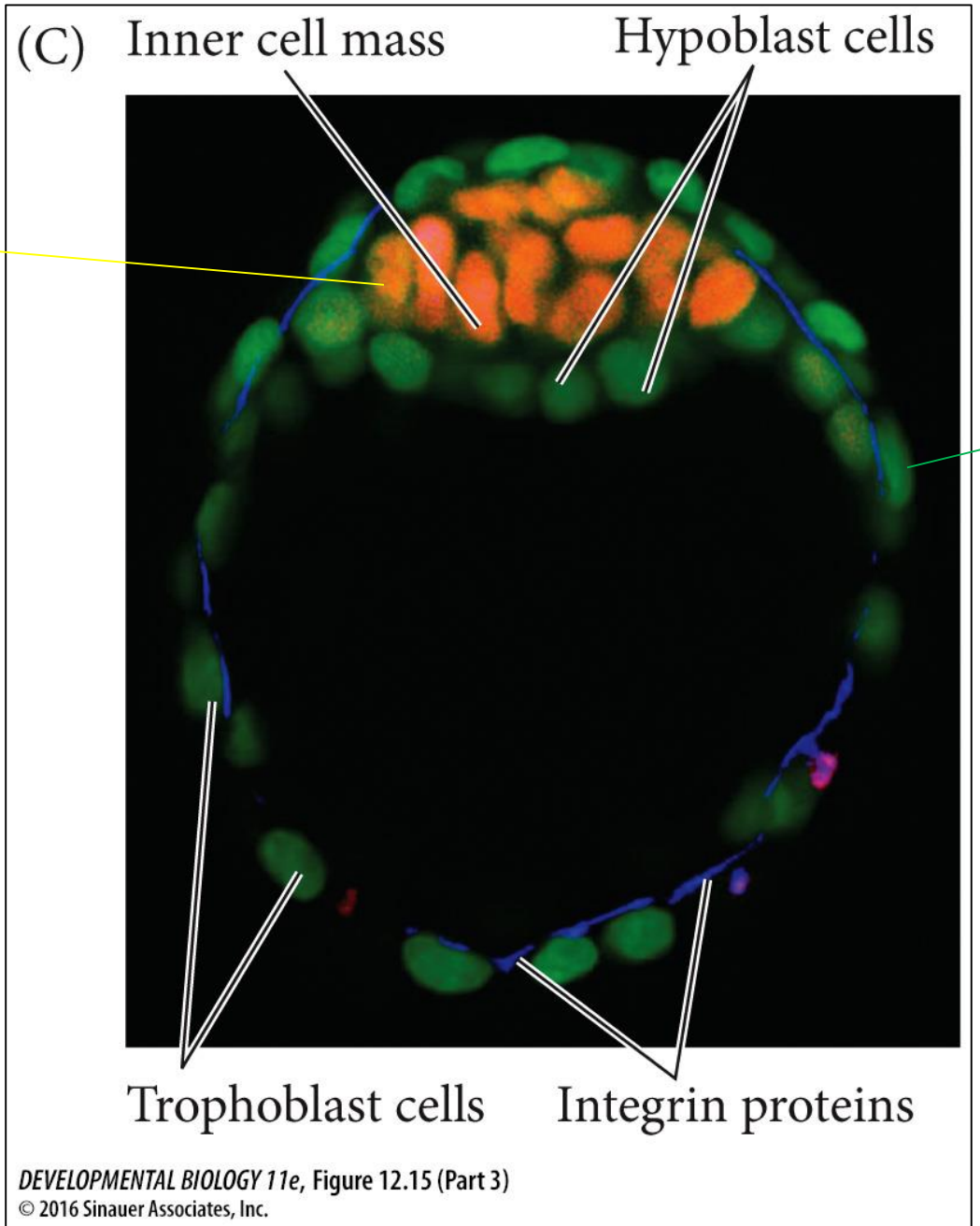
DEVELOPMENTAL BIOLOGY 11e, Figure 5.5

Figure 5.6 Divisions about the apicobasal axis



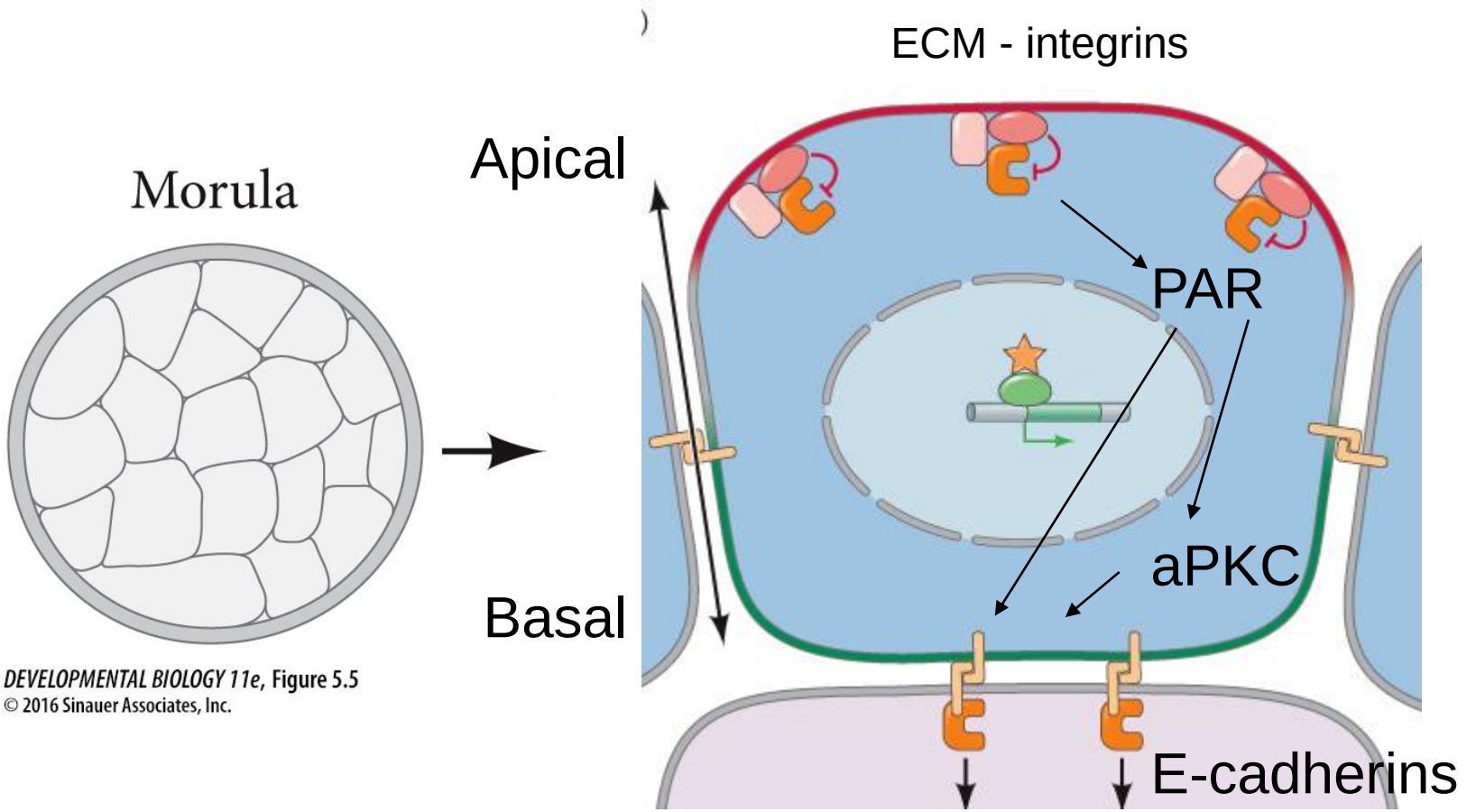
DEVELOPMENTAL BIOLOGY 11e, Figure 5.6

Figure 12.15 Possible pathway initiating the distinction between inner cell mass and trophoblast (Part 3)



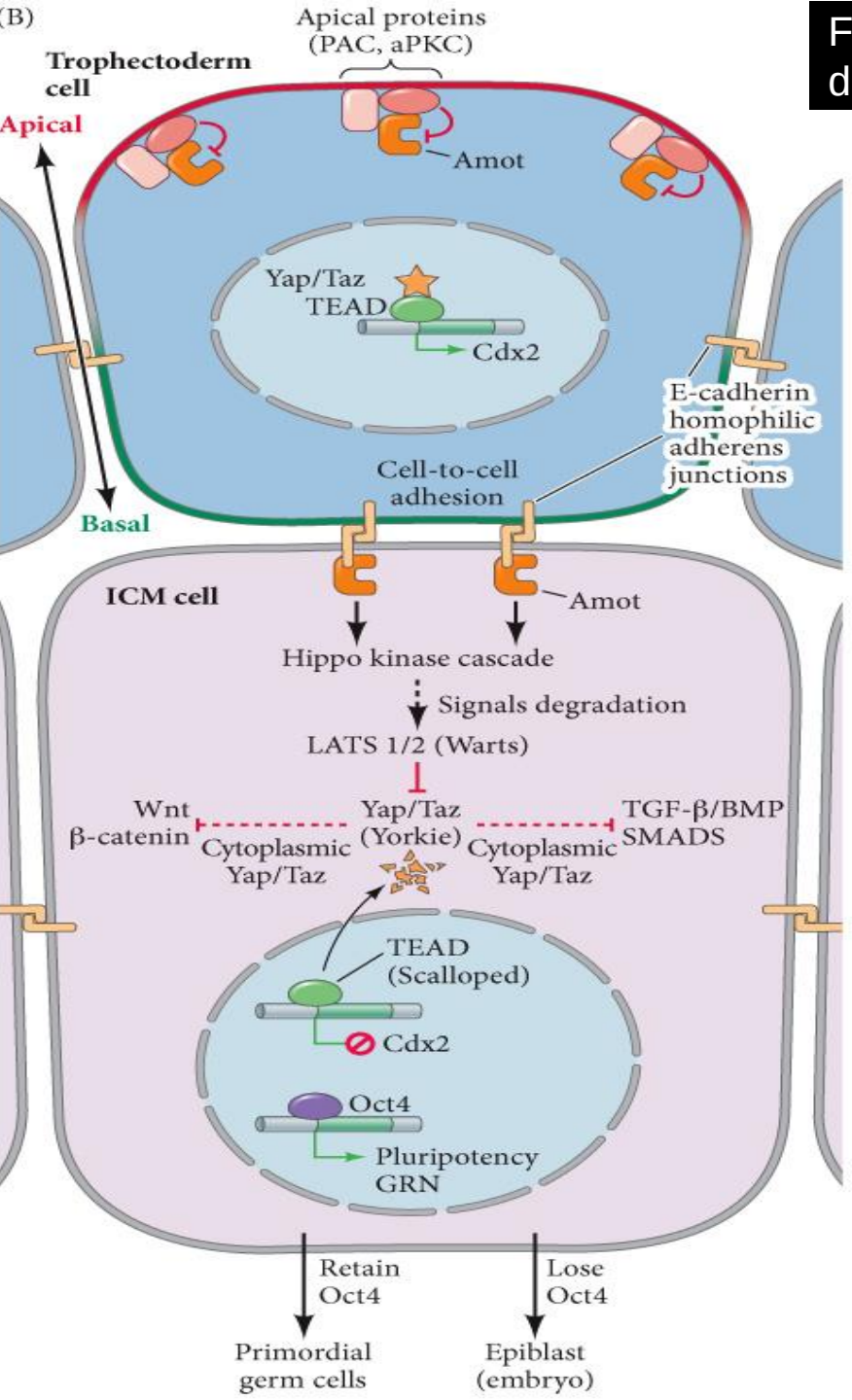
DEVELOPMENTAL BIOLOGY 11e, Figure 12.15 (Part 3)

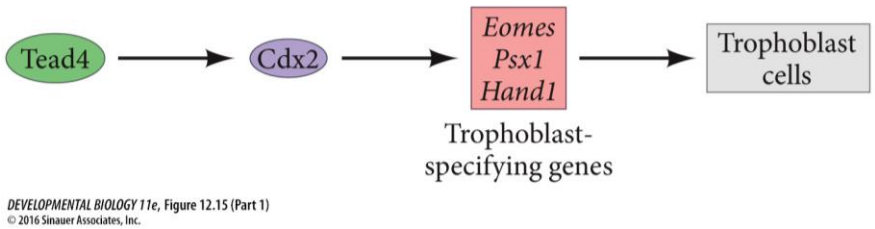
Apicobasal partitioning in Morula



DEVELOPMENTAL BIOLOGY 11e, Figure 5.5

Figure 5.7 Hippo - Possible pathway initiating the distinction between inner cell mass and trophoblast





DEVELOPMENTAL BIOLOGY 11e, Figure 12.15 (Part 1)
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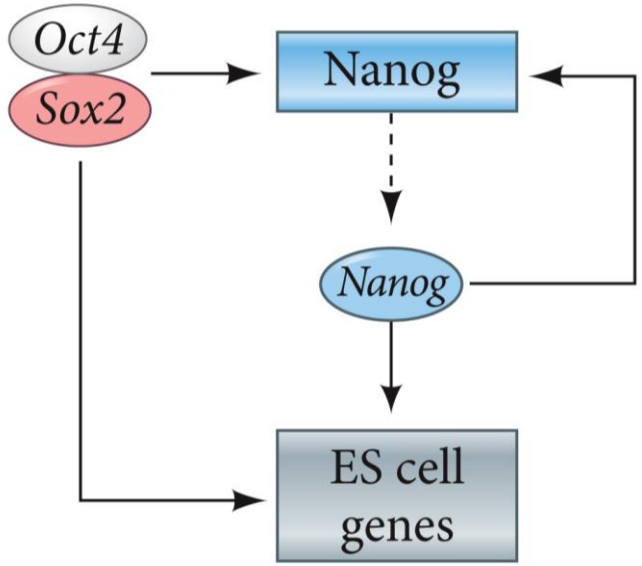

DEVELOPMENTAL BIOLOGY 11e, Figure 12.14 (Part 1)
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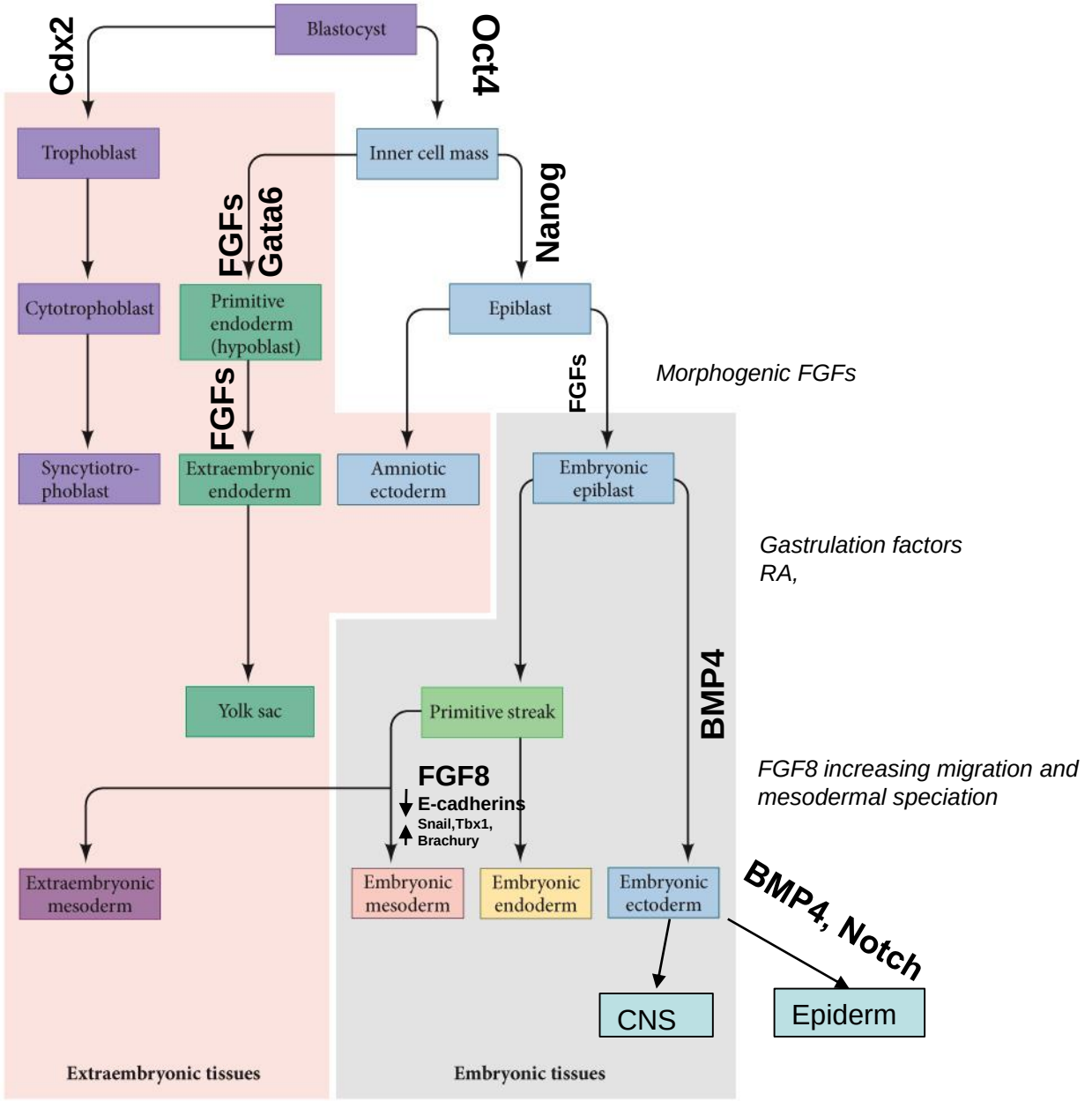
Figure 12.17 Tissue and germ layer formation in the early human embryo (Part 2)



