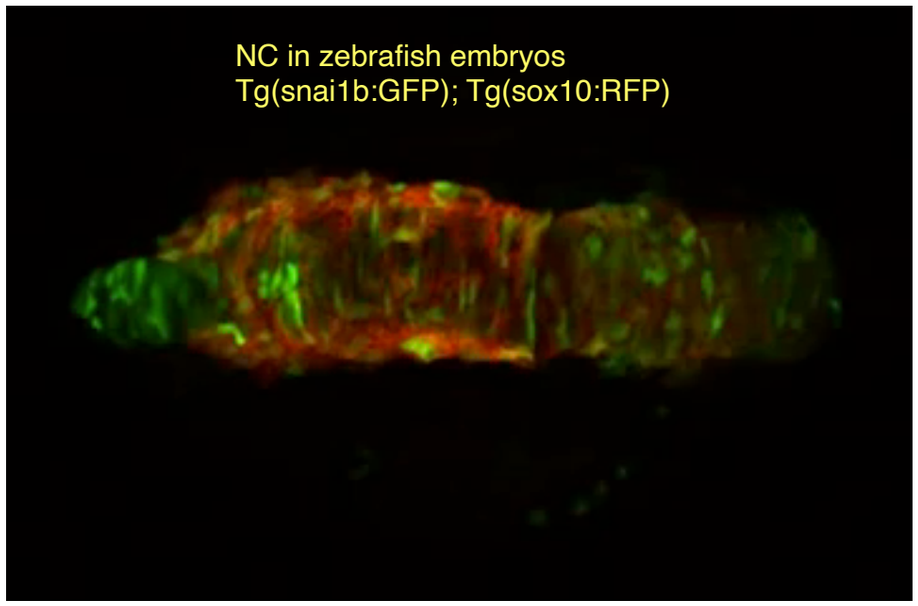
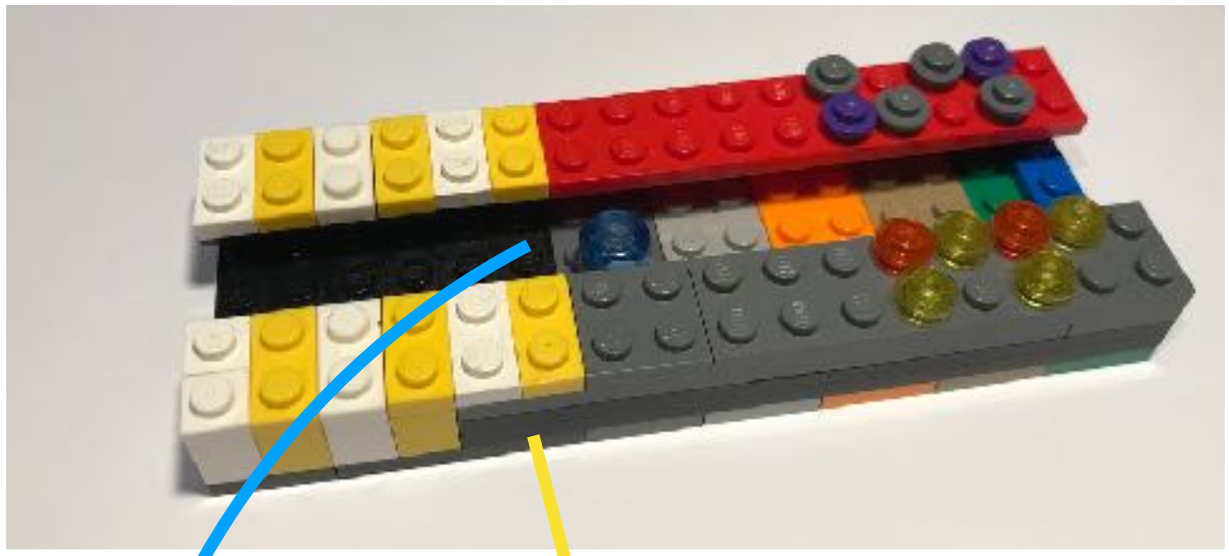
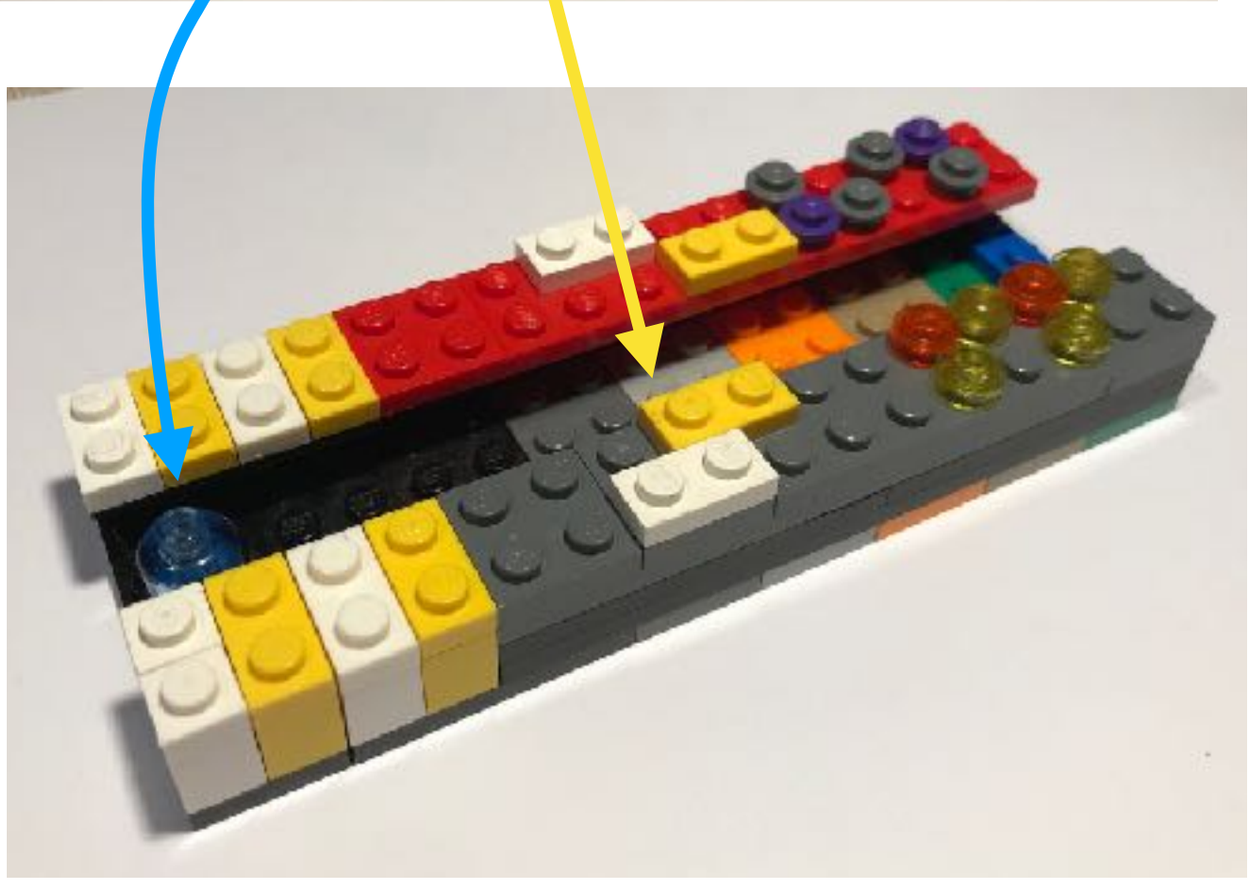
Big questions



Cell migration - finishing touches & completing the cycle for the next generation