DEVELOPMENTAL BIOLOGY 11e, Figure 12.17 (Part 2)

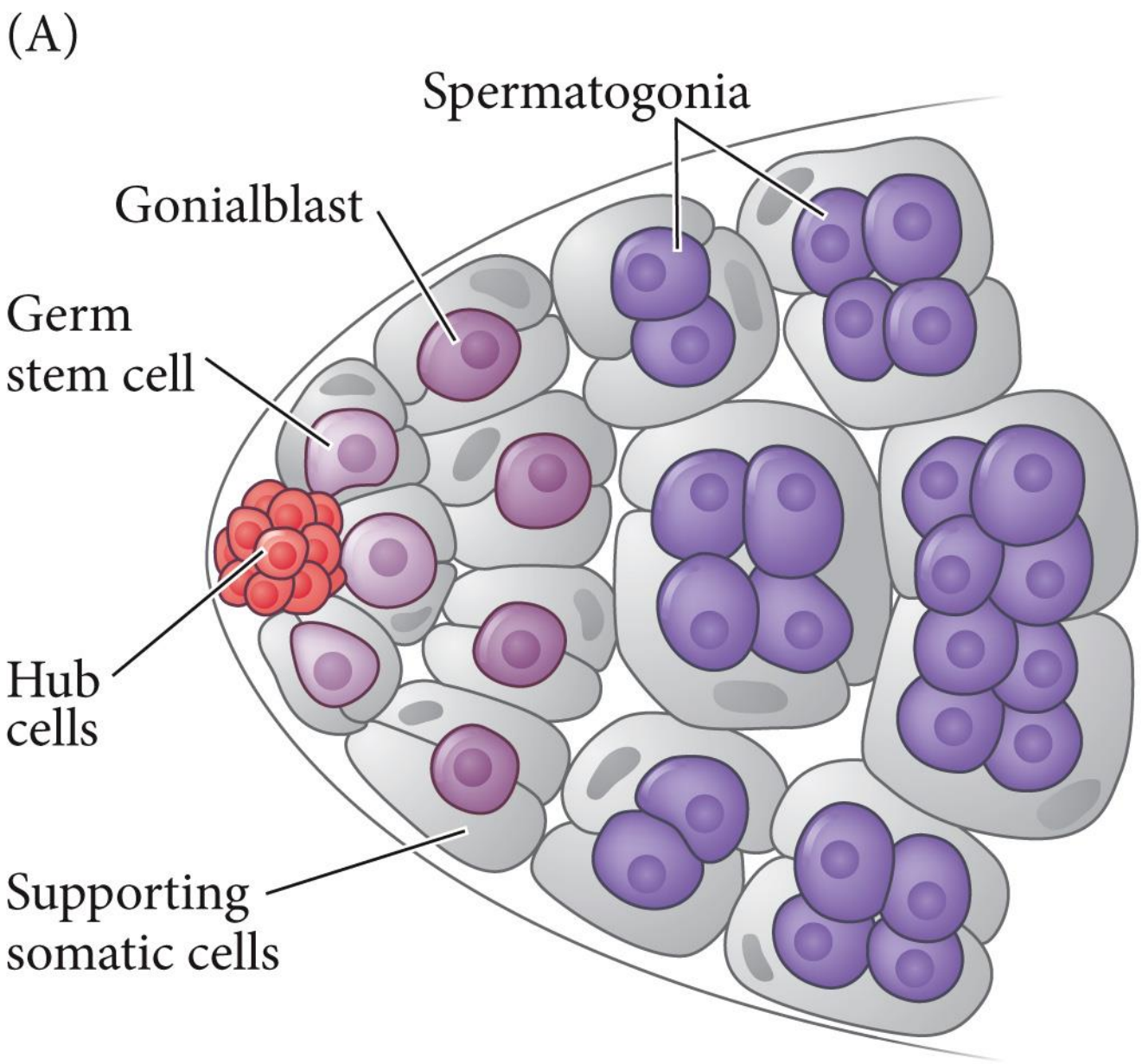
TABLE 5.1 Some stem cell niches of adult humans

Stem cell type	Niche location	Cellular components of niche
LOW TURNOVER[a]		
Brain (neurons and glia)	Ventricular-subventricular zone (V-SVZ; see Figure 5.10), subgranular zone	Ependymal cells, blood vessel epithelium
Skeletal muscle	Between basal lamina and muscle fibers	Muscle fiber cells
HIGH TURNOVER[a]		
Mesenchymal stem cells (MSCs)	Bone marrow, adipose tissue, heart, placenta, umbilical cord	Probably blood vessel epithelium
Intestine	Base of small intestinal crypts (see Figure 5.13)	Paneth cells, MSCs
Hematopoietic (blood-forming) stem cells (HSCs)	Bone marrow (see Figure 5.15)	Macrophages, T_{reg} cells, osteoblasts, pericytes, glia, neurons, MSCs
Epidermis (skin)	Basal layer of epidermis	Dermal fibroblasts
Hair follicle	Bulge (see Figure 16.17)	Dermal papillae, adipocyte precursors, subcutaneous fat, keratin
Sperm	Testes	Sertoli cells (see Figure 6.21)

[a] Niches with low rates of cell turnover generate stem cells for repair, slow growth, and (in the case of neurons) learning. Niches with high turnover are constantly producing new cells for bodily maintenance.

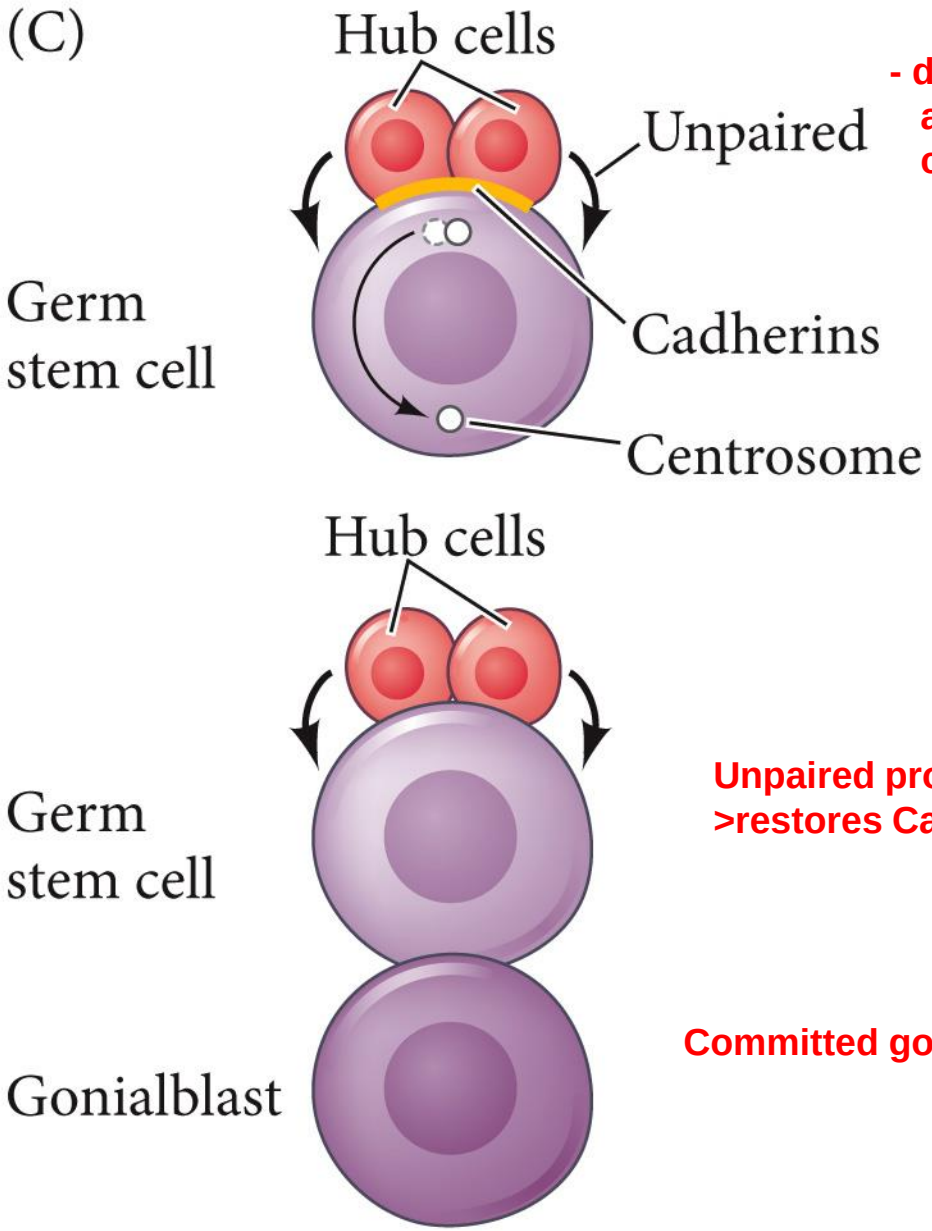
DEVELOPMENTAL BIOLOGY 11e, Table 5.1

Figure 5.8 Stem cell niche in *Drosophila* testes (Part 1)



DEVELOPMENTAL BIOLOGY 11e, Figure 5.8 (Part 1)

Figure 5.8 Hub cells “Unpaired” dictates an assymetrical fate of the Stem cell progeny



- dictates centrosome migration and mitotic plane, cadherin distribution

Unpaired proximal cell effect >JAK-STAT>pluripotency, >restores Cadherin

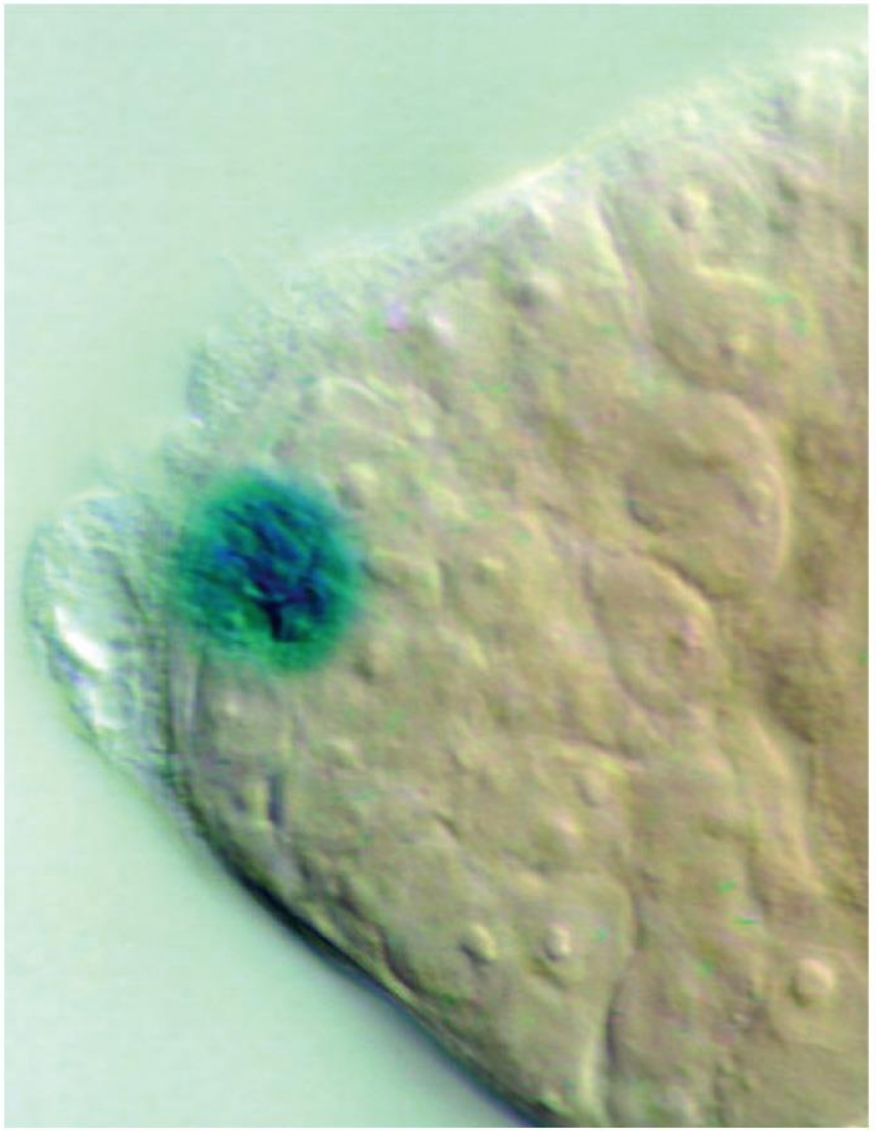
Committed gonioblast > spermatozoid

DEVELOPMENTAL BIOLOGY 11e, Figure 5.8 (Part 3)

Figure 5.8 Unpaired dictates an assymetrical fate of the Stem cell progeny

Unpaired gene expressed in Hub cells
Reporter β-galactosidase inserted into the gene for Unpaired reveals that this protein is transcribed in the somatic hub cells.

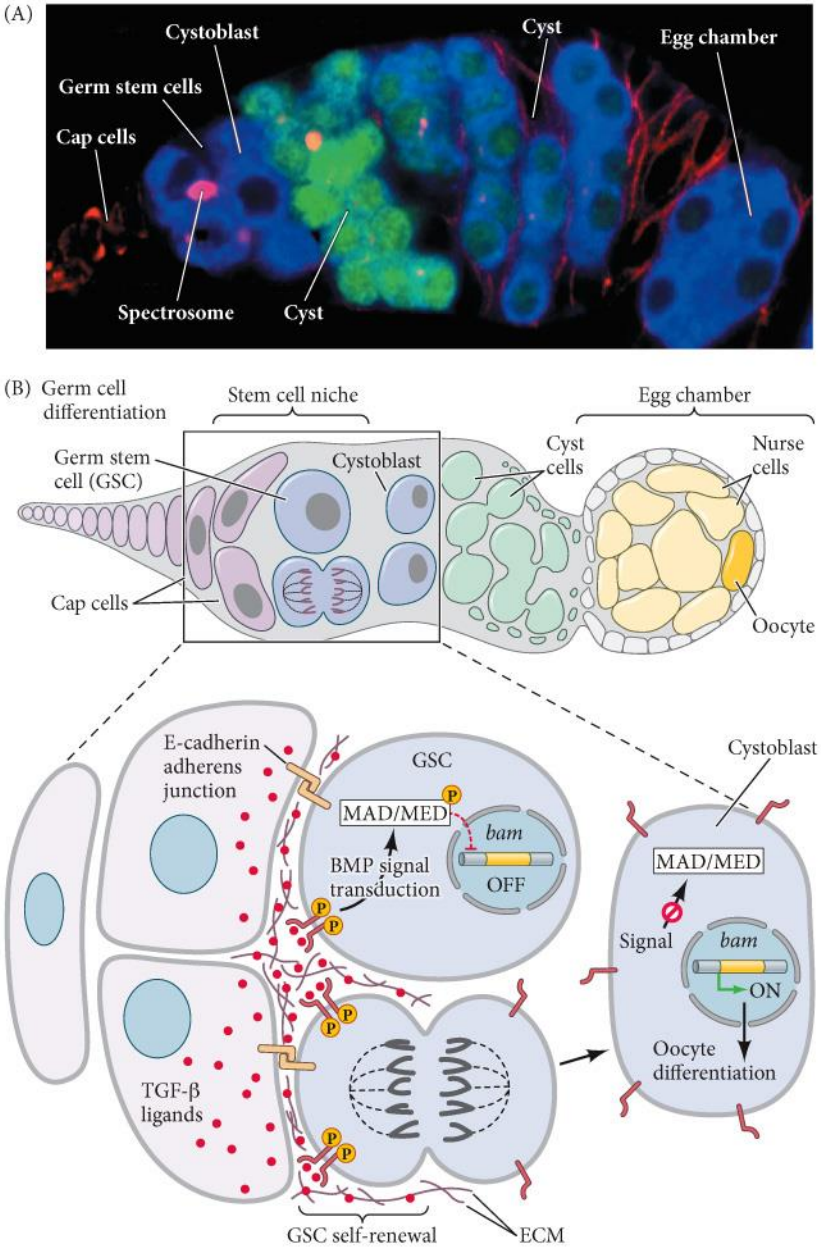
(B)



DEVELOPMENTAL BIOLOGY 11e, Figure 5.8 (Part 2)

Figure 5.9 *Drosophila* ovarian stem cell niche germanium.