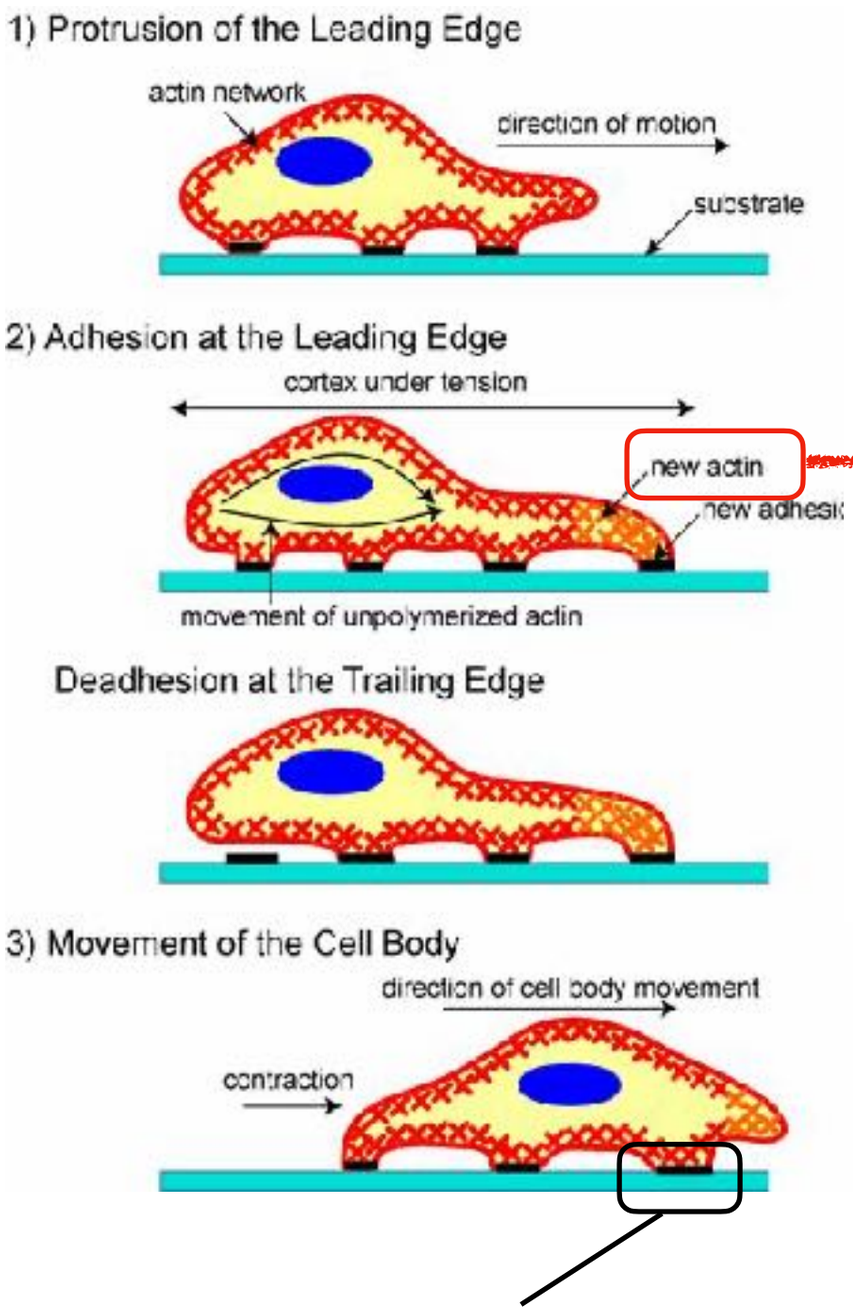


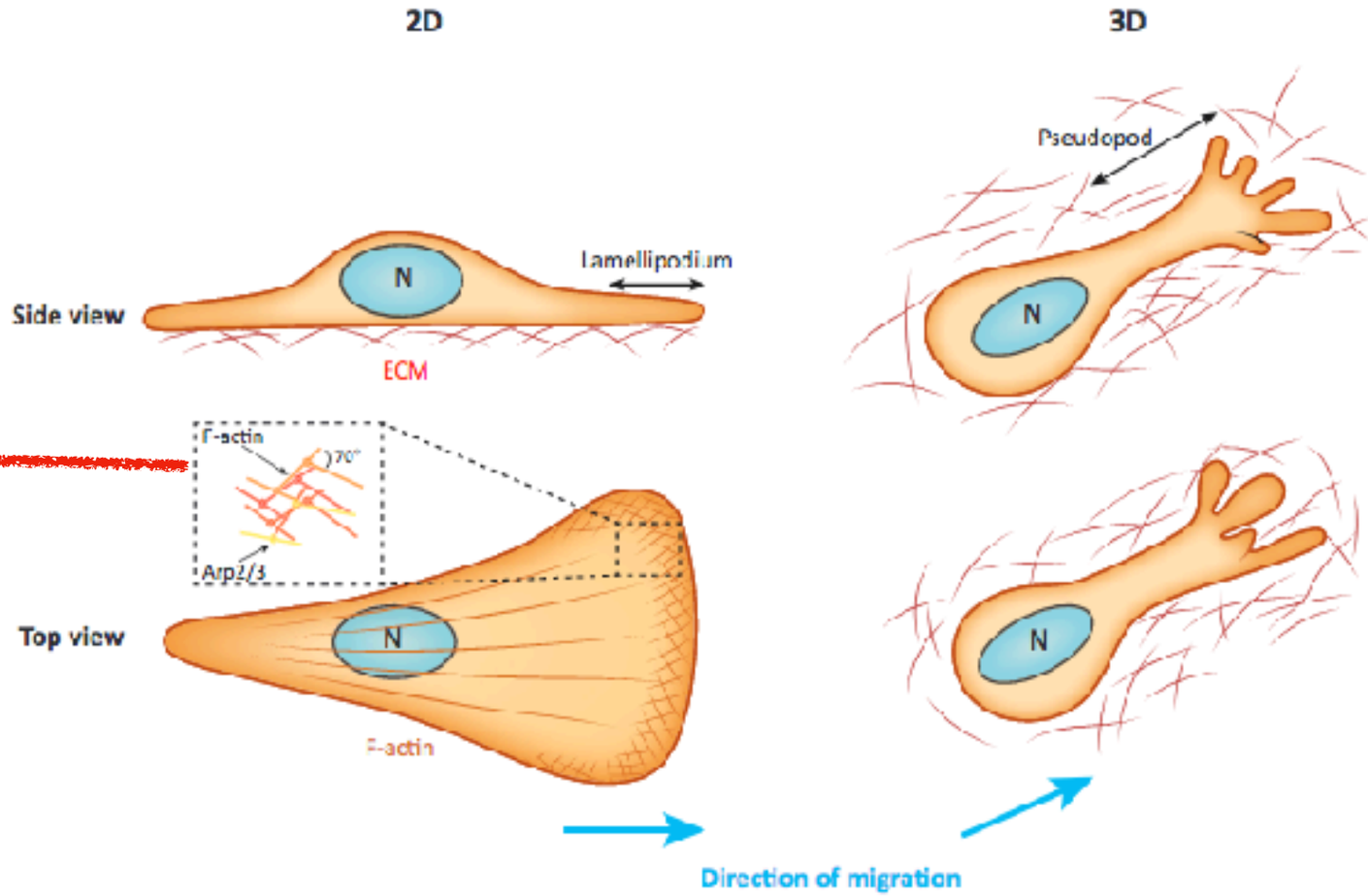
Today's menu

- **Cell migration**
  - ***Basic cellular mechanisms***
    - actomyosin + adhesion = traction forces
    - motility + polarization = migration
- **The neural crest and placodes**
  - ***The "4th germ layer"***
    - Sculpting face, heart, gut, sensory systems
- **Germ cell migration**
  - ***Completing the cycle of life***
    - Wiping and silencing the genome
    - Long Range migration
    - Bi-potency

Migration - Basic cellular mechanisms

- Actomysin + adhesion = traction forces





Adhesion receptors: Integrin, Cadherin, etc

Migration - Basic cellular mechanisms

- Actin polymerization and branching at leading edge

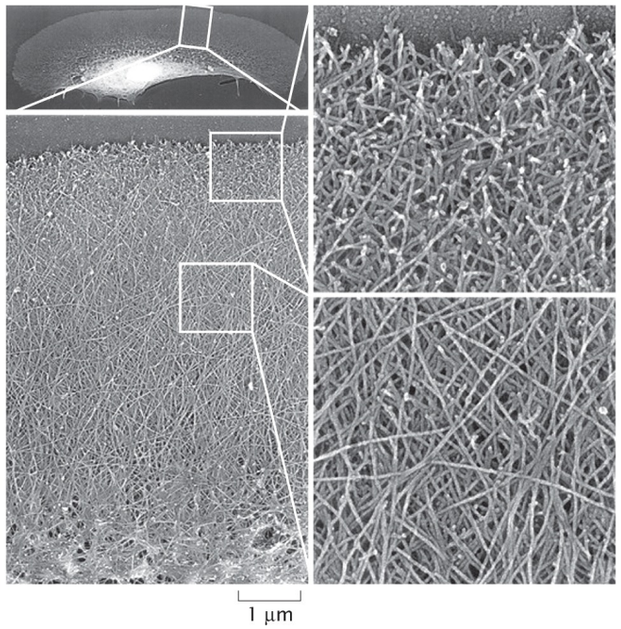


Figure 14.2 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

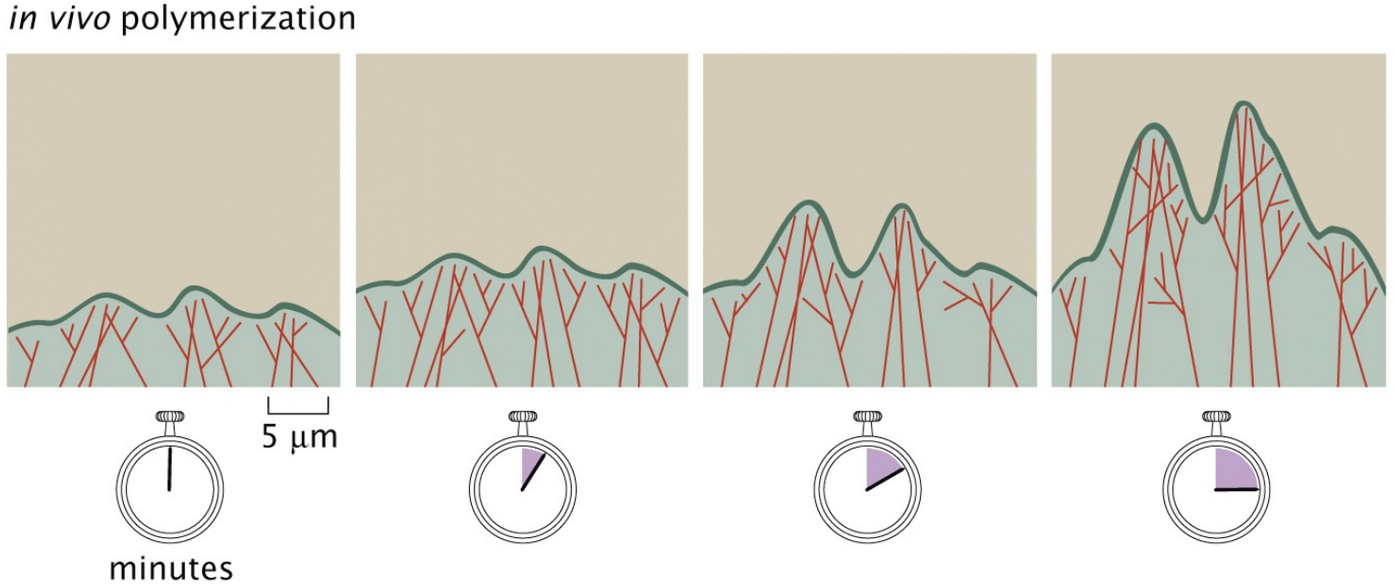
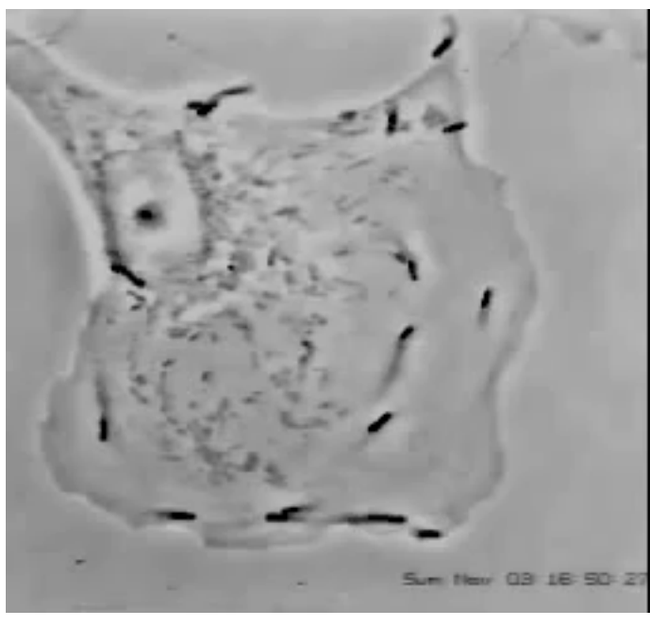
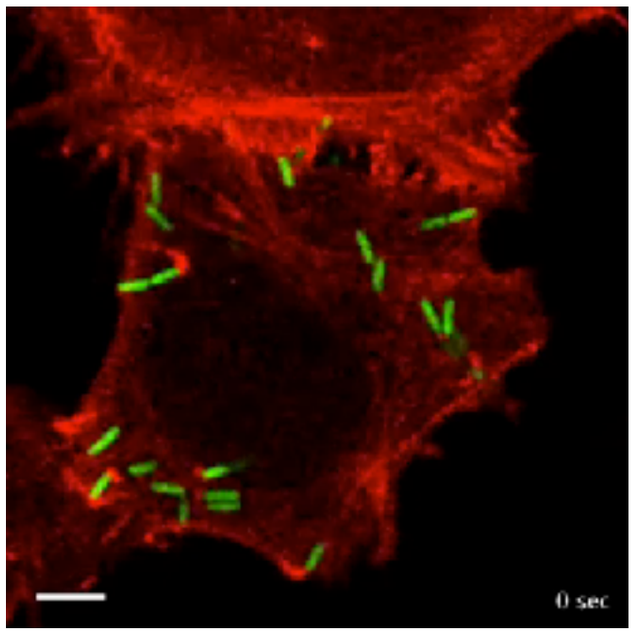


Figure 15.1b Physical Biology of the Cell, 2ed. (© Garland Science 2013)



Listeria propelled inside cell



Listeria (green), actin (red)

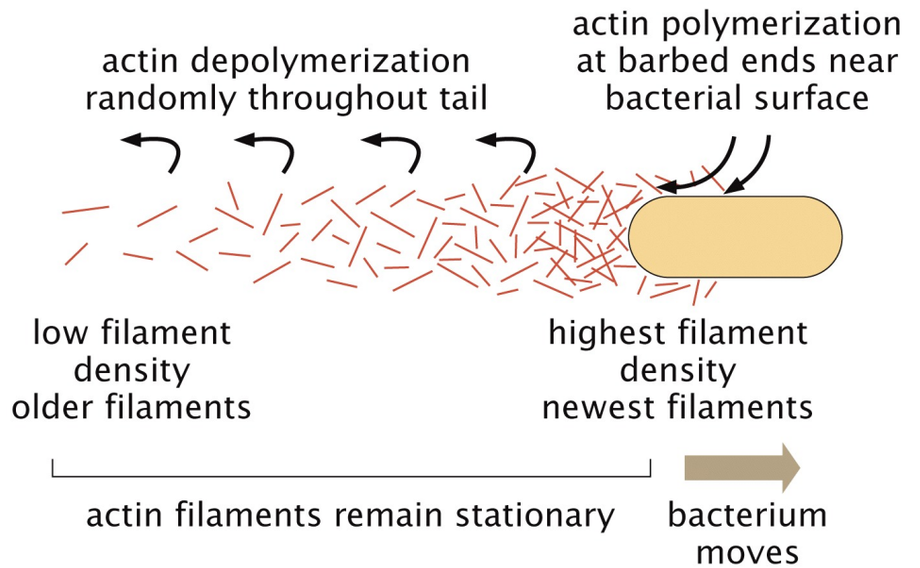
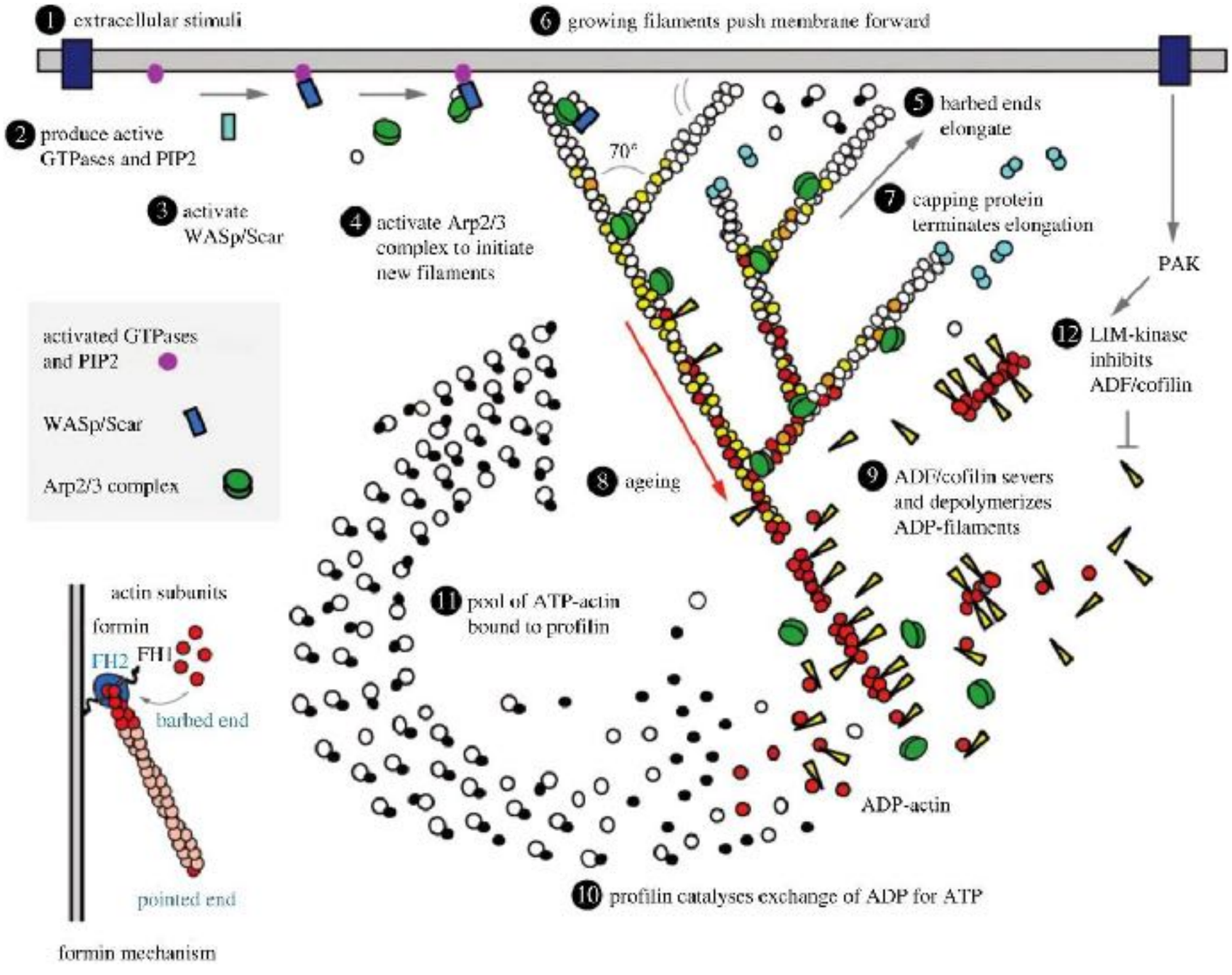


Figure 15.3b Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Julie Theriot says: https://www.youtube.com/watch?v=FIT0fdt6c3Y

Migration - Basic cellular mechanisms

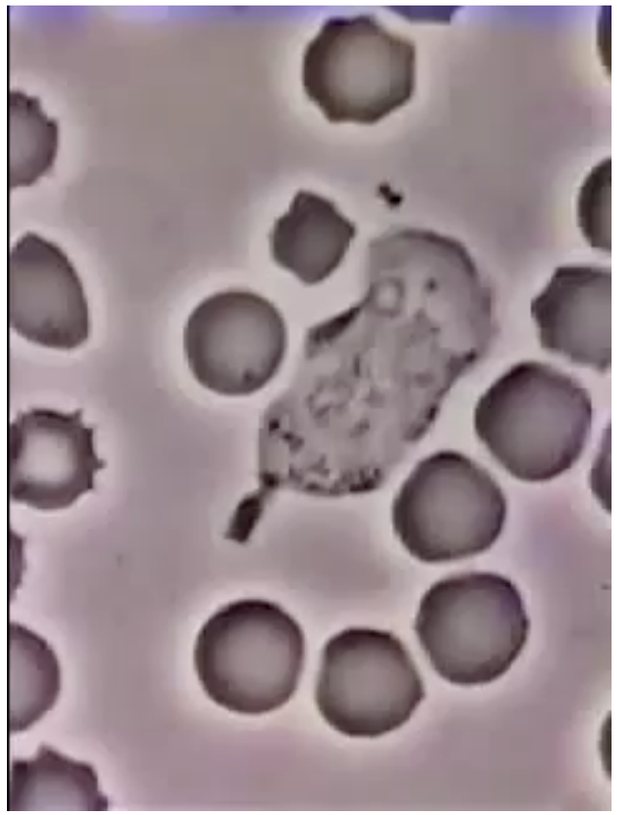
- Actin polymerization and branching at leading edge



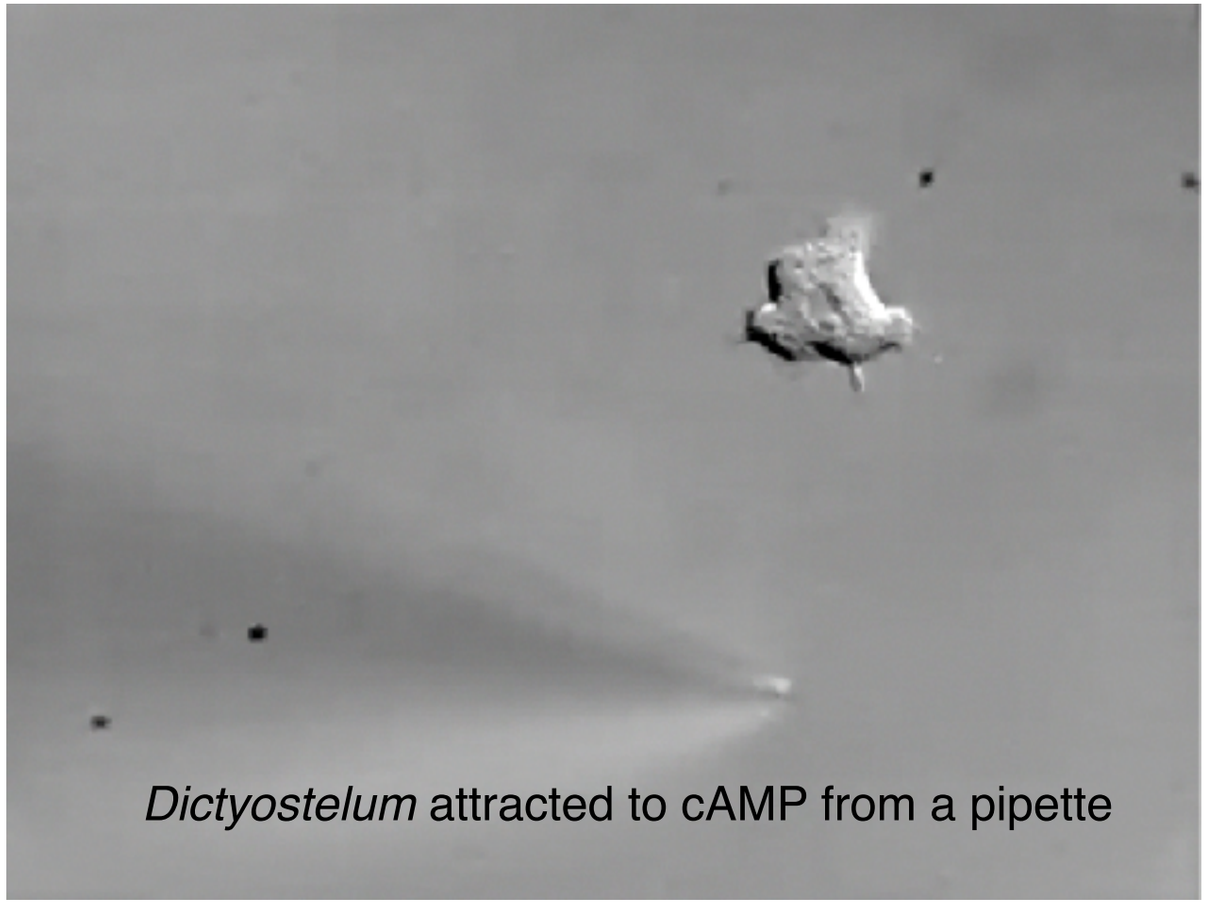
Julie Theriot says: https://www.youtube.com/watch?v=wQID2zmeWTQ