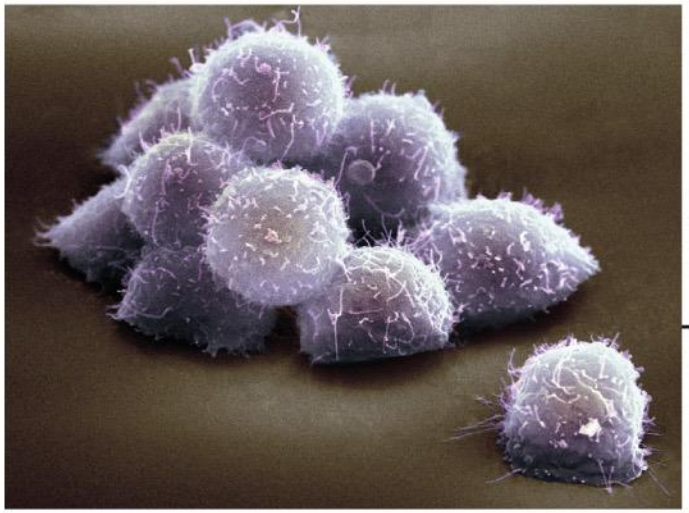
E-cadh arrests GSC in space
BMP prevents differentiation



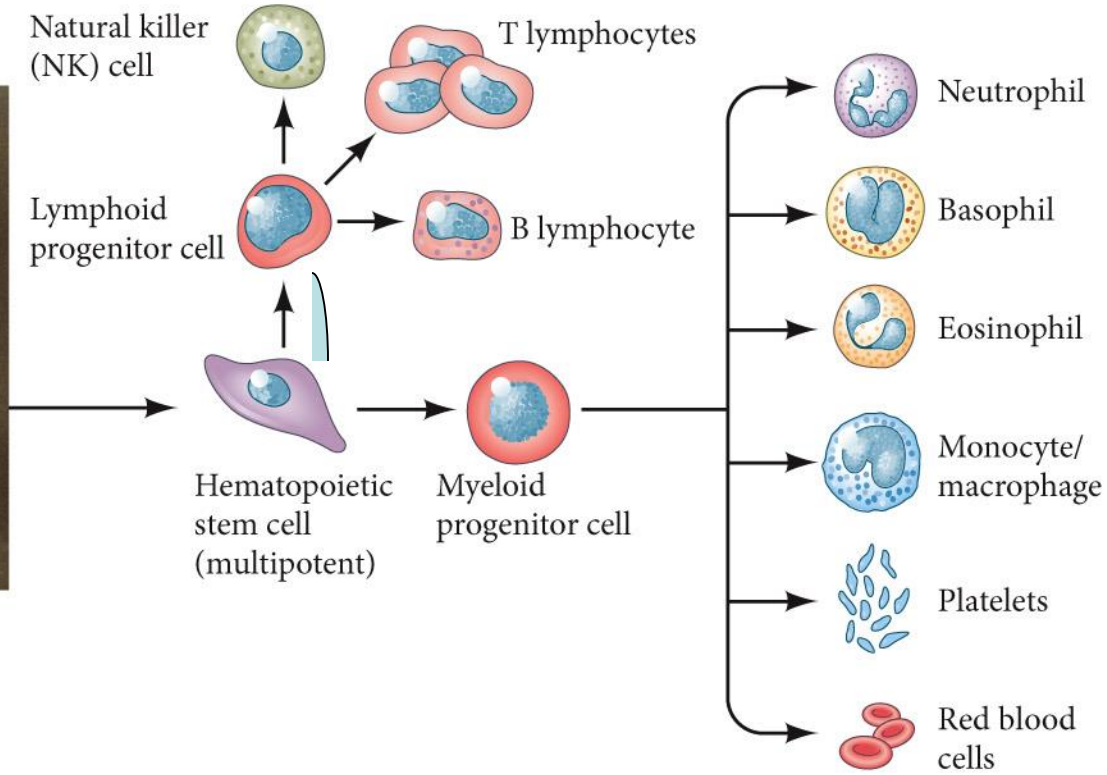
DEVELOPMENTAL BIOLOGY 11e, Figure 5.9

Figure 5.3 Blood-forming (hematopoietic) stem cells (HSCs)

Best know adult stem cells - Hematopoietic multipotent stem cells > all blood cells



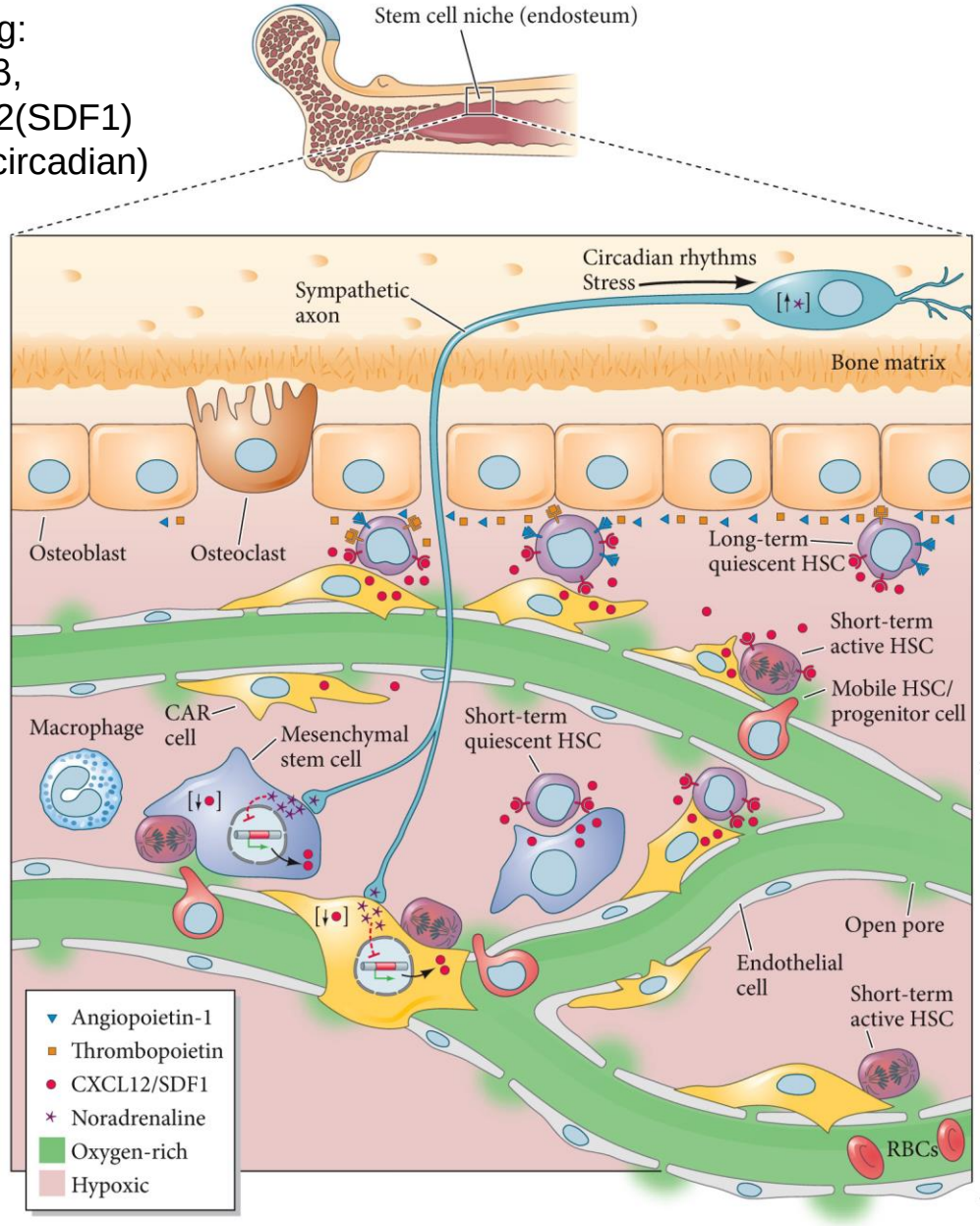
Hematopoietic stem cells



DEVELOPMENTAL BIOLOGY 11e, Figure 5.3

Figure 5.15 Model of adult HSC Hemataopetic Stem Cell niche

Factors controlling:
Wnt, Notch, TGFβ,
integrins, CXCL12(SDF1)
Norepinephrine (circadian)



Contact with osteoblasts
Long-term reservoir
More hypoxic
Inhibited by angiopetin, thrombopoetin

Contact with blood vessels
short-term reservoir
Less hypoxic
Activated by MSC

DEVELOPMENTAL BIOLOGY 11e, Figure 5.15

Mesenchymal Stem Cell : Supporting a variety of adult Tissues

Multipe Sources and Niches:

- Bone marrow (original finding - bone marrow derived stem cells)
- dermis of the skin, bone, fat, cartilage, tendon, muscle, thymus, cornea, and dental pulp, umbilical cord and placenta
- MSC - “Split personality” as (1) supportive stromal cells secreting ECM and (2) self-renewing stem cells on the other.

Clonal plasticity

- In culture MSC clonal populations can form different organs, examples: eosteoblasts (green) and adipocytes (red)

- **Paracrine control:**
  - PDGF & TGF-β signaling > chondrogenesis,
  - FGF > bone cells

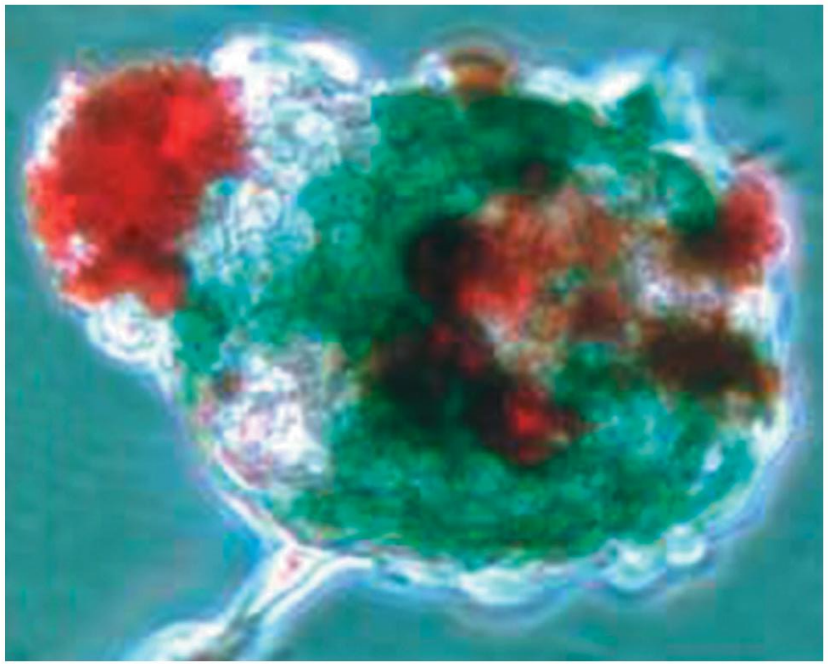
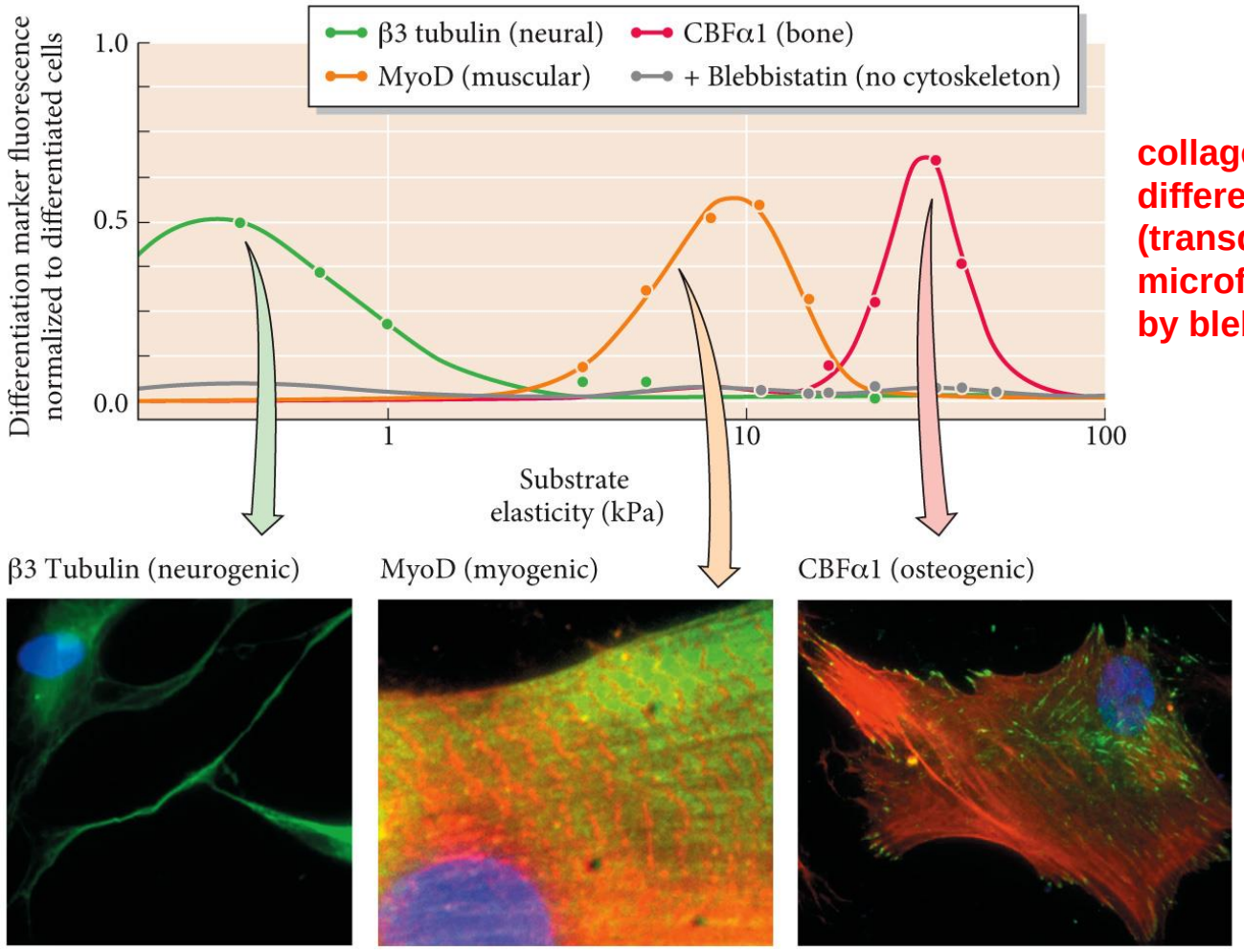


Figure 5.17 A mesensphere containing two derived cell types

Figure 5.18 Mesenchymal stem cell differentiation is influenced by the elasticity of the matrices upon which the cells sit

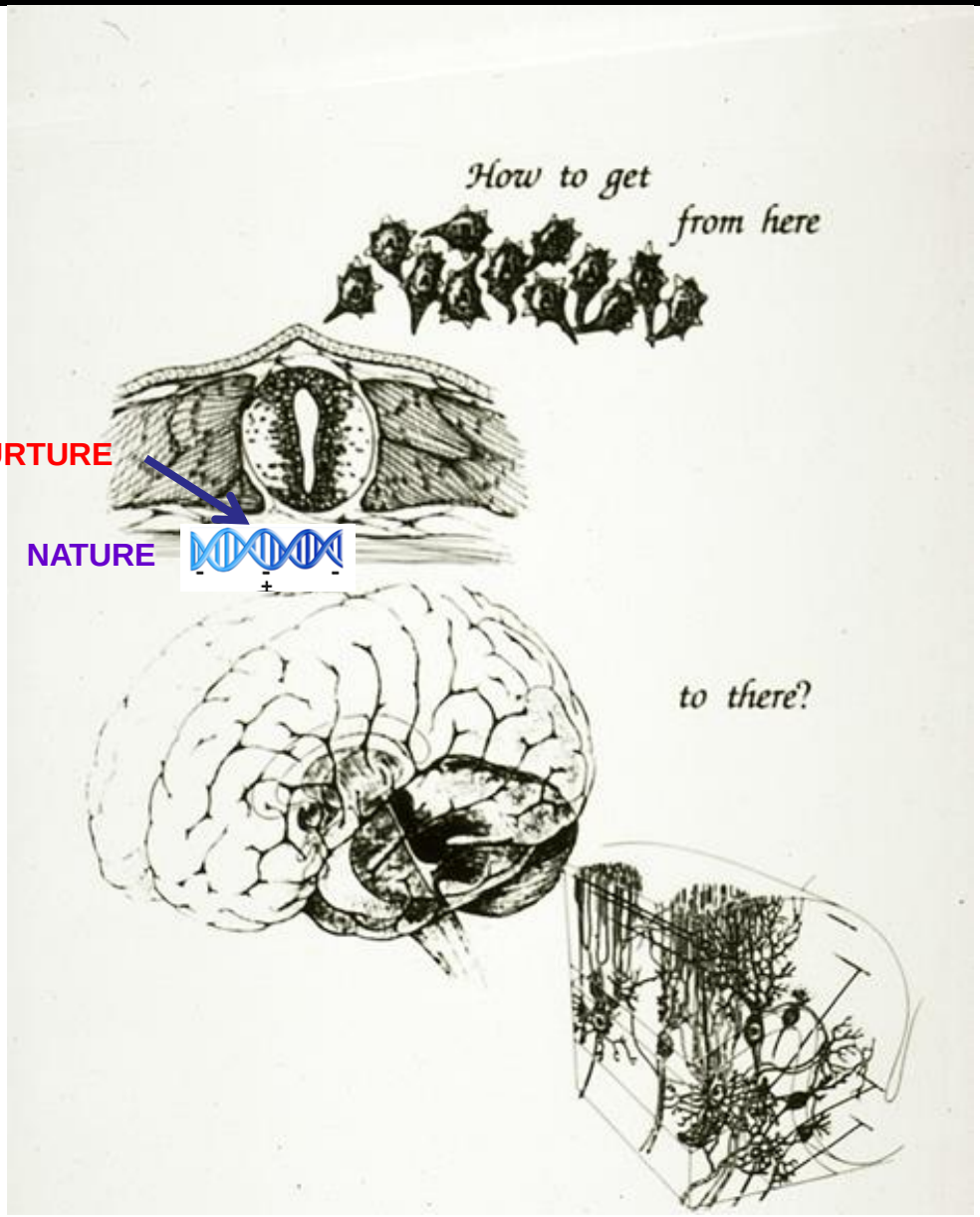
ECM laminin keep MSCs in a state of undifferentiated “stemness”
Physical matrix elasticity controls cell differentiation



collagen-coated gels of different elasticity (transduced via microfilament – blocked by blebbisttin)

DEVELOPMENTAL BIOLOGY 11e, Figure 5.18

Neural Stem Cells Niche in Developing CNS



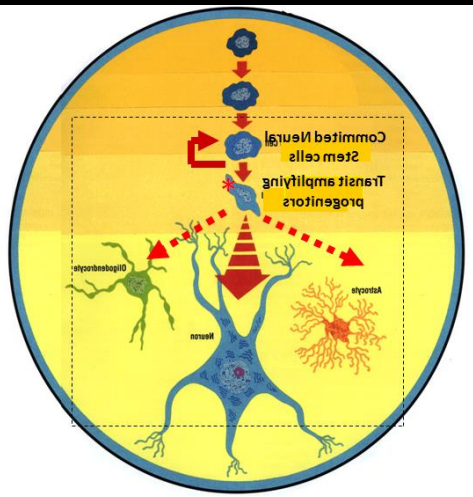
Can cells proliferate to make new neurons in adult brain?