Migration - Basic cellular mechanisms

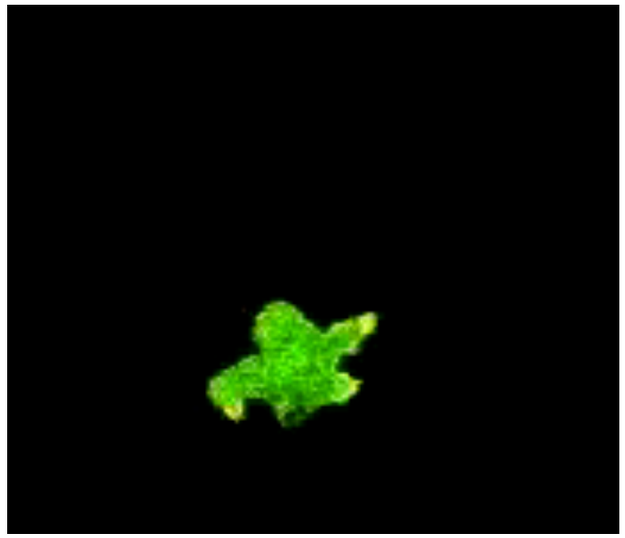
- motility + polarization = migration



Human neutrophil
chasing bacterium



Dictyostelum attracted to cAMP from a pipette

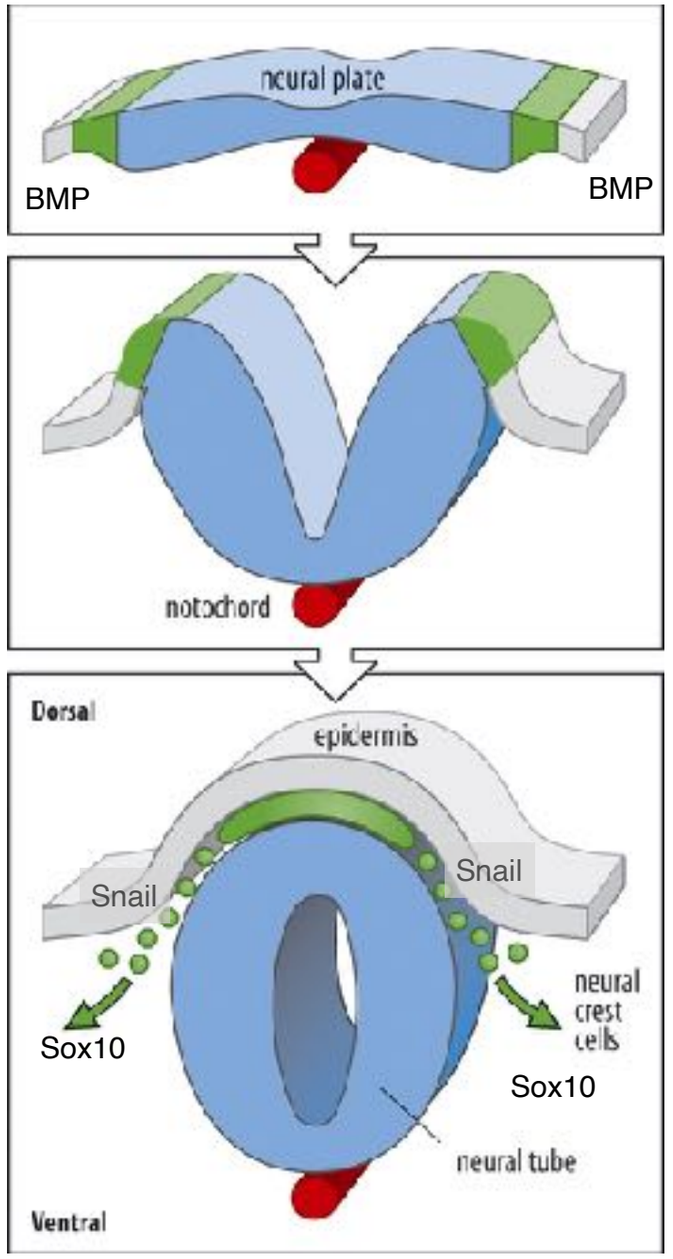


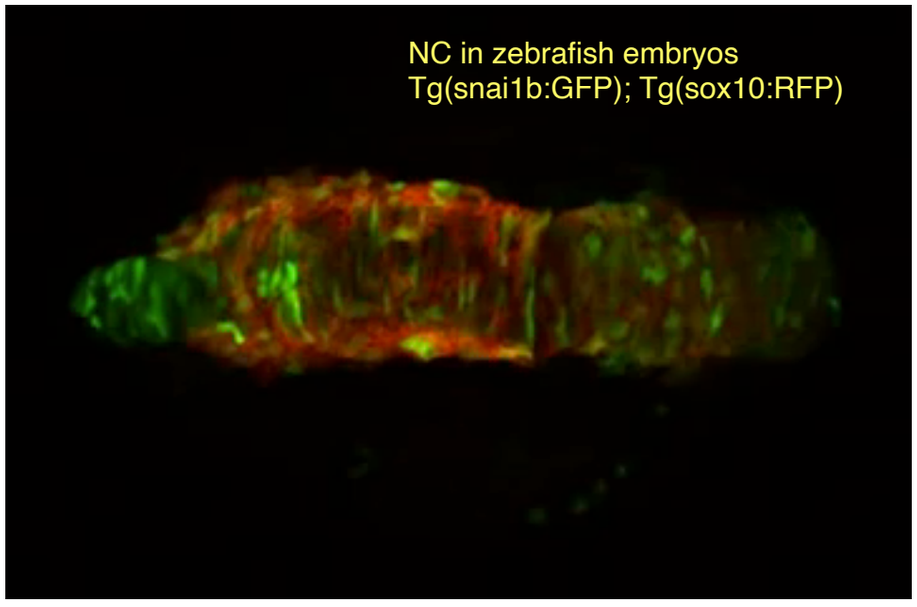
Green = membrane
Red = LimE-RFP = F-actin

- Polarization - *persistent* directed motion
- Chemoattractact receptors engaged on one side of cell
- Engage $Ca^{2}+$ and small GTP effectors
- Remodel cytoskeleton

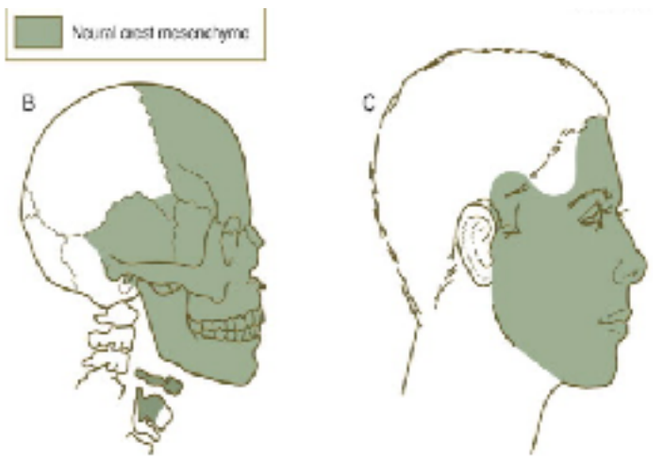
The neural crest and sensory placodes

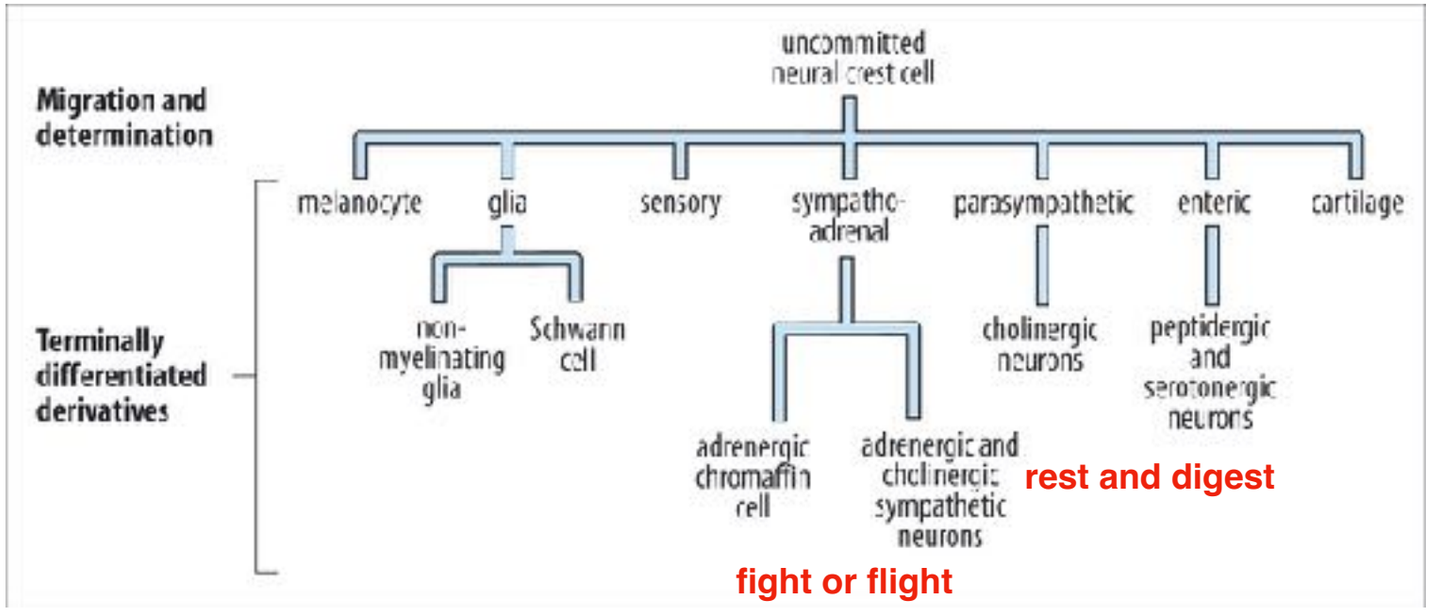
- Derived from neuroepithelium
- NC cells delaminate and migrate away
- Placodal cells deform epithelium + migrate
- Seed exisiting structures / build new structures