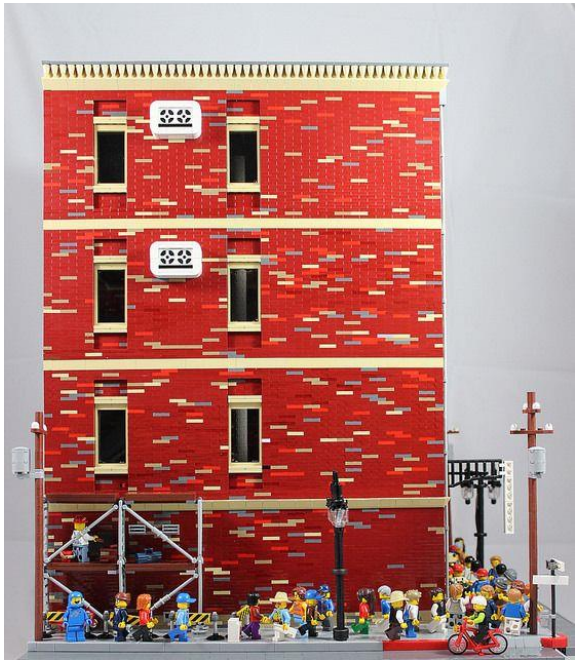
NO - new neurons be made Santiago Ramon y Cajal's dogma: "Everything may die, nothing may be regenerated"

YES - Altman and Das 1965; Nottebohm 1985) reported the occurrence of adult neurogenesis in rats, cats, and birds' brains as early as 1962.

NO - (Rakic 1985; Eckenhoff and Rakic 1988) - had tried to identify, to no avail, stem cells in the adult brains of higher primates

YES - (Eriksson et al. 1998) discovered an in vivo neurogenesis occurring in the adult human brain by injecting a non-radioactive Bromodeoxy Uridine (BrdU), a synthetic analog of thymidine, to monitor neuronal proliferation in terminal cancer patients. BrdU labelled cells expressed neuronal markers



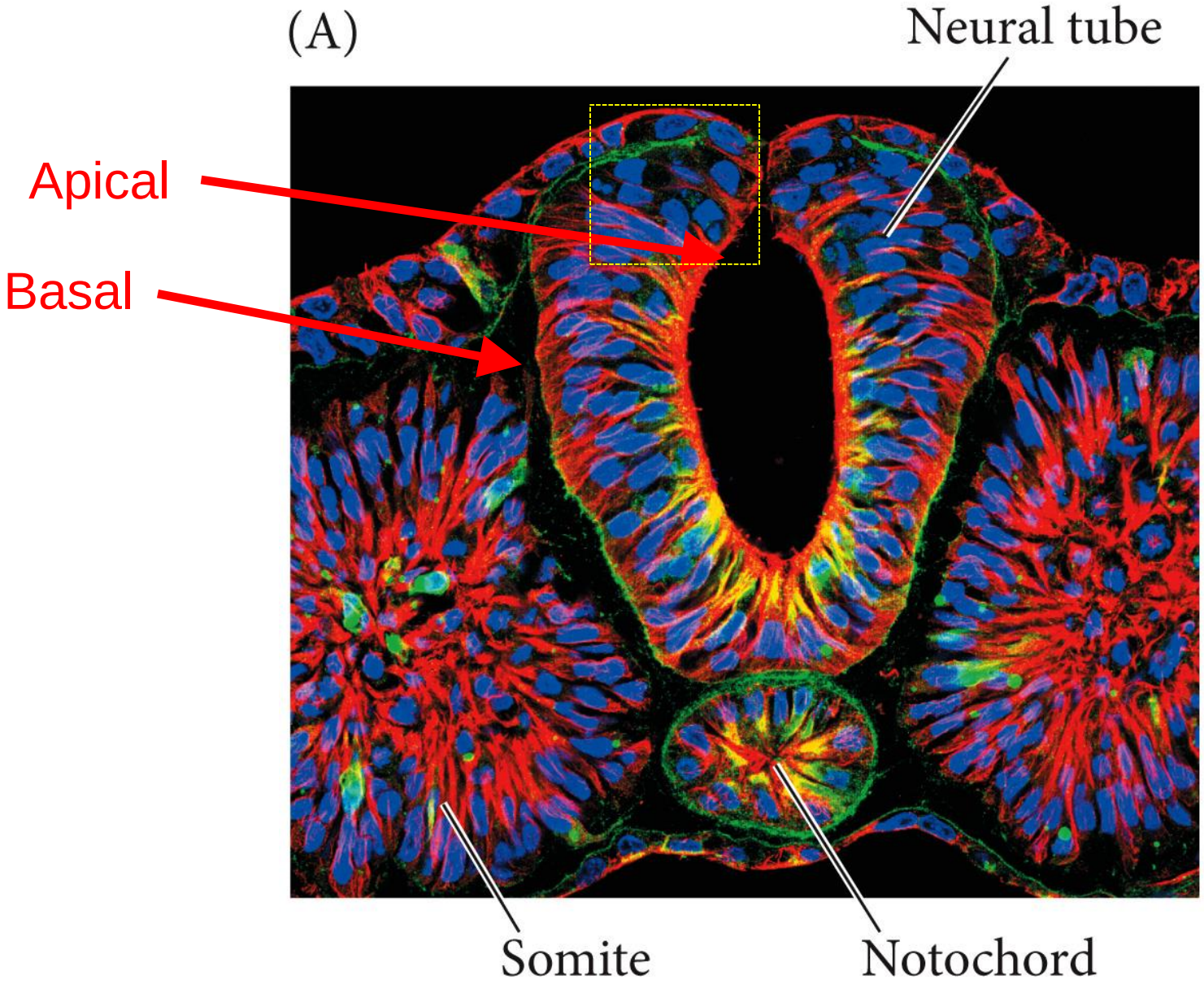


NCS: Neuroepithelial cells

ventricular
Radial Glial

subventrricular (outer)
Radial Glia

Figure 1.9 Two types of microscopy are used to visualize the notochord and its separation of vertebrate embryos into right and left halves (Part 1)



DEVELOPMENTAL BIOLOGY 11e, Figure 1.9 (Part 1)

Neuroepithelial (stem) cells (NEC):

- the first multipotent neural stem cells of the embryo, make up the neural plate and early neural tube (later transform to radial glia cells RGC),
- NEC are polarized along their apical to basal axis, single spans the tube wall.
- the apical NEC surface borders the internal cavity to be filled with the CSF in neural tube,
- NCE basal surface forms an endfoot - swelling of its basal membrane, pial matter a fibrous membranes that surround nervous tissues.

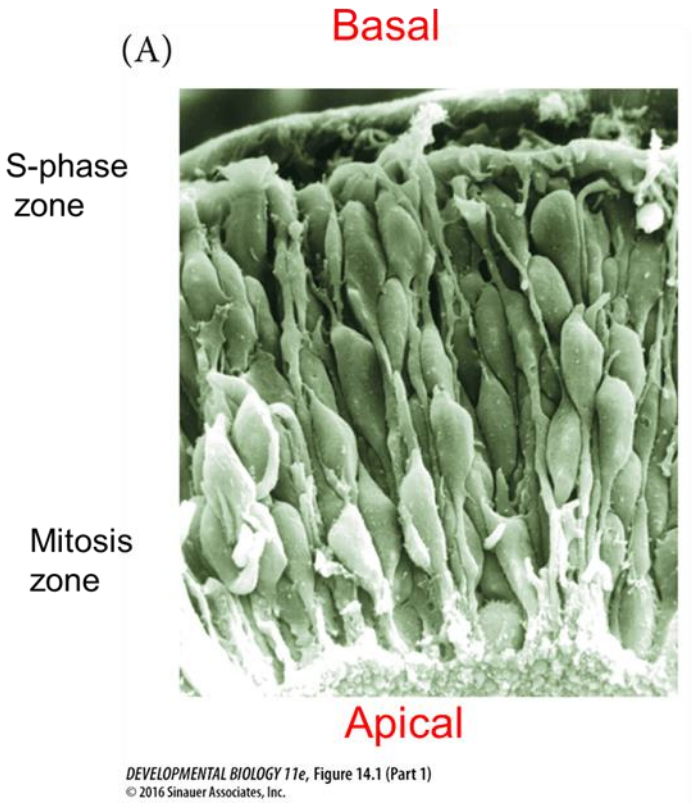
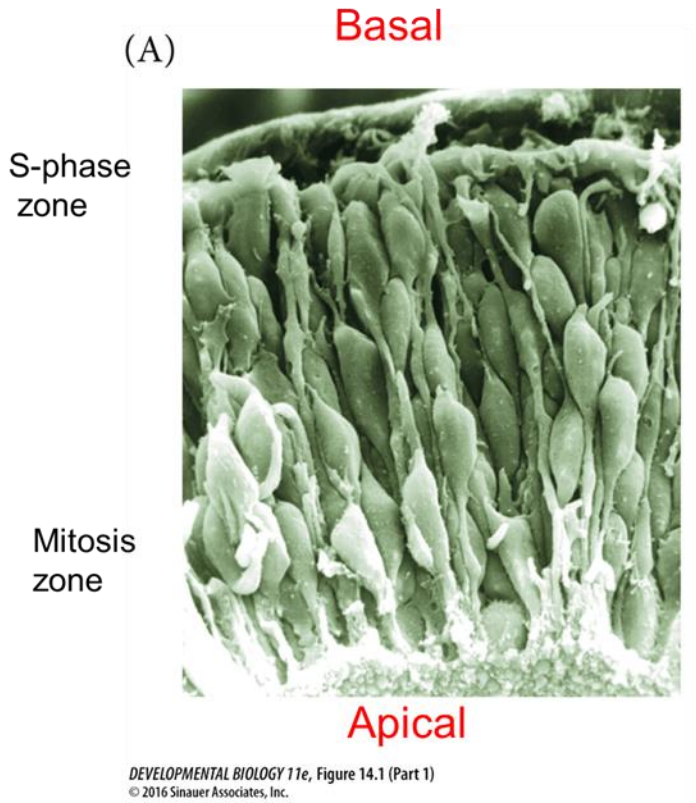
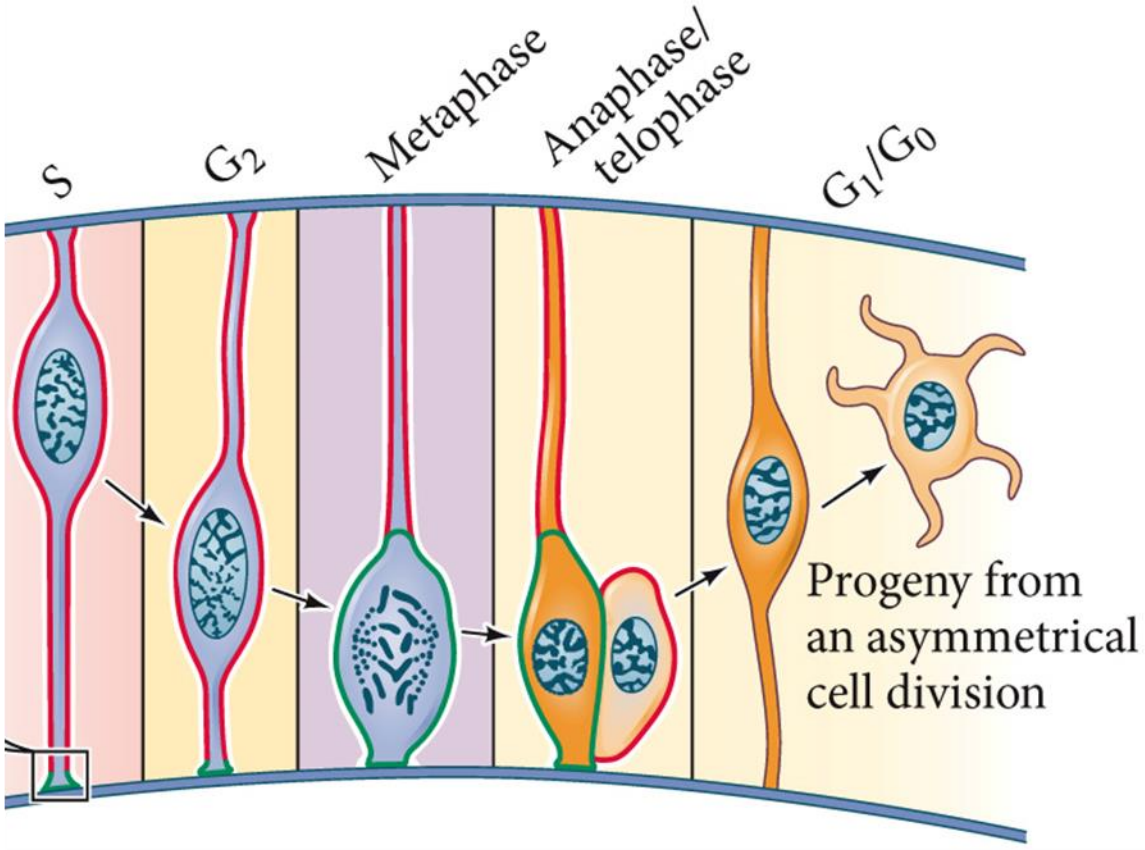


Figure 14.1 Cell types of the CNS. (A) Scanning electron micrograph of a newly formed chick neural tube, showing neuroepithelial cells at different stages of their cell cycles spanning the full width of the epithelium.