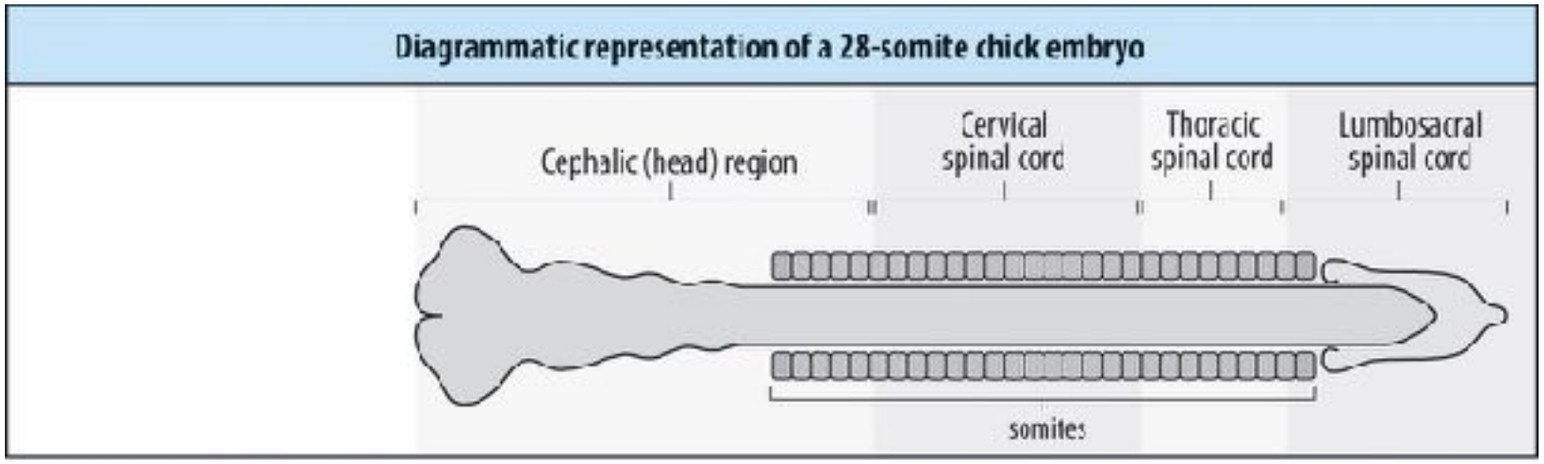


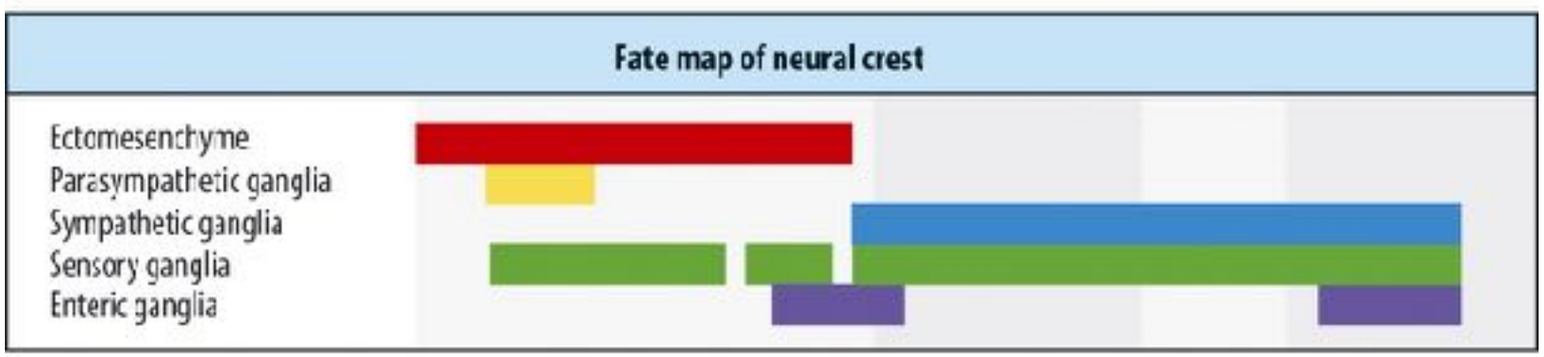


Neural crest-derived structures

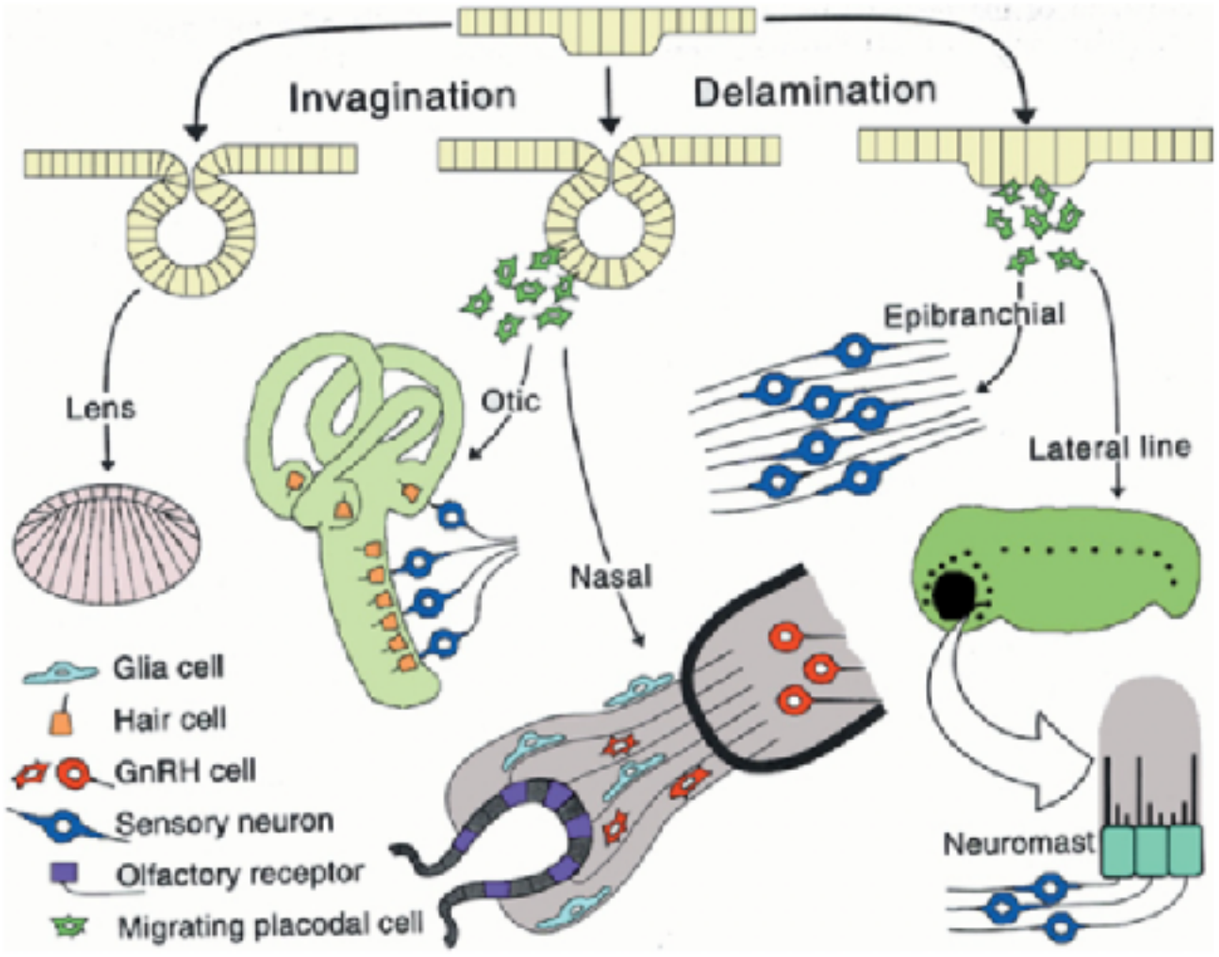


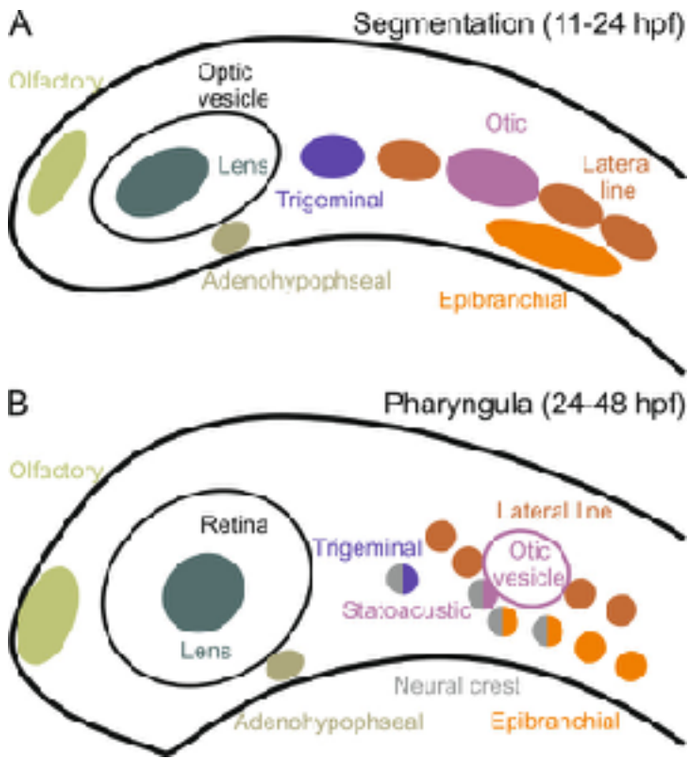


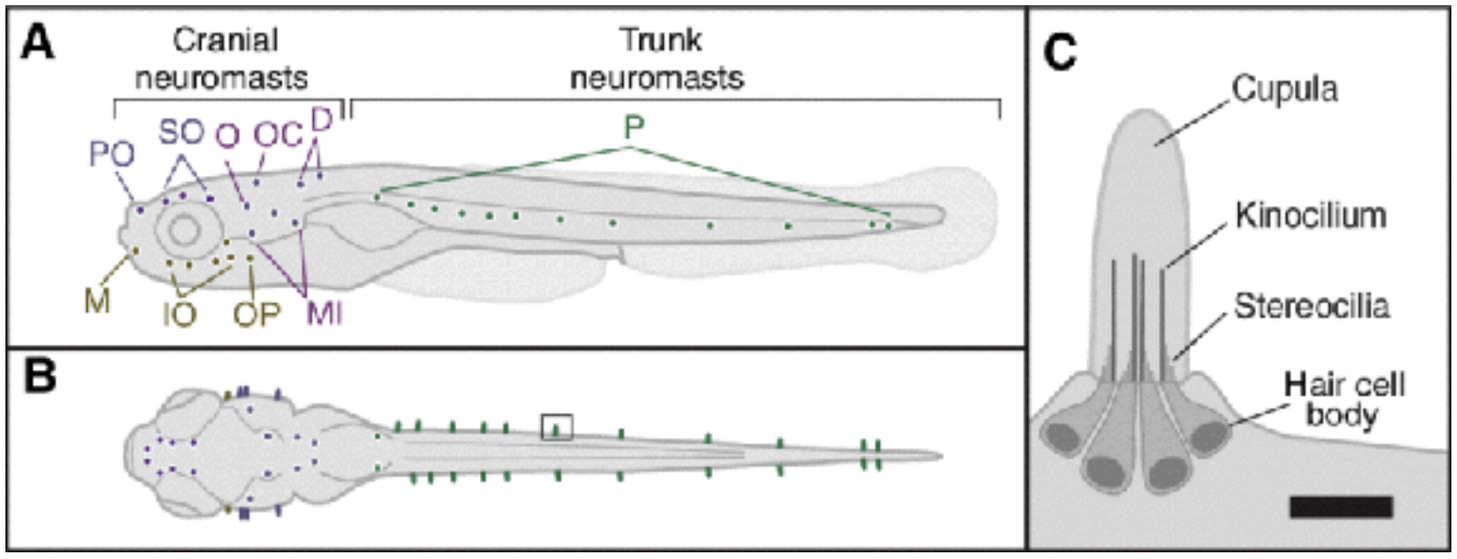