Microtubule and dynein dependent interkinetic nuclear migration (Fig. 14.1A; 14.1)

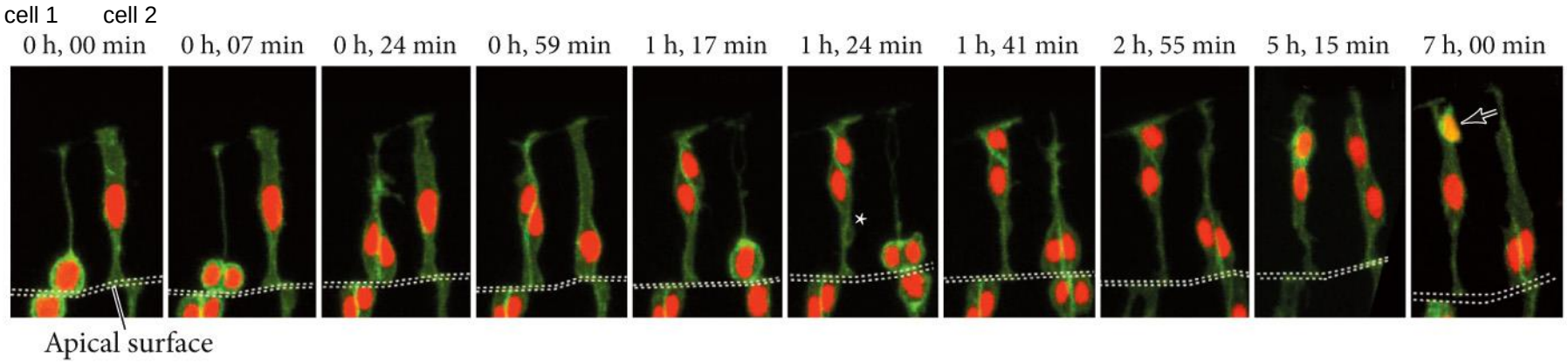




Asymmetric (shown) or symmetric division

Figure 14.9 Live imaging of neuroepithelial cell interkinetic nuclear migration and division of neural stem cells in the zebrafish embryonic hindbrain

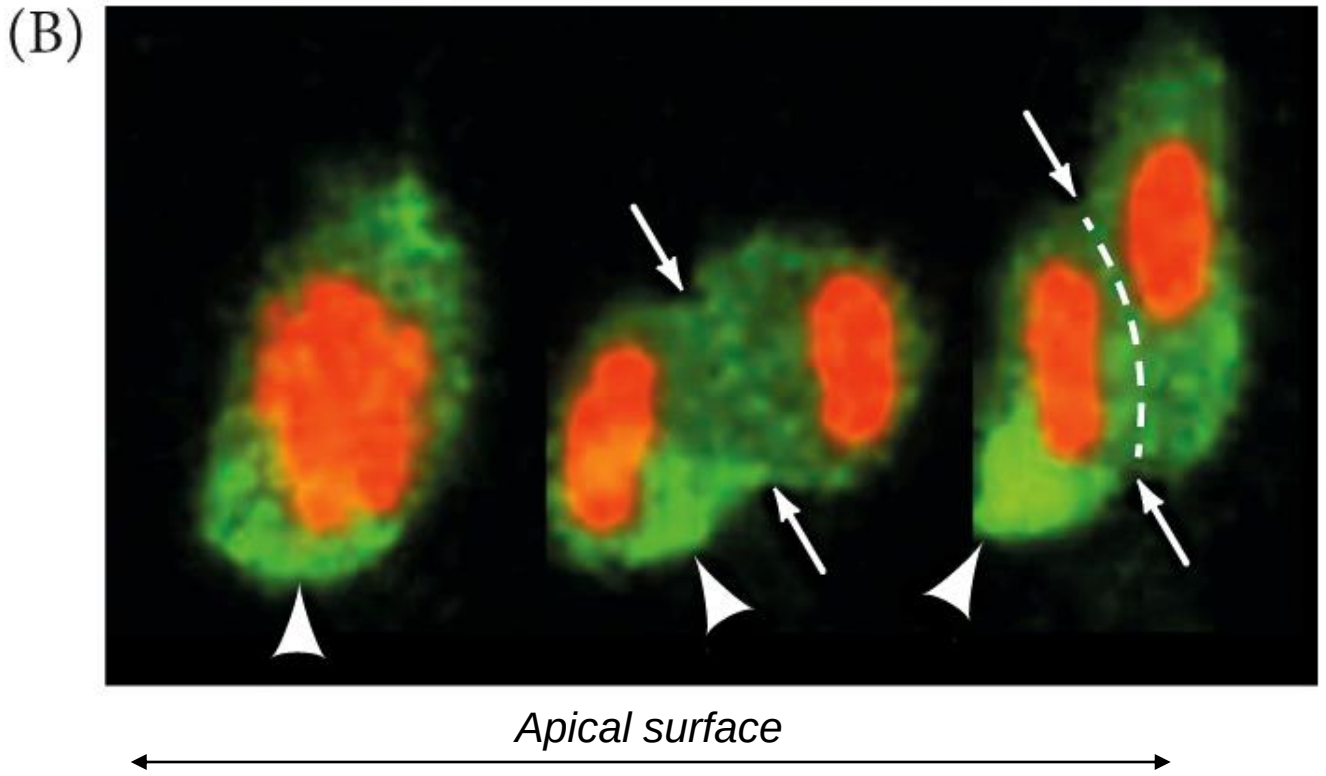
asymmetrical (1) and symmetrical (2) division



DEVELOPMENTAL BIOLOGY 11e, Figure 14.9

Figure 14.9 Live imaging of neuroepithelial cell interkinetic nuclear migration and cell division cells zebrafish embryonic hindbrain. Two adjacent progenitor cells in the germinal epithelium were recorded over 7 hours (cell membranes (green) and nuclei (red). A reporter gene specifically marks neurons (yellow**).**
Cell 1 – asymmetric division,
CeLL 2 – symmetric division

Figure 14.14 symmetrical versus asymmetrical division depends on the **plane of division**
Mitotic spindle parallel – **symmetric**
Mitotic spindle oblique **- asymmetric**



DEVELOPMENTAL BIOLOGY 11e, Figure 14.14

Figure 14.14 Asymmetrical division of radial glia mediated by Par3 and Notch

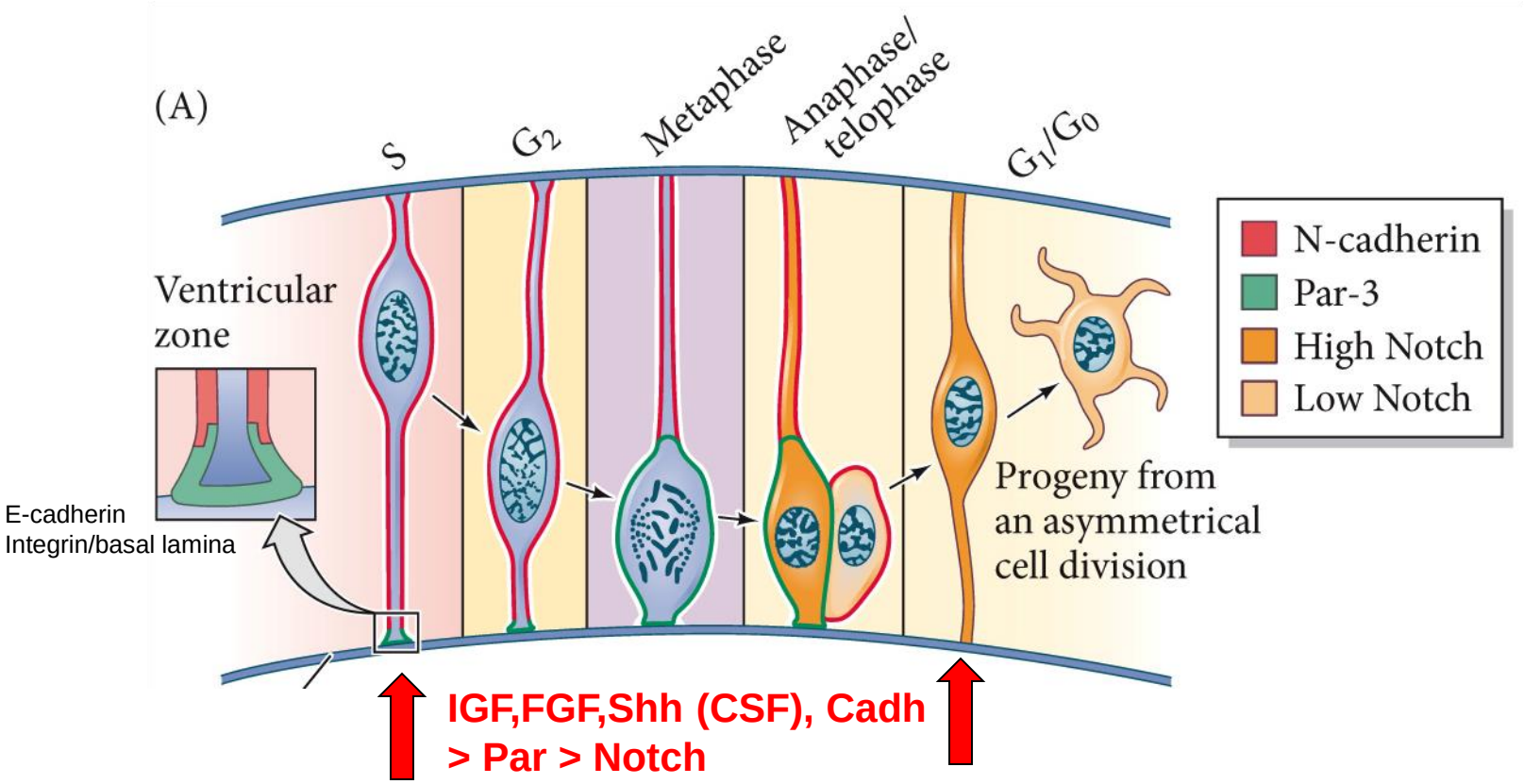


Figure 14.14 Asymmetrical division of radial glia mediated **by Par3 and Notch.**

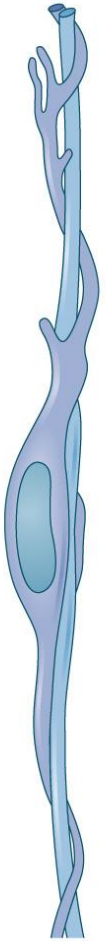
Inheritance matters:
Old centriole + old luminal cilium = exposure to mitotic factors
New centriole +new basal = no mitotic factors

More Par-3 >high Notch, N-cadherin >stem cell
Less Par-3 >Delta > neuron

Figure 14.11 NEC and later radial glia cells (RGC) provide tracks for neuron migration)

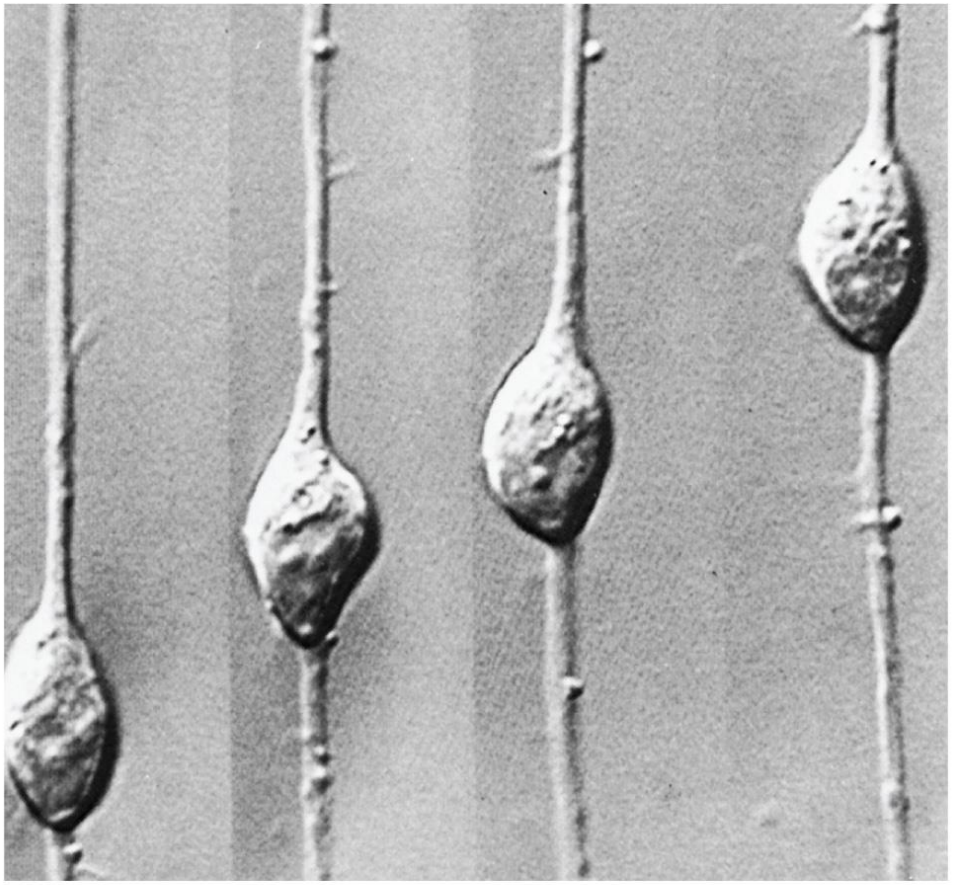
Neuron- epithelial cells ***Neuron-Glia (****astroctactin, N-cadherins)*

(A)

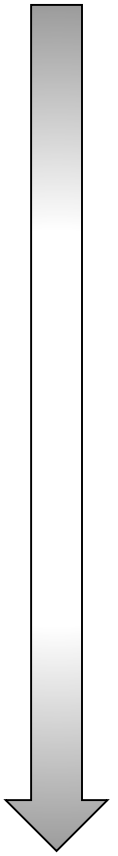


DEVELOPMENTAL BIOLOGY 11e, Figure 14.11 (Part 1)

(B)

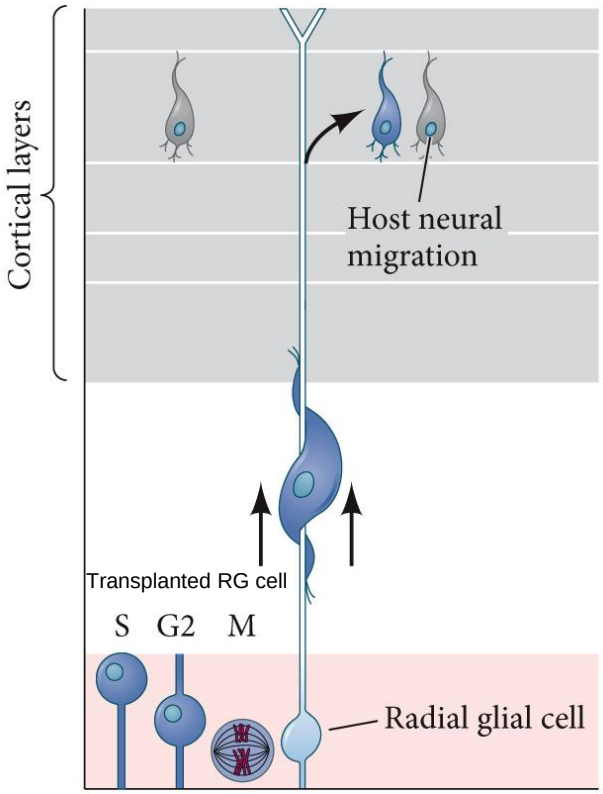


BDNF

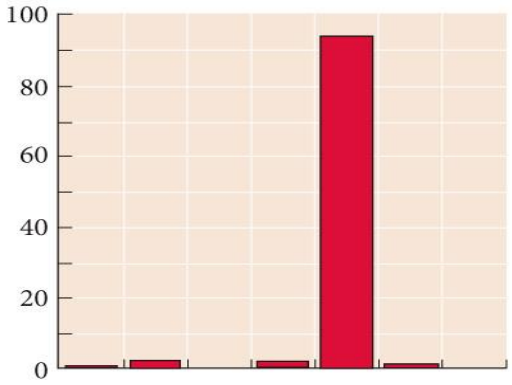


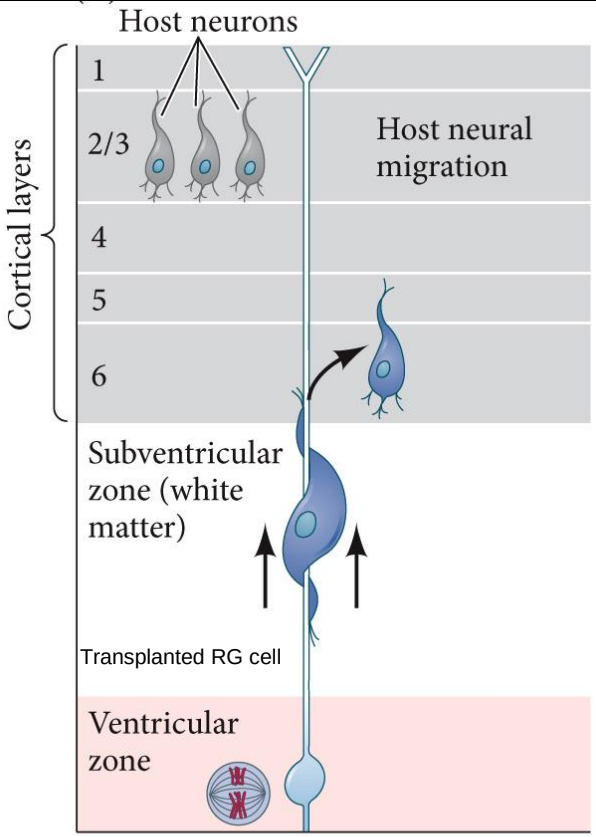
DEVELOPMENTAL BIOLOGY 11e, Figure 14.11 (Part 2)

Figure 14.12 Determination of cortical laminar identity in the ferret cerebrum (Part 3)

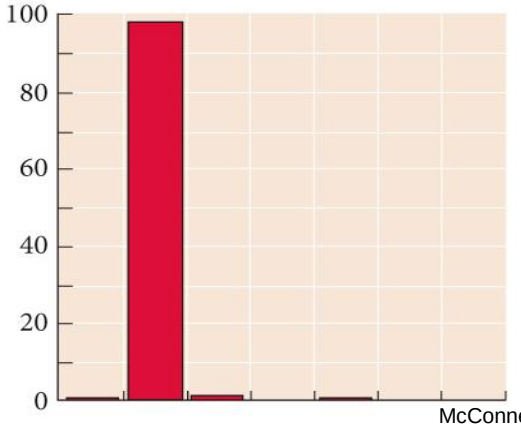


Host (conditional) fate when transplanted in S phase



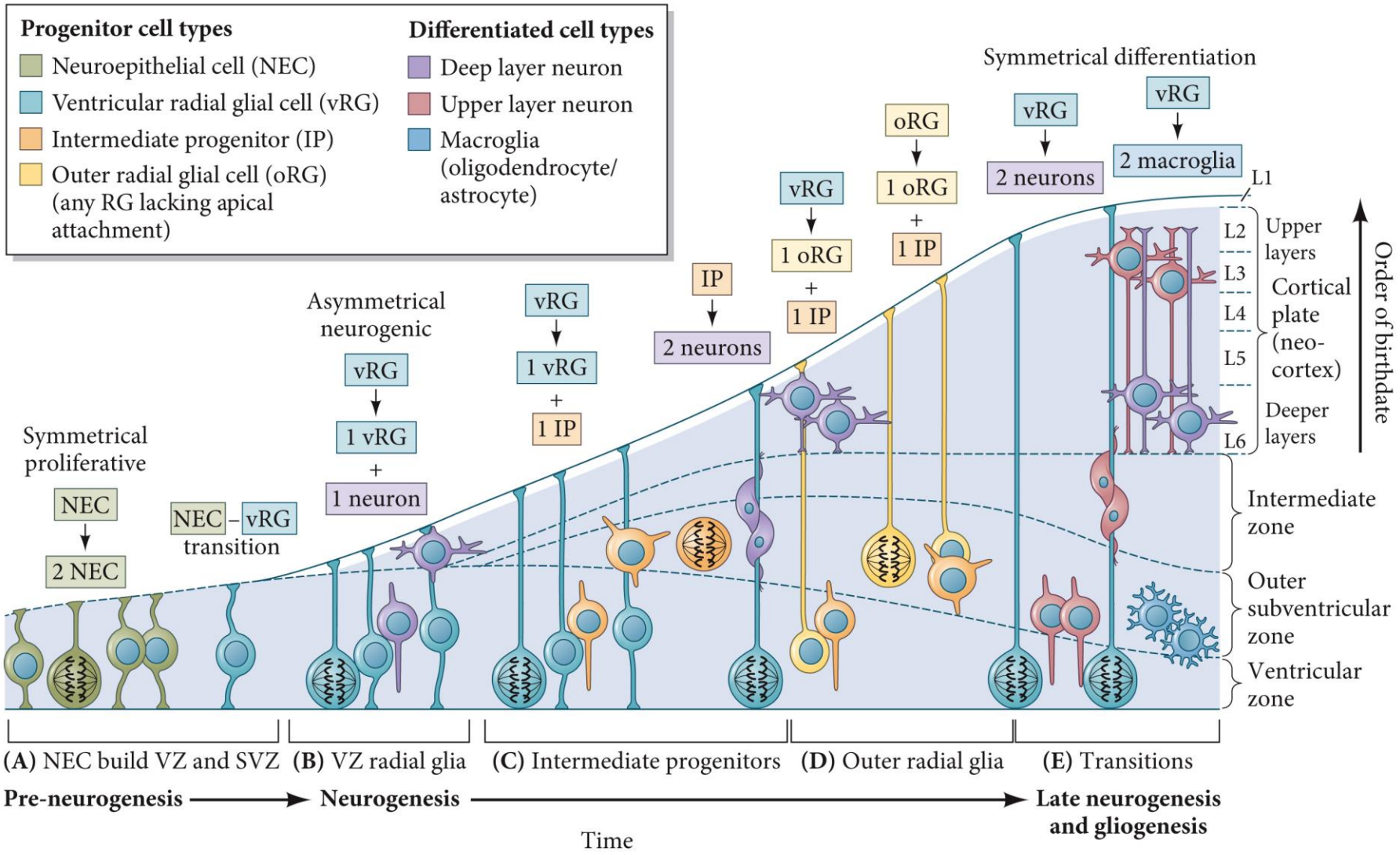


Cell-autonomous fate when



McConnell and Kaznowski 1991

Figure 14.10 Summary model of neurogenesis in the cerebral cortex



DEVELOPMENTAL BIOLOGY 11e, Figure 14.10

Figure 14.13 Building cortical layers by Caja-Retzius cells secreted *reelin & Disabled-1 signaling*

(A)

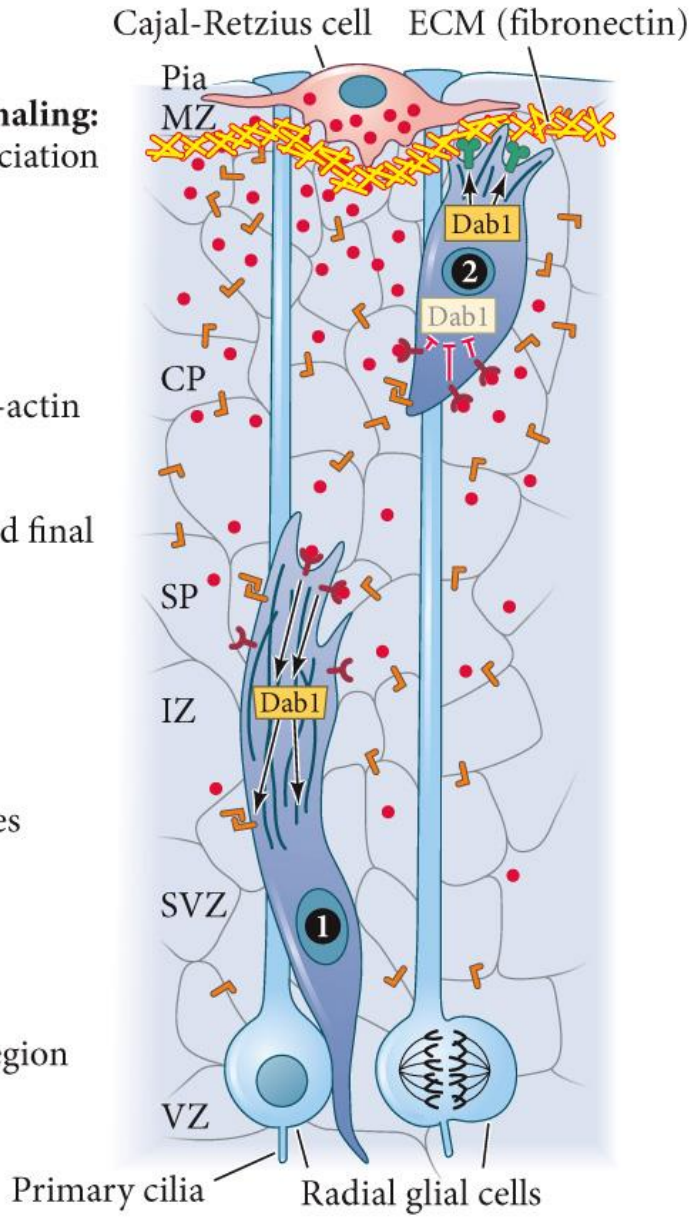
❷ **Reelin-Disabled-1 signaling:**
Promotes integrin association with filopodial tip

High levels of Reelin inhibit Disabled-1 (negative feedback):
Leads to destabilized F-actin

Result:
Destabilized F-actin and final translocation

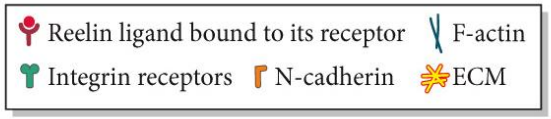
❶ **Moderate levels of Reelin activate Disabled-1 to:**
Activates N-cadherin expression and stabilizes F-actin

Result:
Promotes filopodial extensions and cell translocation toward region of highest N-cadherin



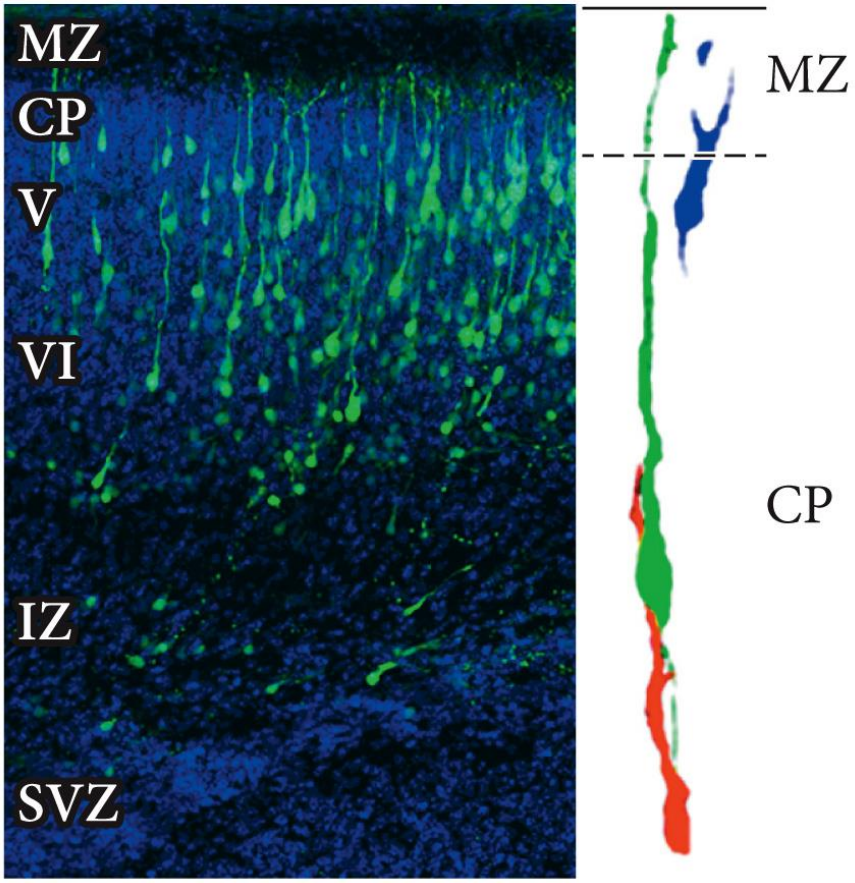
Attracting factors for gradients:

reelin **N-cadherin**

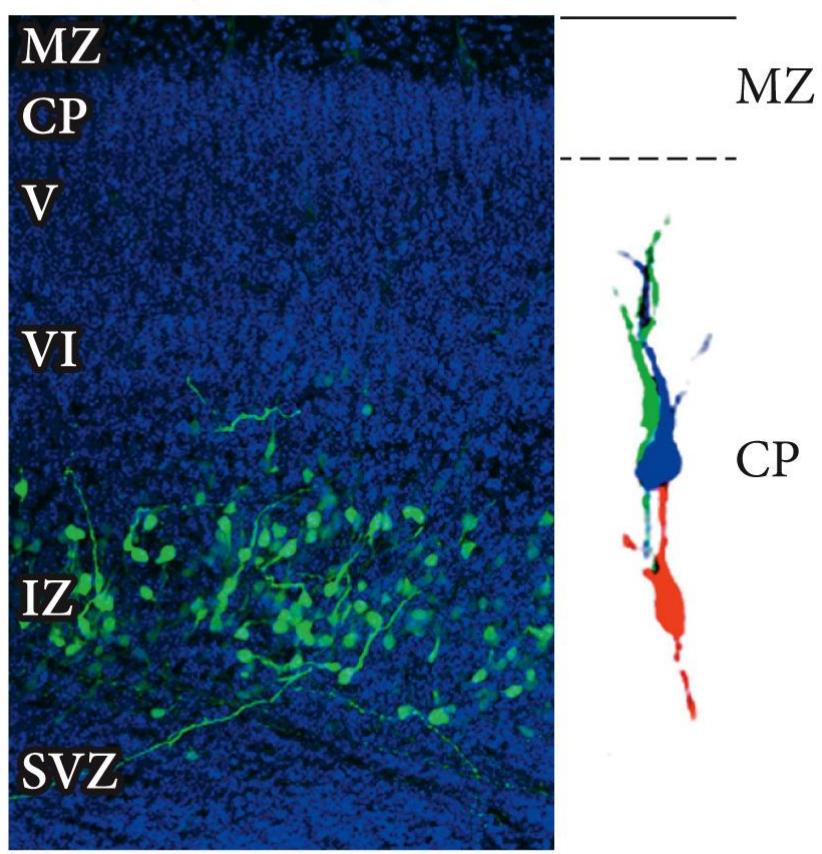


DEVELOPMENTAL BIOLOGY 11e, Figure 14.13 (Part 1)

Figure 14.13 Model of Reelin regulation of directed neuronal migration (Part 2)



DEVELOPMENTAL BIOLOGY 11e, Figure 14.13 (Part 2)

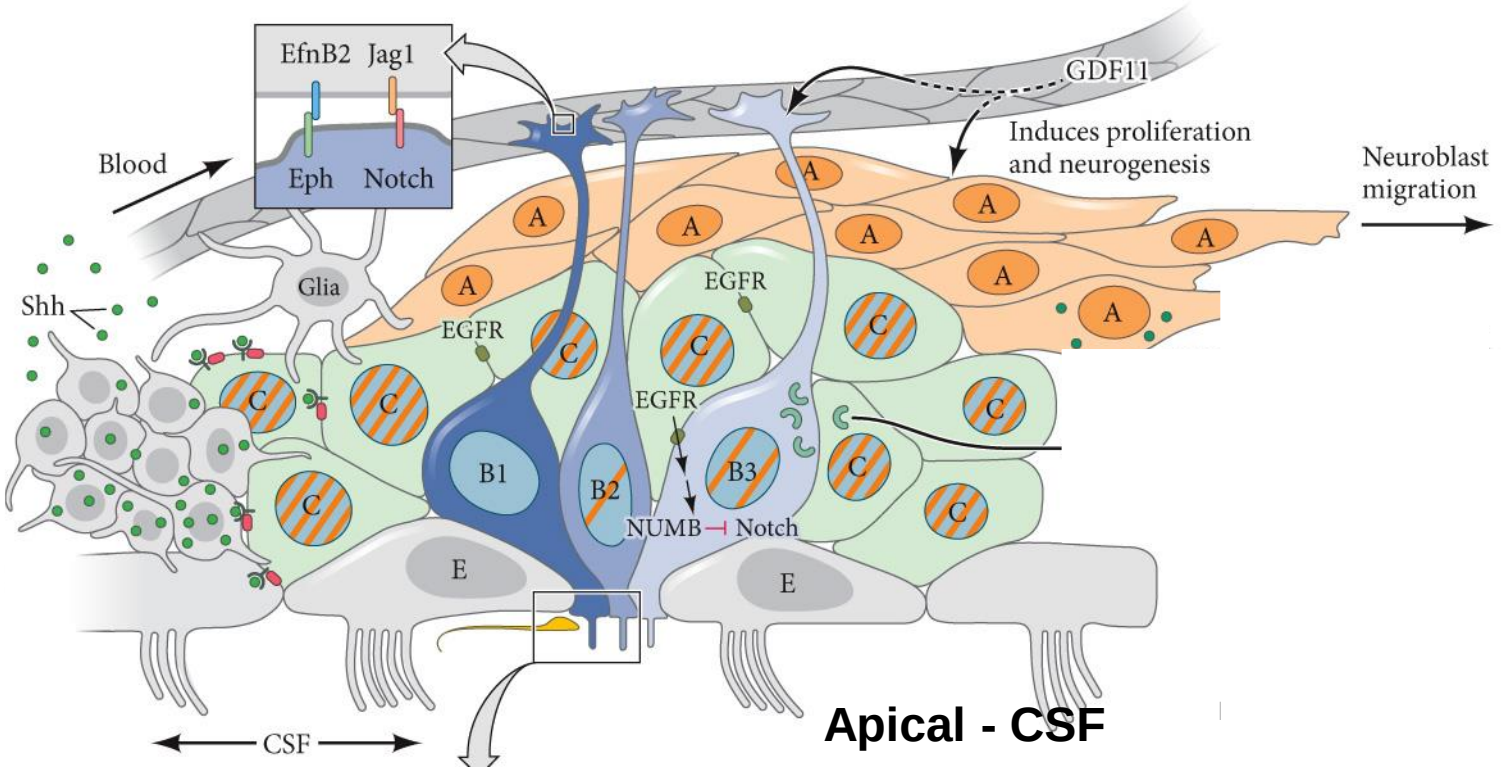


DEVELOPMENTAL BIOLOGY 11e, Figure 14.13 (Part 3)

GFP expressing progenitors

Figure 5.10 Modified Niche - ventricular-subventricular zone stem cell niche and its regulation

Basal
bloo



Developmental progression of NSC (Radial Glial Cells):