Placodal-derived sensory structures



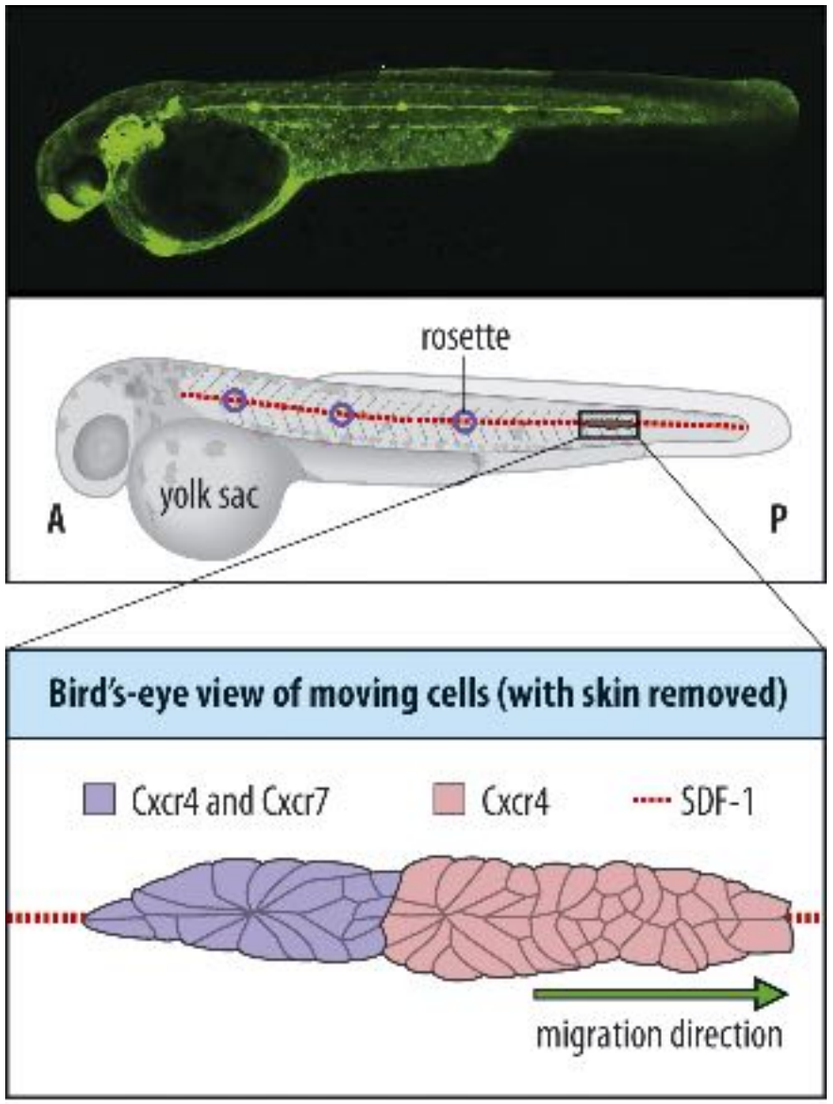


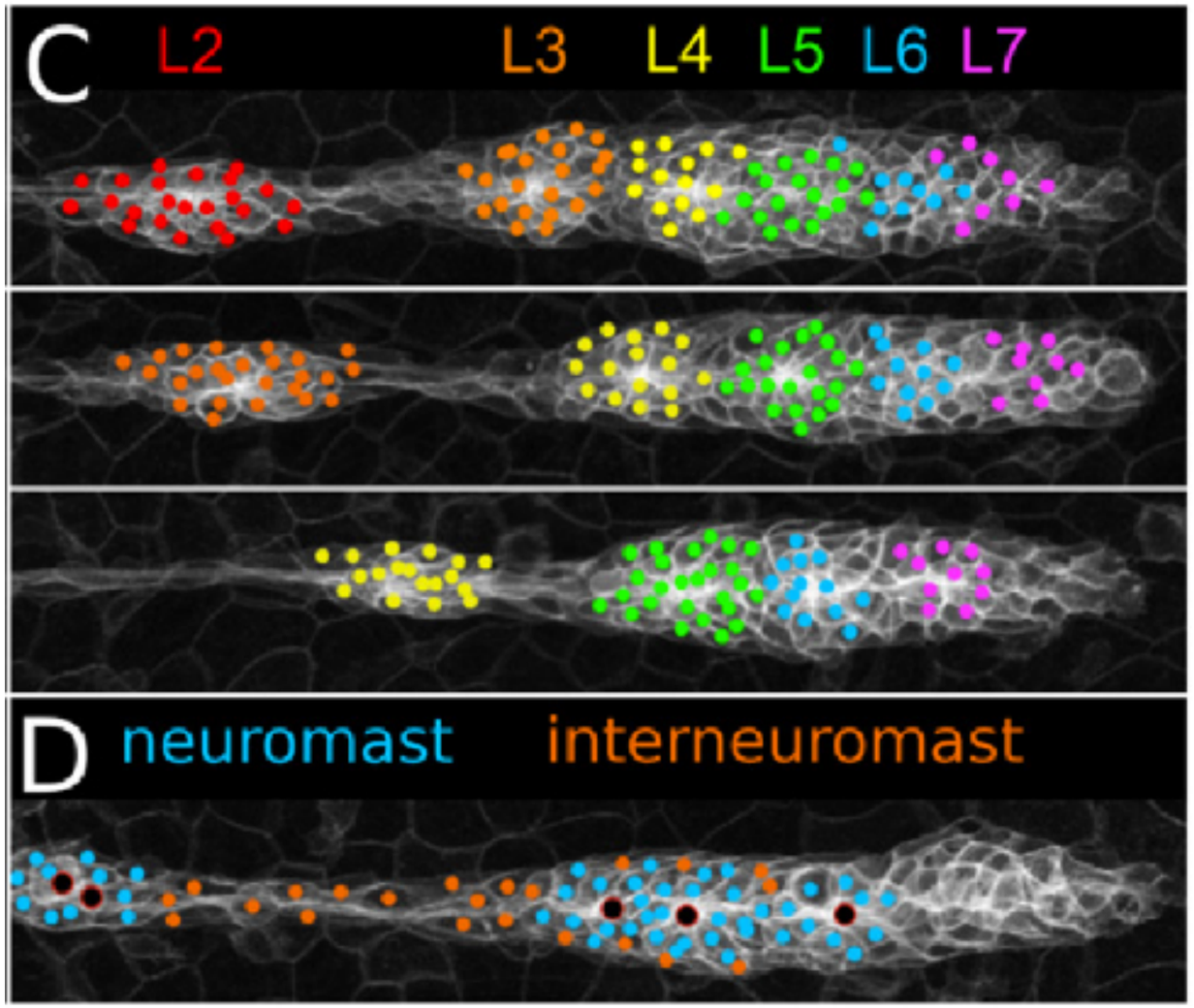


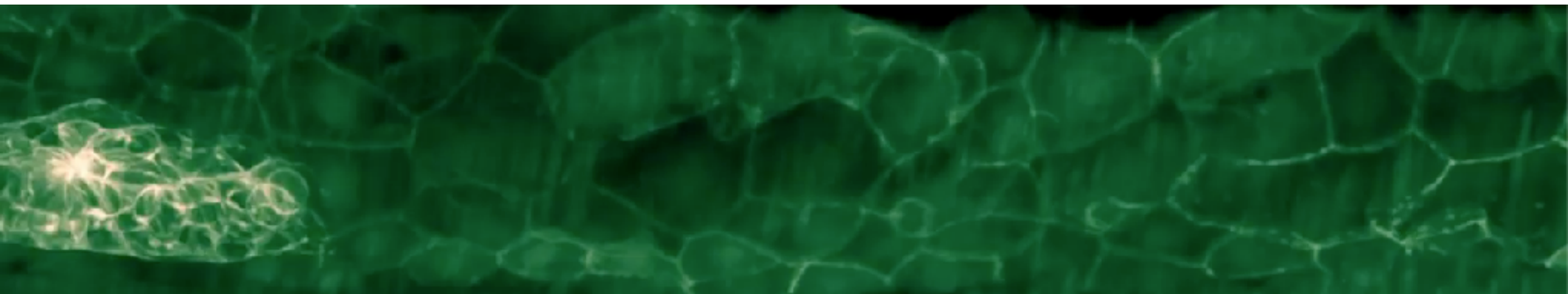
Sensory organ to measure water pressure waves