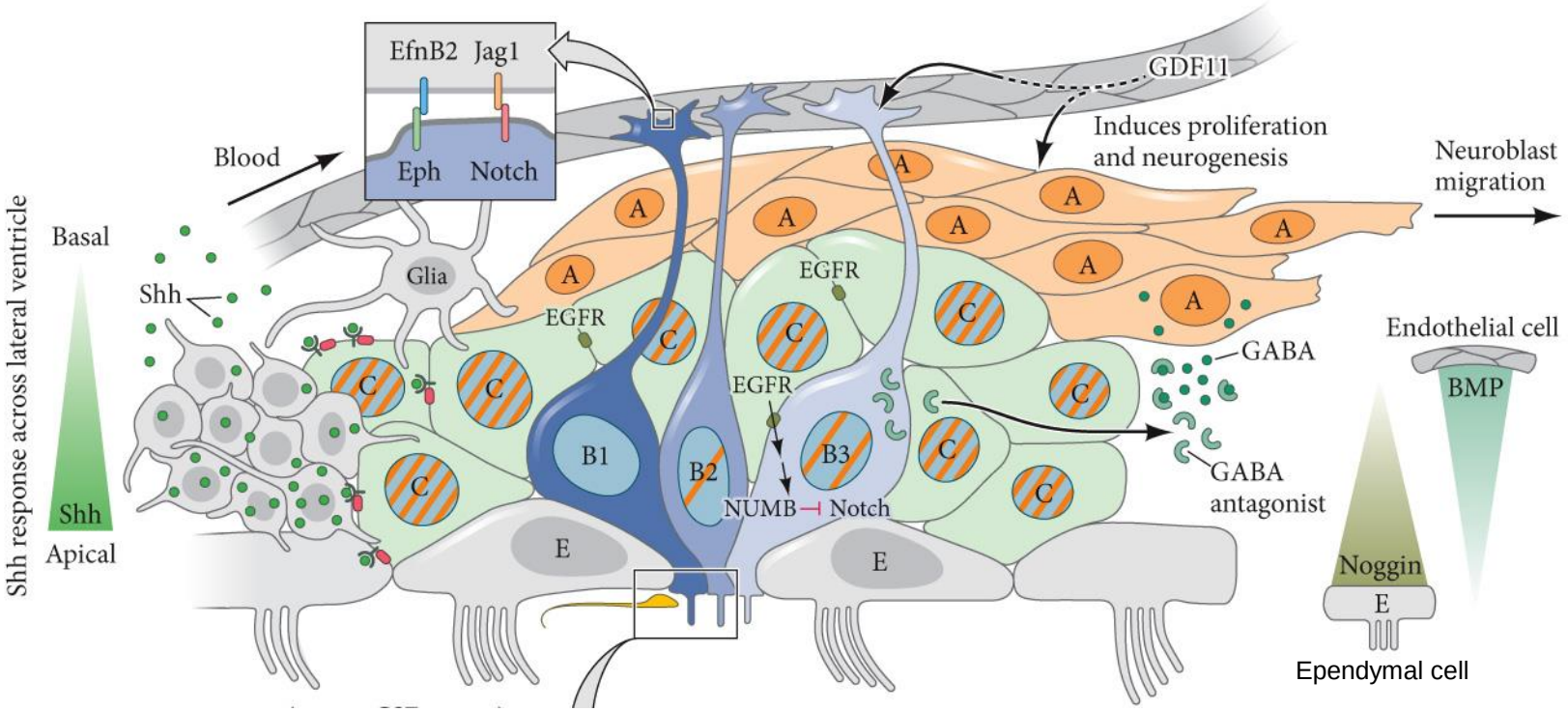
B1 quiescent (GFAP; (Notch-Asc-1) >

B2, B3 - activated proliferating (GFAP, Oscillating Notch-Asc-1; BIBP) **>**

C – proliferating Progenitor cells C (GFAP, Oscillating Notch-Asc-1, EGFR) **>**

A - migratory neuroblasts (Constant ASC-1> doublecortin)

Figure 5.10 Schematic of the ventricular-subventricular zone stem cell niche and its regulation

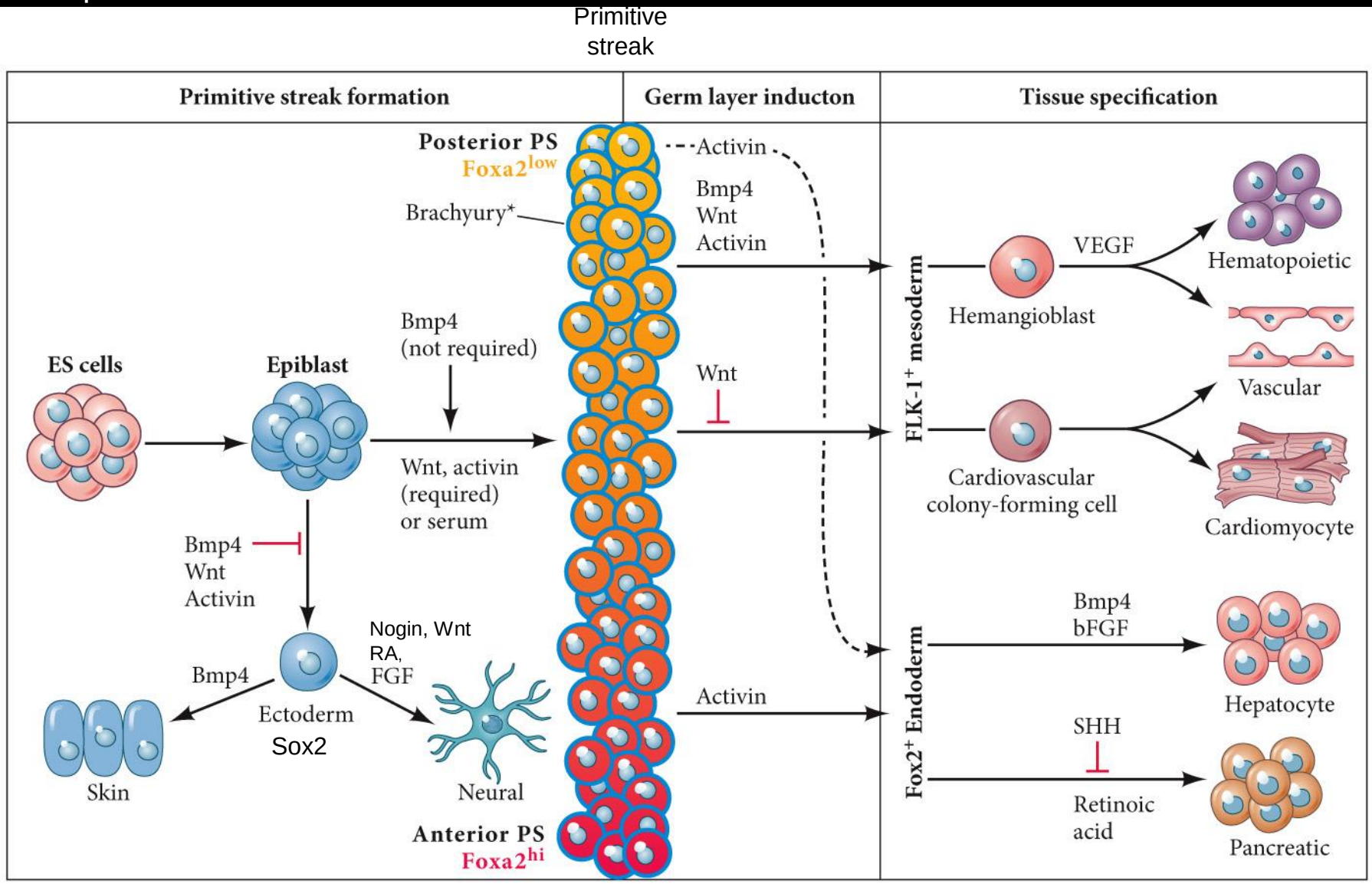


- Morphogenic gradients: BMP/Nogin; Shh
- Neuronal activity
- Bloodborne Growth Differentiation Factor (GDF11)
- Ependymal cell VCAM
-diminishing Notch signaling B1>B2>B3 (increasing proliferation) > A (off – differentiation)

STEM CELLS IN VITRO TECHNOLOGIES

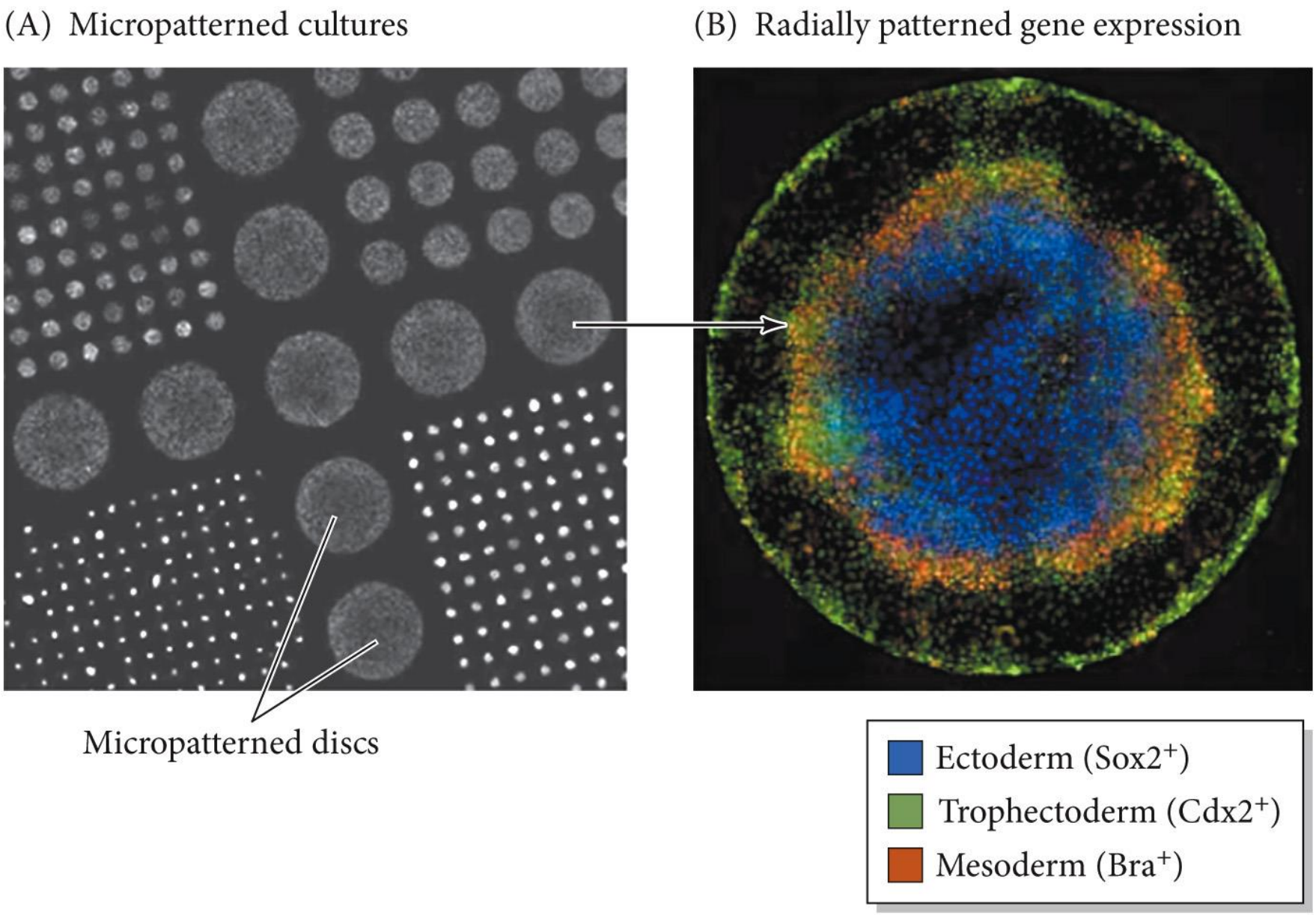
workshop

Figure 5.21 Inducing Experimental stem cell differentiation from ESCs using Paracrine & Transcription factors

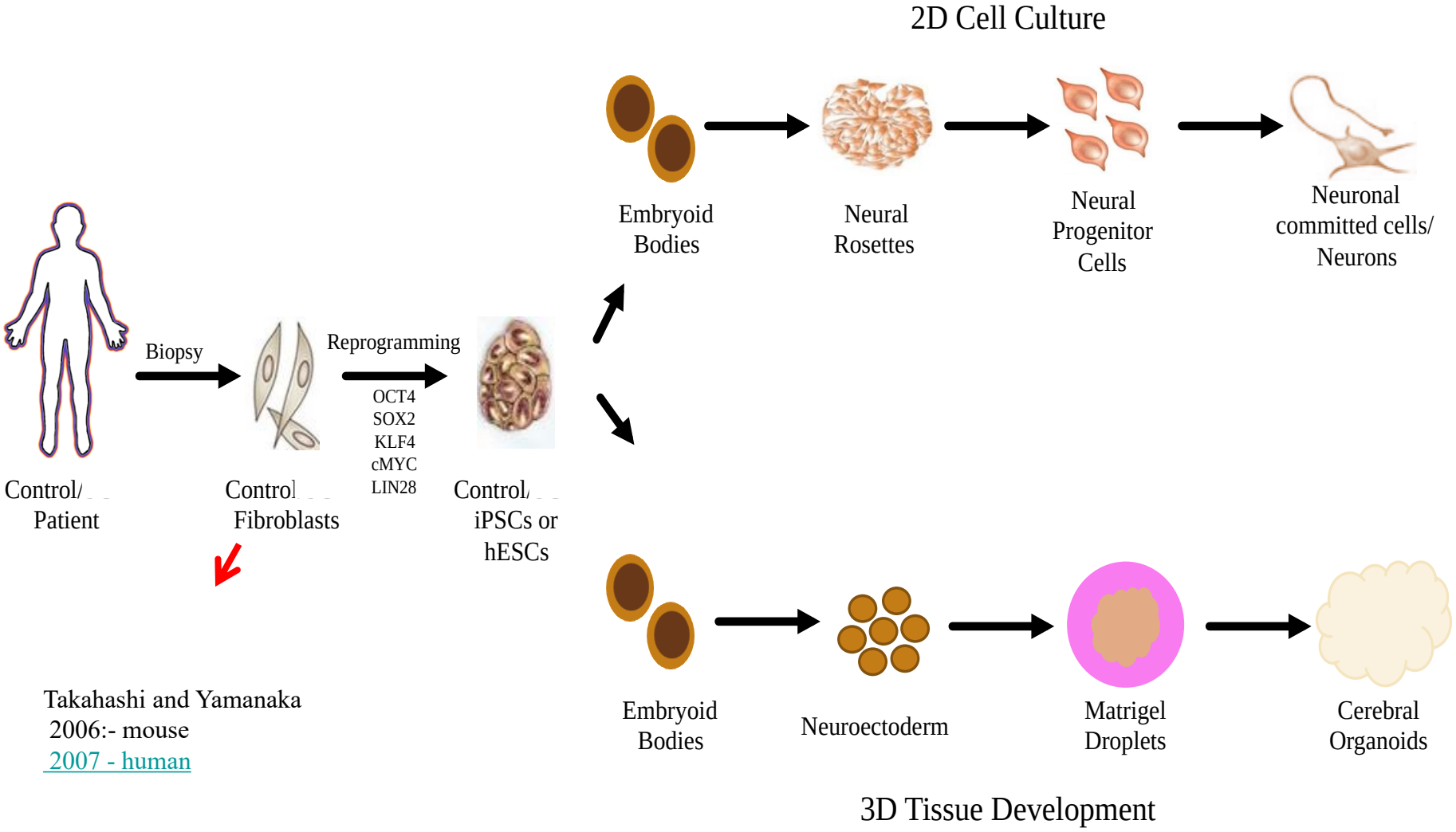


DEVELOPMENTAL BIOLOGY 11e, Figure 5.21

Figure 5.22 Human ESCs cultured in confined micropatterned discs demonstrate a pattern of differential gene expression similar to that seen in the early embryo