Blind fish can school

The zebrafish lateral line - collective migration



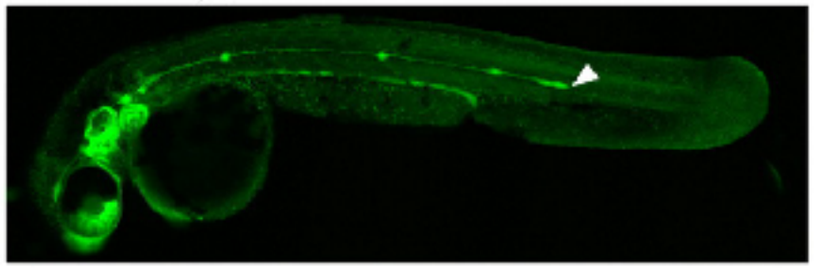




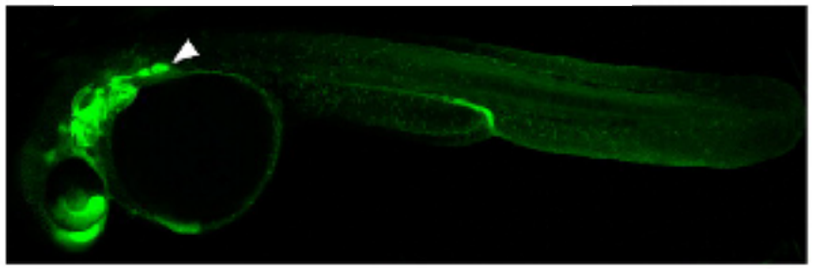
Individual puzzle

Three genes required for primordium migration

A Wild type

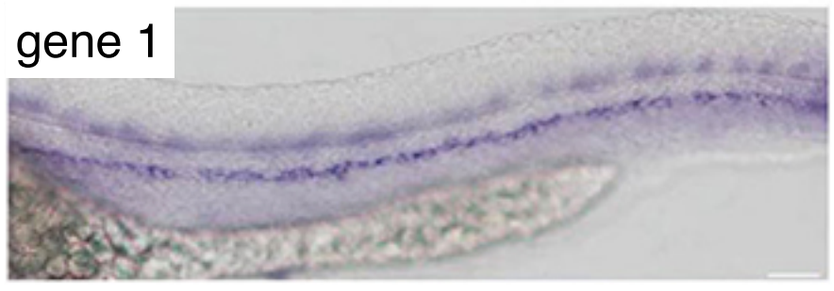


B Mutants' lateral lines

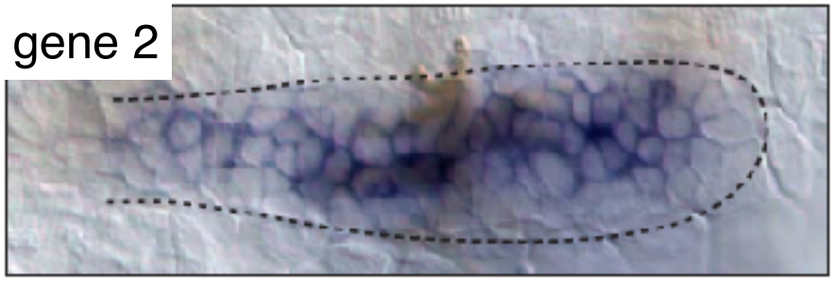


Gene expression patterns

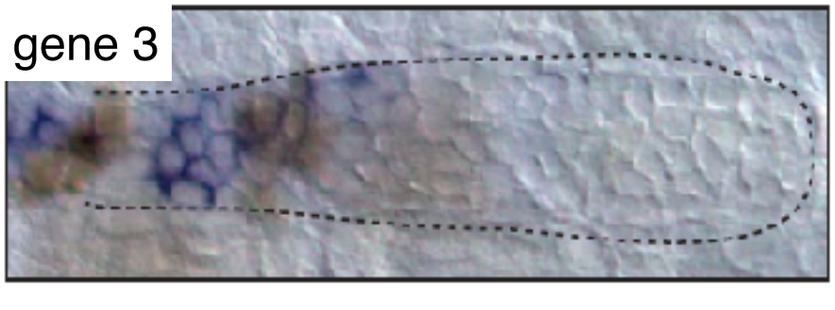
gene 1



gene 2



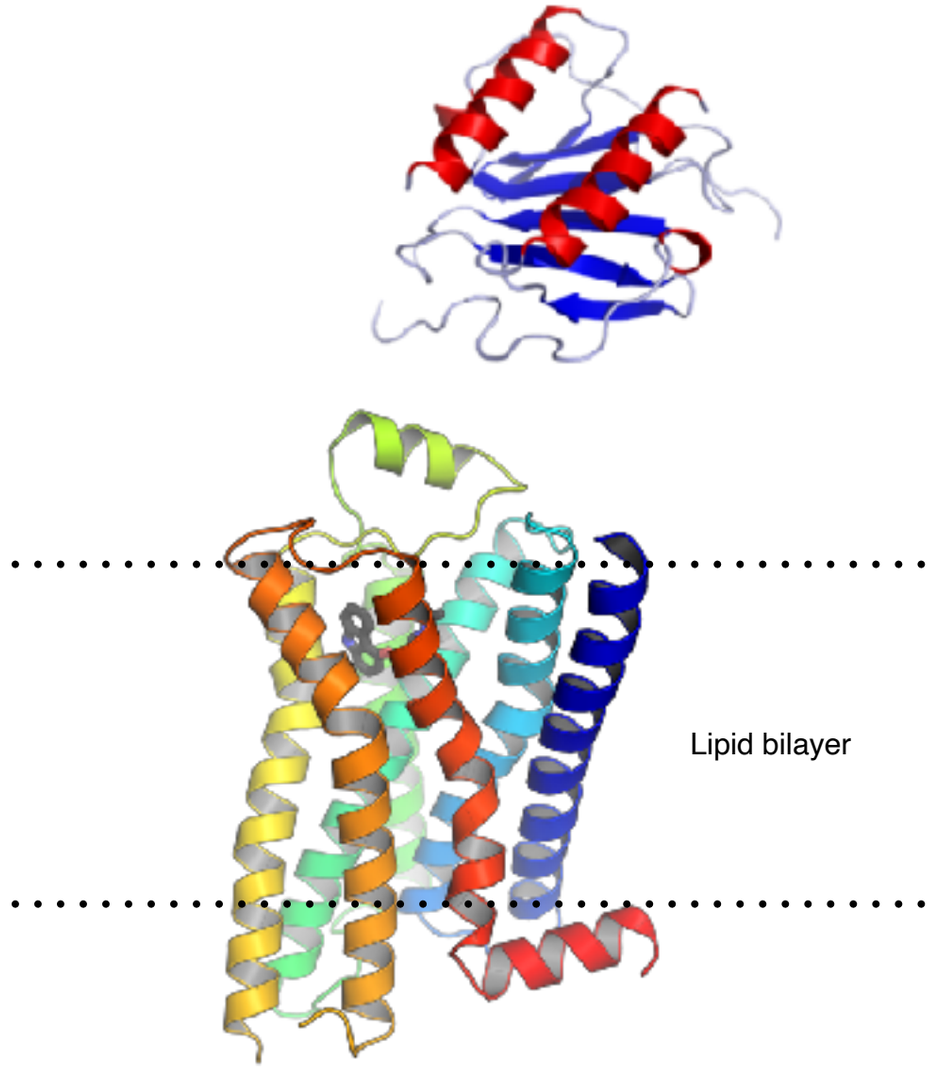
gene 3



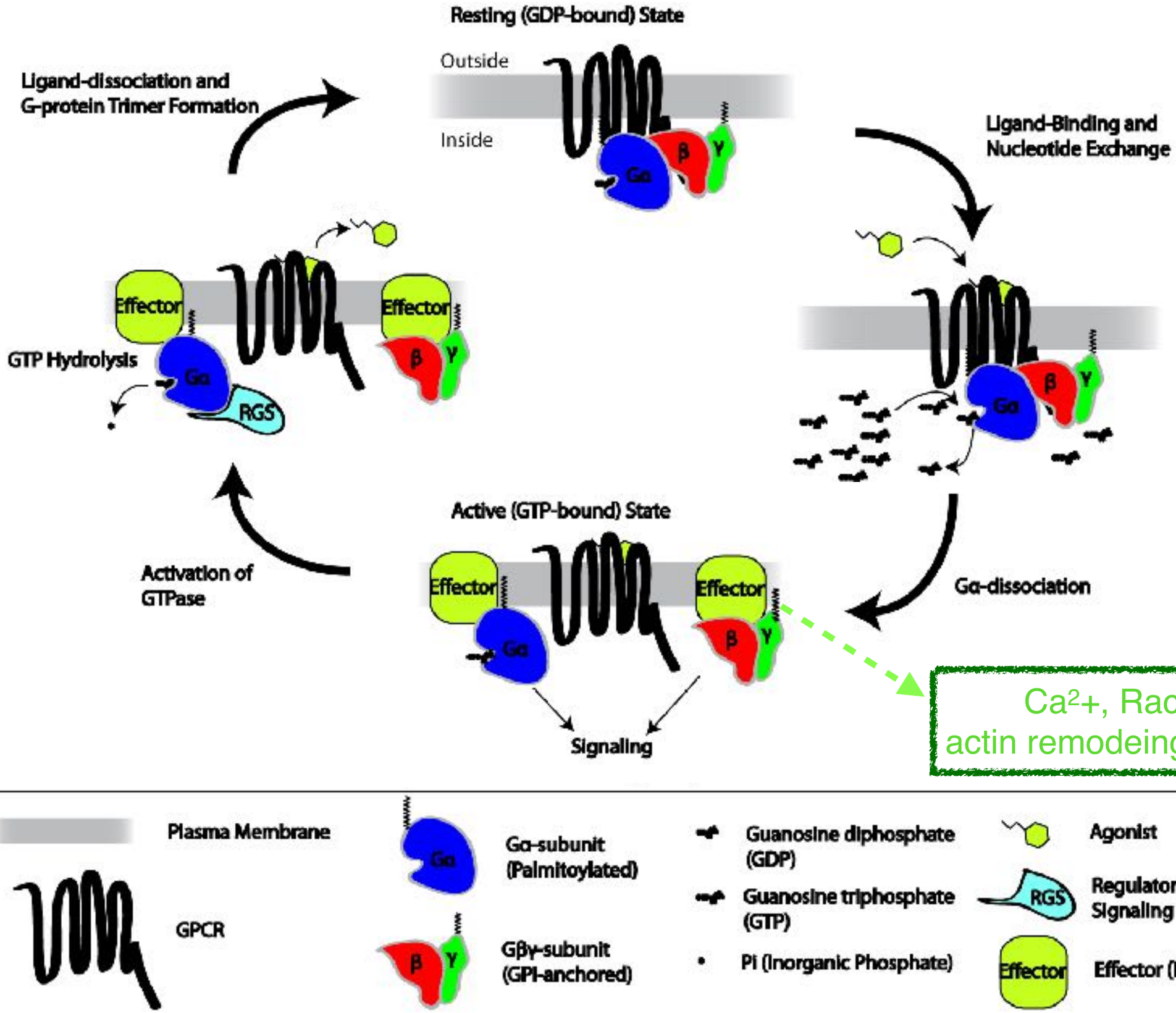
What sort of protein/ function might these three genes encode?

Chemokine signaling

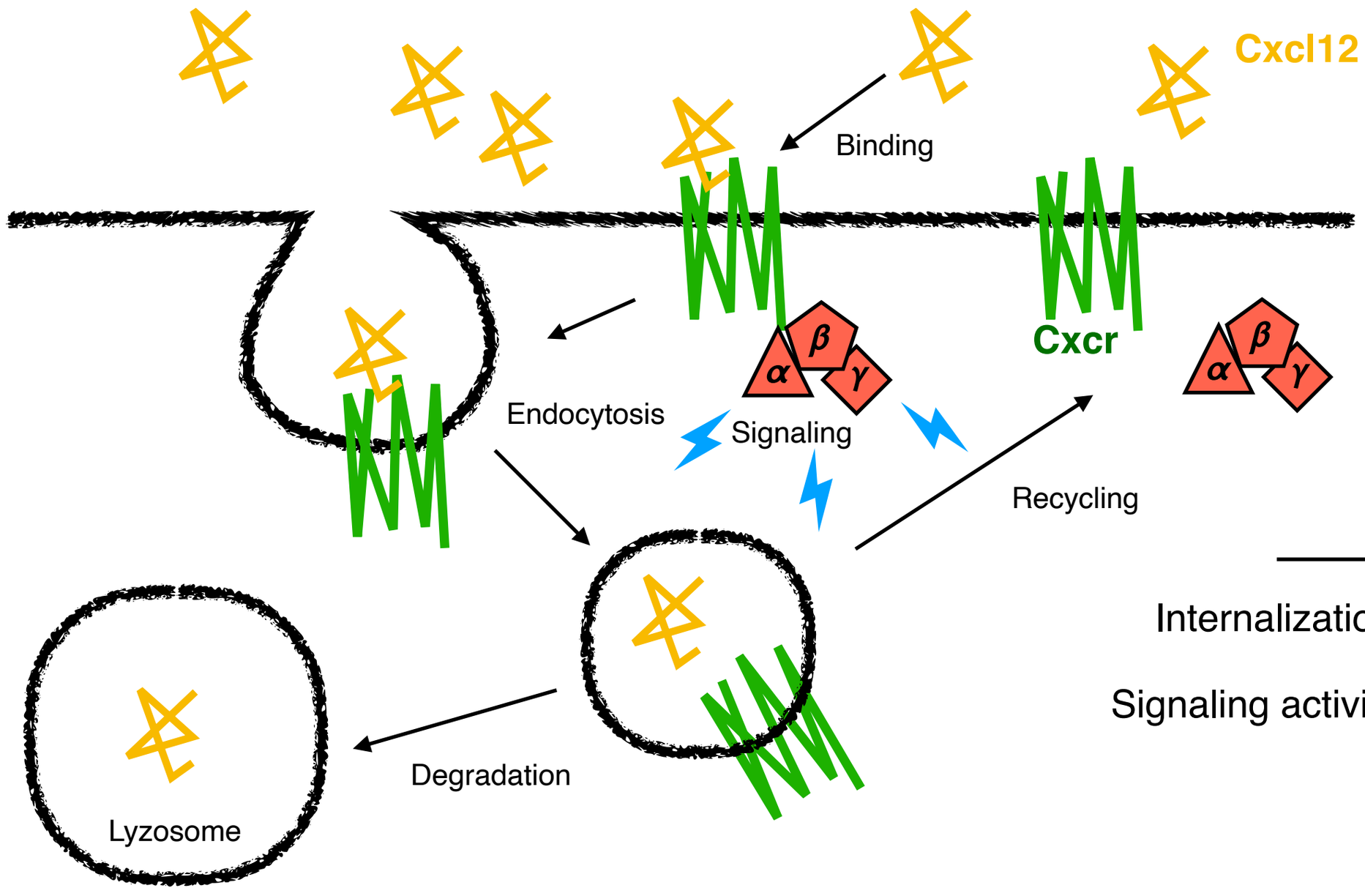
- **chemo**tactic cyto**kines**
- Receptor = CXCR, Ligand = CXCRL
- 7-pass trans-membrane receptor
- G-protein coupled
- Discovered in immune cells…



Chemokine signaling cycle



Differential internalisation and activity of Cxcr4 and Cxcr7

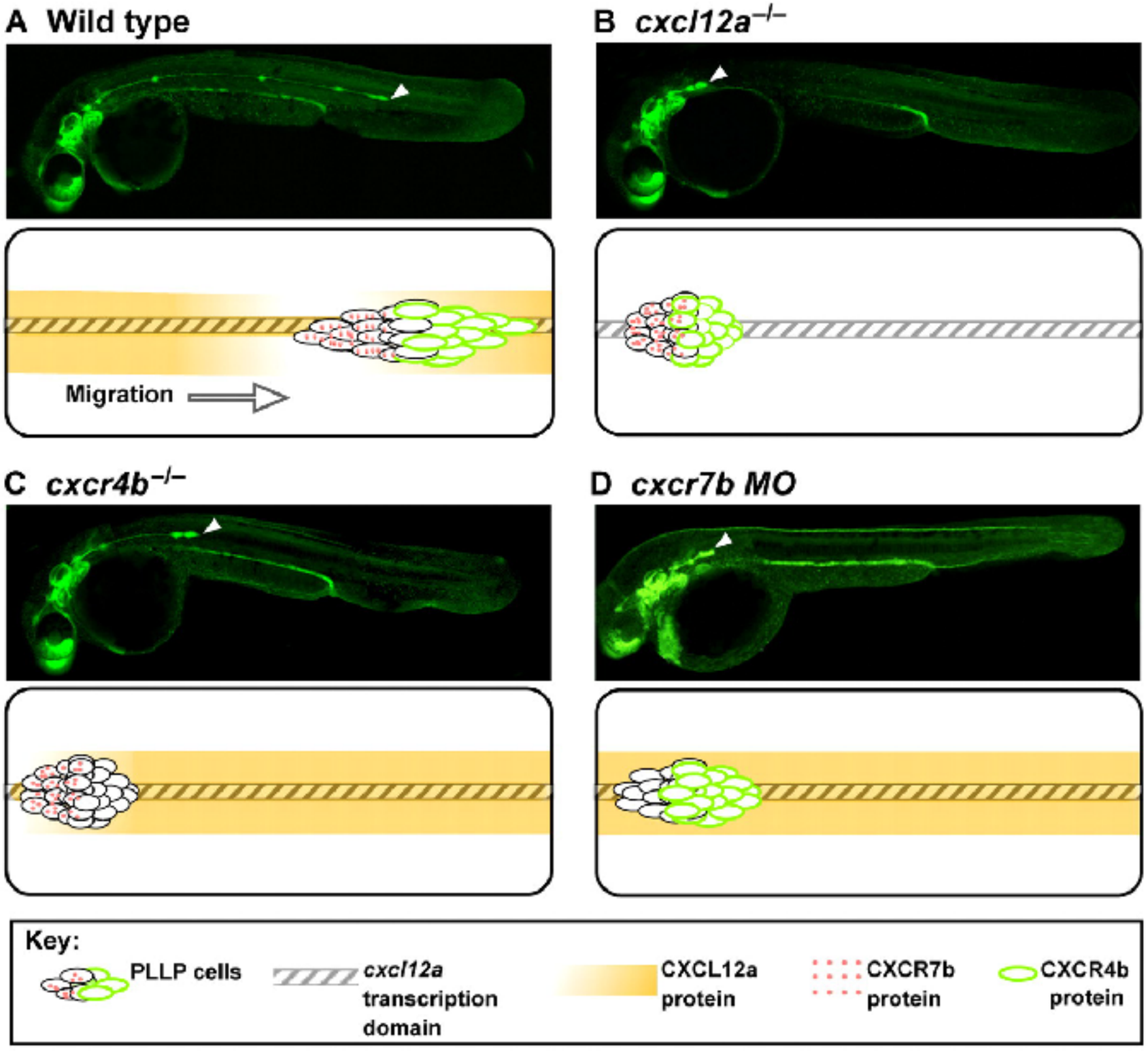


	Cxcr4	Cxcr7
Internalization	Slow	Fast
Signaling activity	High Ca^{2+} ERK Migration	Low