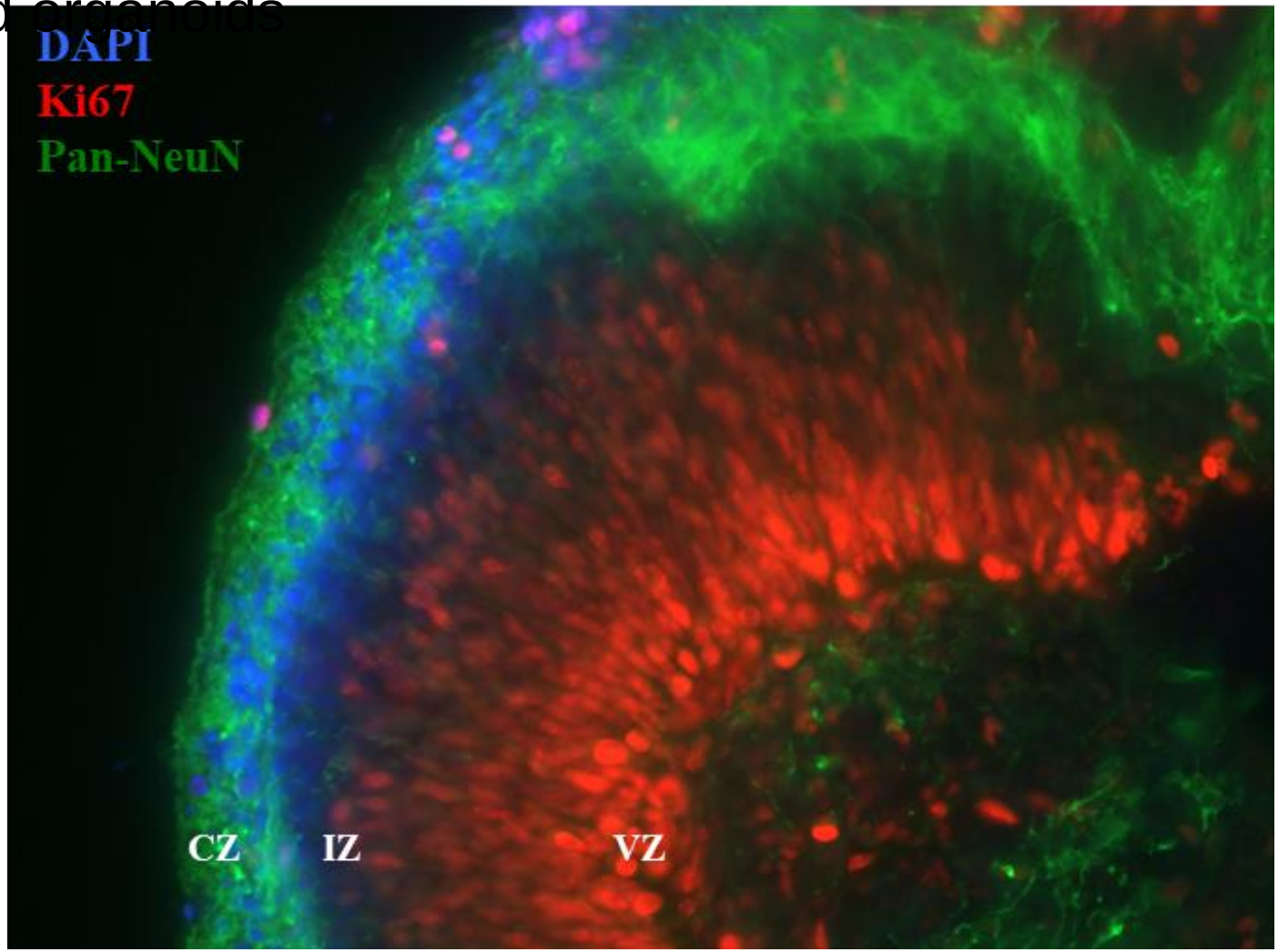


Modeling neurodevelopment in vitro

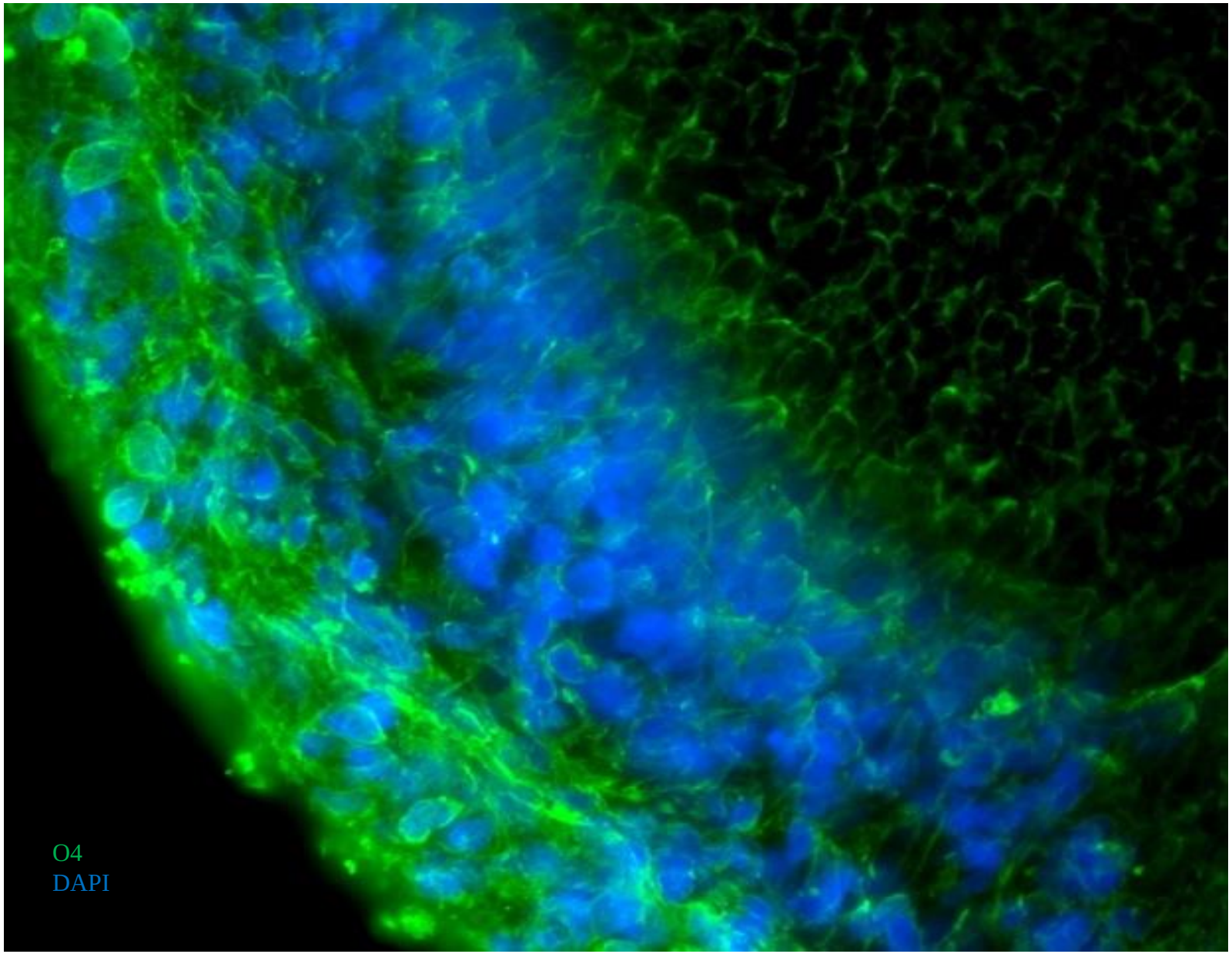


Apical to basal pattern of brain and organoid cortex development

14 day old organoids

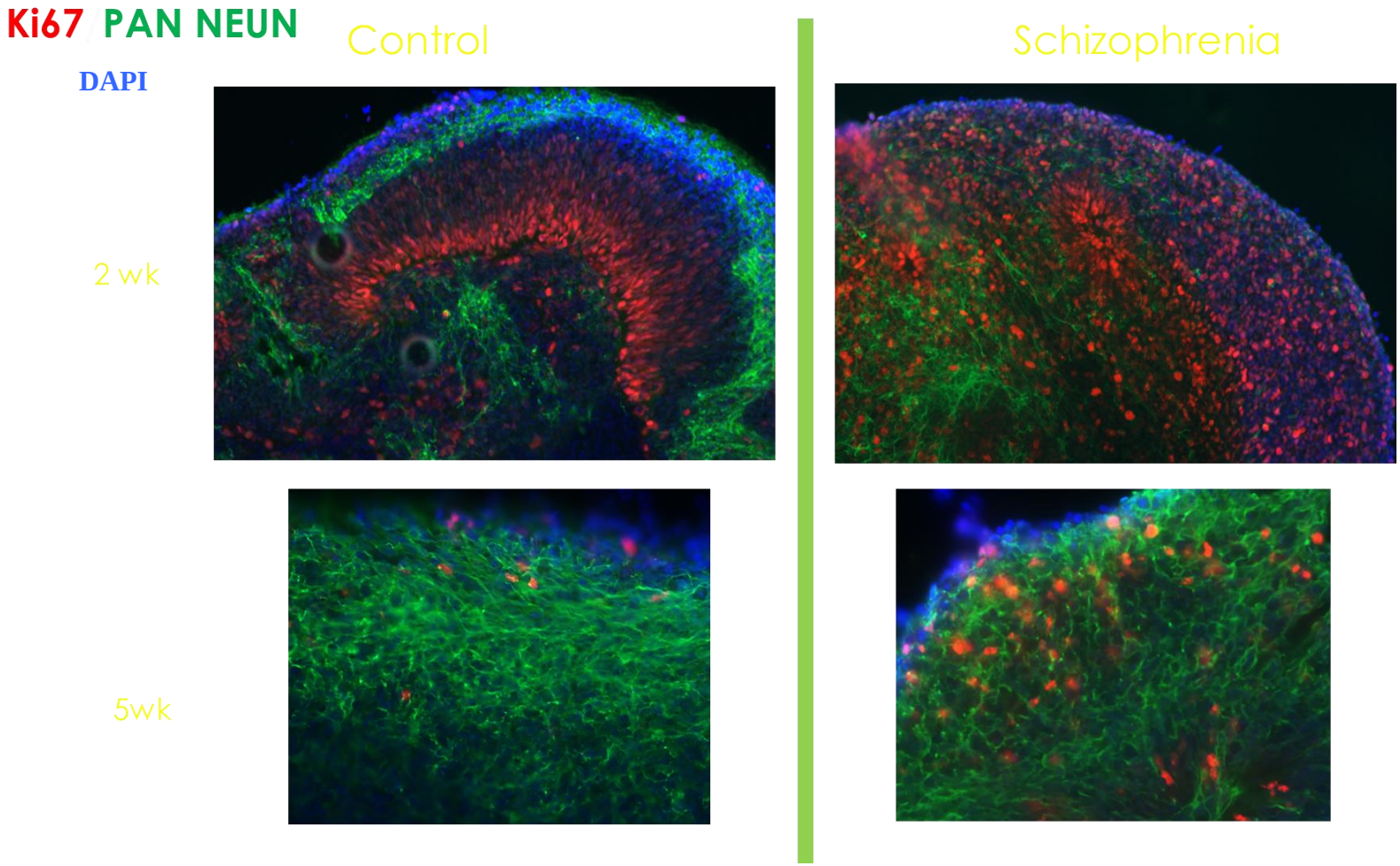


Inner zone: proliferating Ki67^{+} stem cells; Intermediate zone: Ki67+



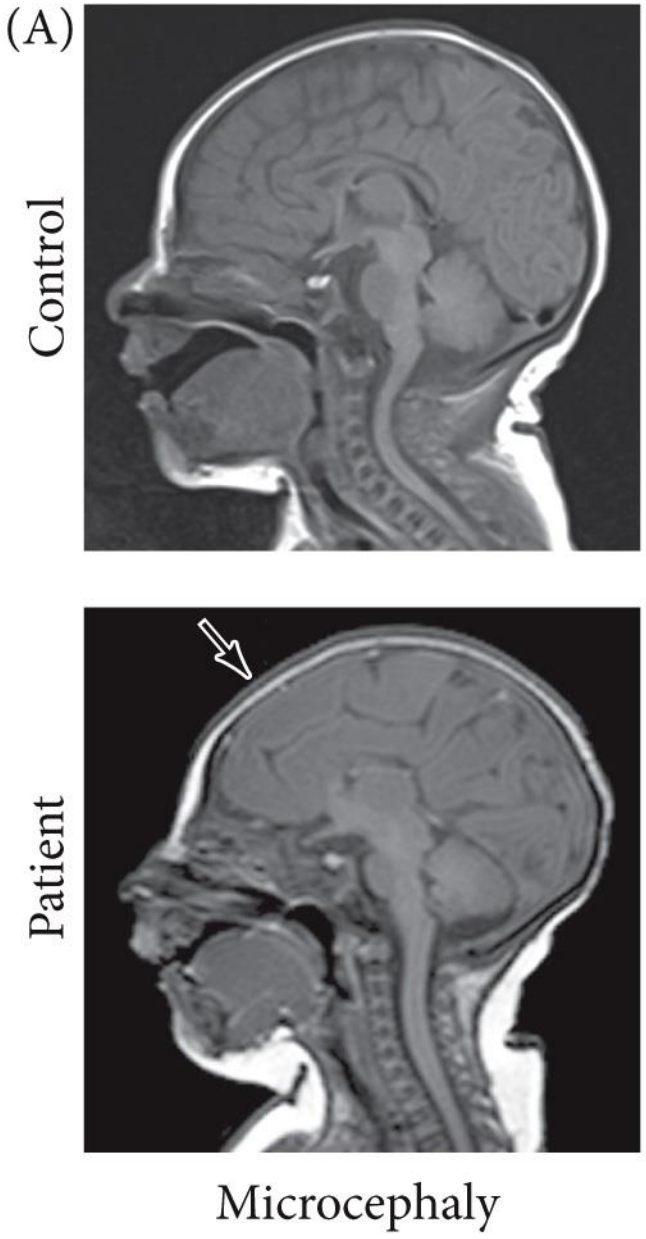
22 day old organoids see Olig4+ cells (marker for mature oligod

MODELLING ABNORMAL BRAIN DEVELOPMENT WITH SCHIZOPHRENIA IPSC



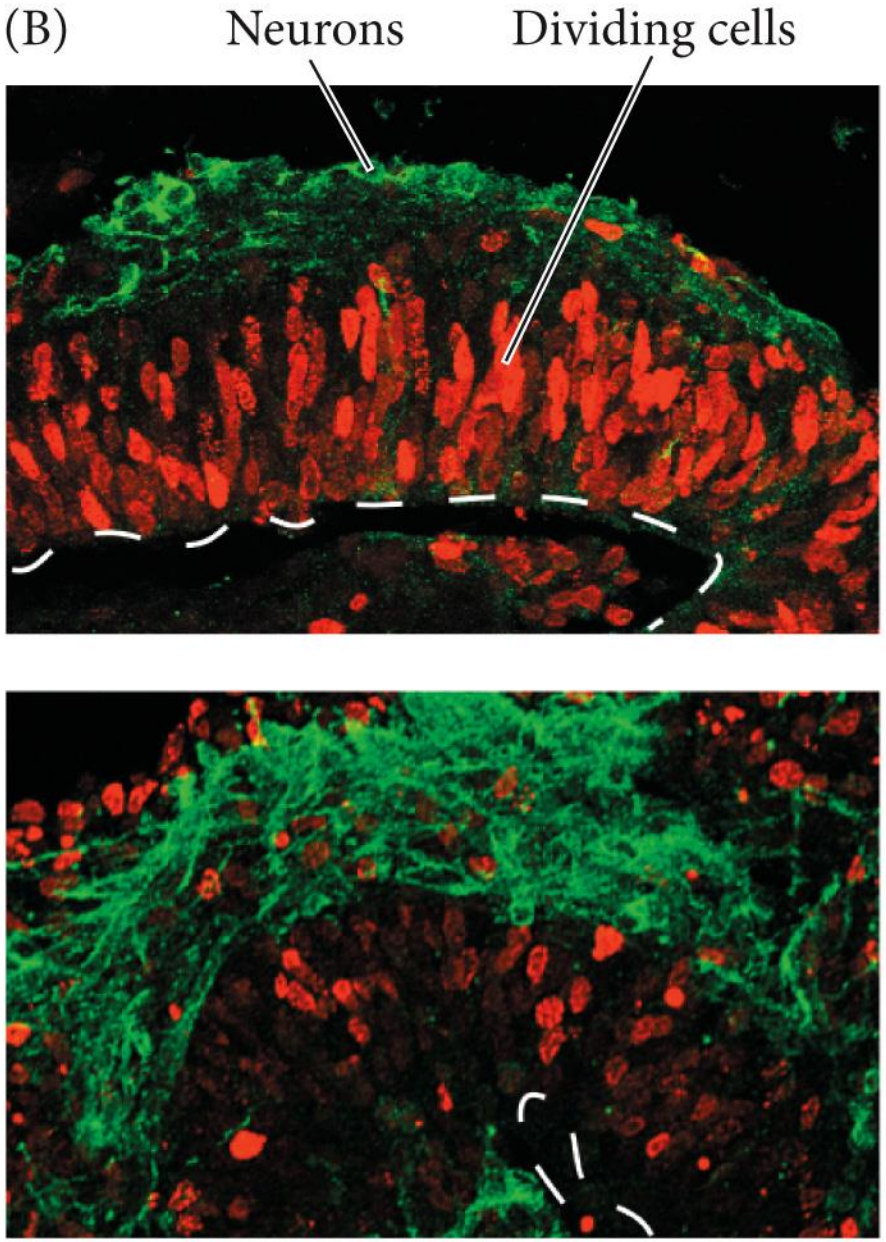
Stachowiak, **C.A. Benson**, Elahi, Narla, Freedman, Brennand, Klejbor, Stachowiak. Cerebral organoids reveal early cortical maldevelopment in schizophrenia – role of FGFR1. *Nature Translation Psych.*

Figure 5.27 Modeling human microcephaly with a patient-specific cerebral organoid (Part 1)



DEVELOPMENTAL BIOLOGY 11e, Figure 5.27 (Part 1)

Figure 5.27 Modeling human microcephaly with a patient-specific cerebral organoid (Part 2)



DEVELOPMENTAL BIOLOGY 11e, Figure 5.27 (Part 2)

THE END