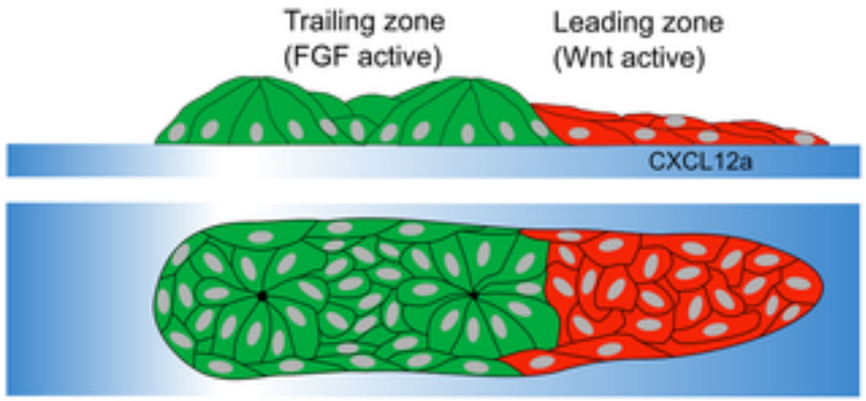
In mulitple cell types, Cxcr7 is a “scavenger receptor”

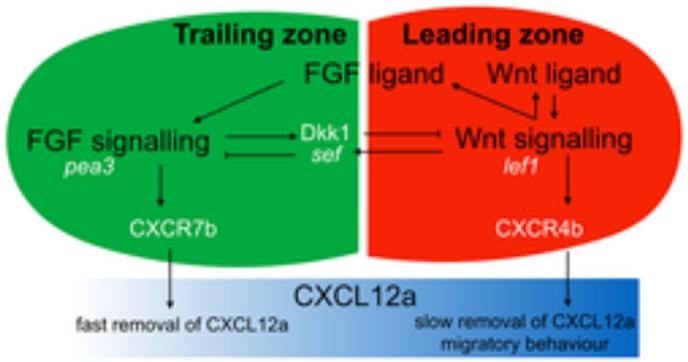
PLoS ONE 5(2):e9175. doi:10.1371/journal.pone.0009175 DOI 10.1016/j.cell.2007.12.034 JEM Vol. 203, 2006 2201–2213 www.jem.org/cgi/doi/10.1084/jem.20052144

Model: the *primordium* generates the *cxcl12* gradient



Bistable Wnt and FGF signaling defines leading and trailing zones & activates CXCRs





- How is initial Wnt and FGF symmetry broken?
- What are the adhesion systems?
- How is proliferation balanced with rosette deposition?
- What marks the drop-off points?

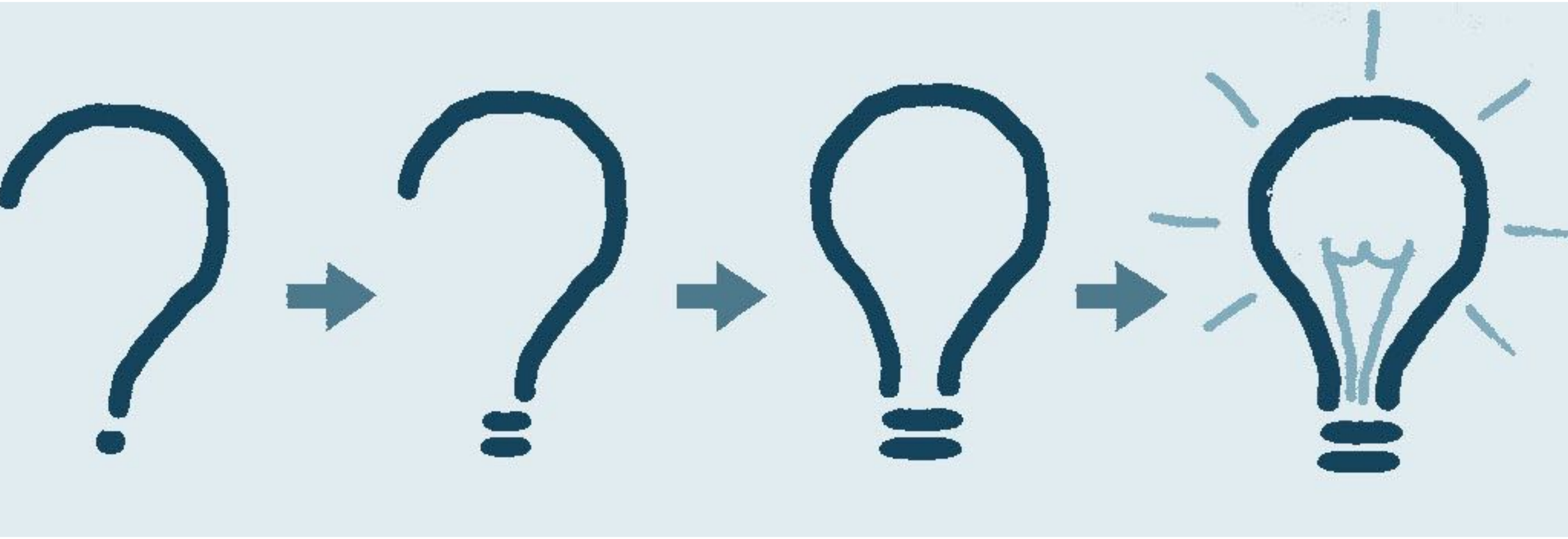
Summary

- Cell migration results from motility and polarization
- Mulitple structures are formed from migratory cells
- Chemokine signaling can direct long-range migration
- Individual and collective migration

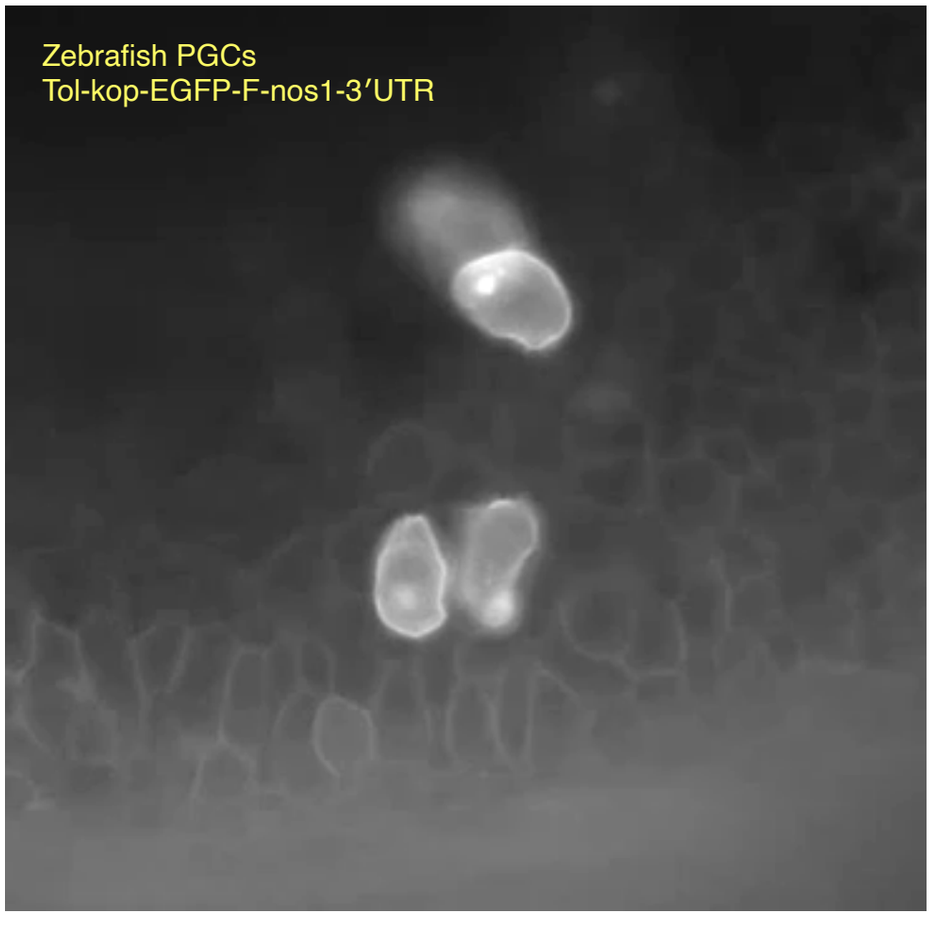
    ✳ We didn’t cover this, but also critical in wound healing and metastasis in cancer…

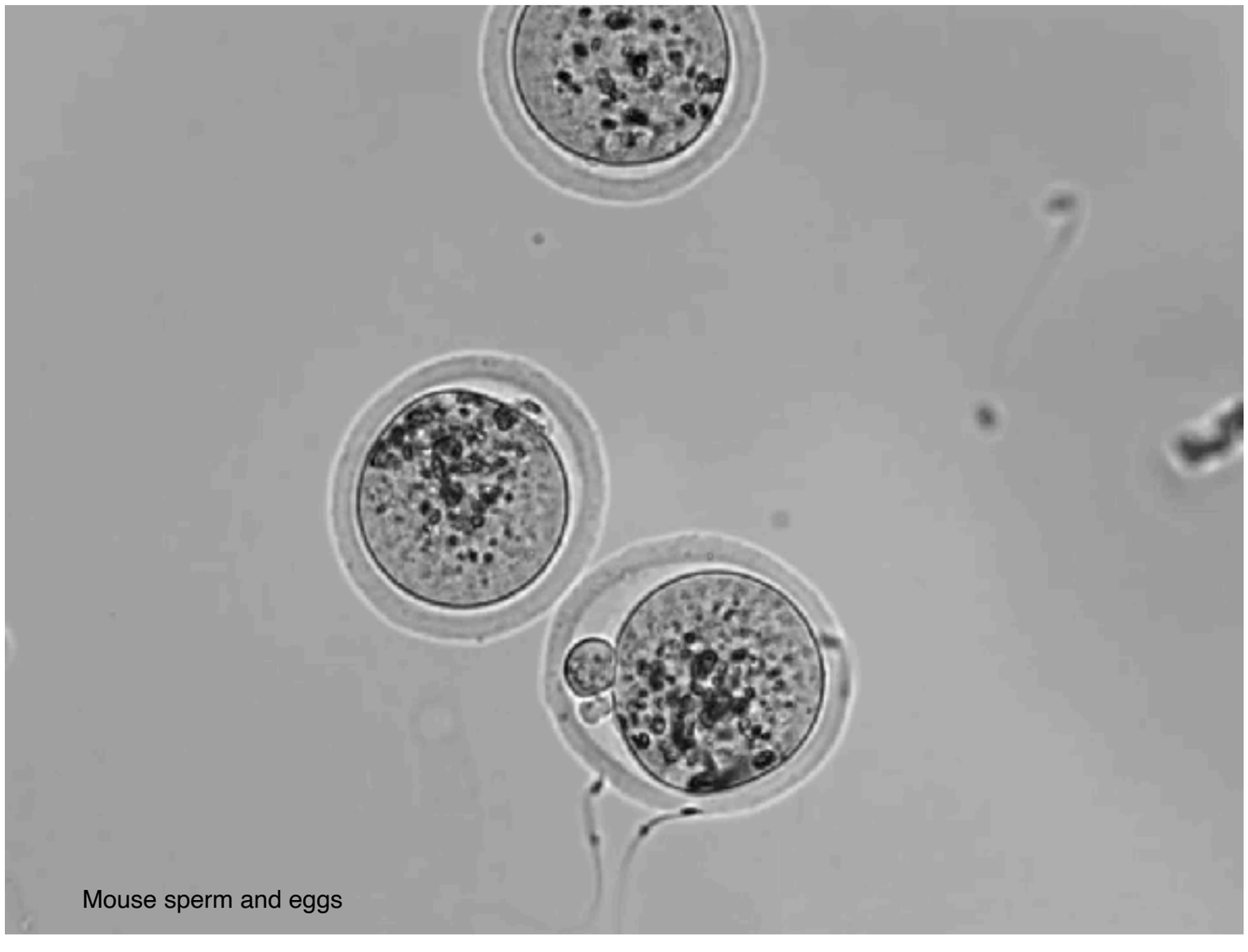
- Collective migration requires internal self-organization

Questions?



Big questions





Mouse sperm and eggs

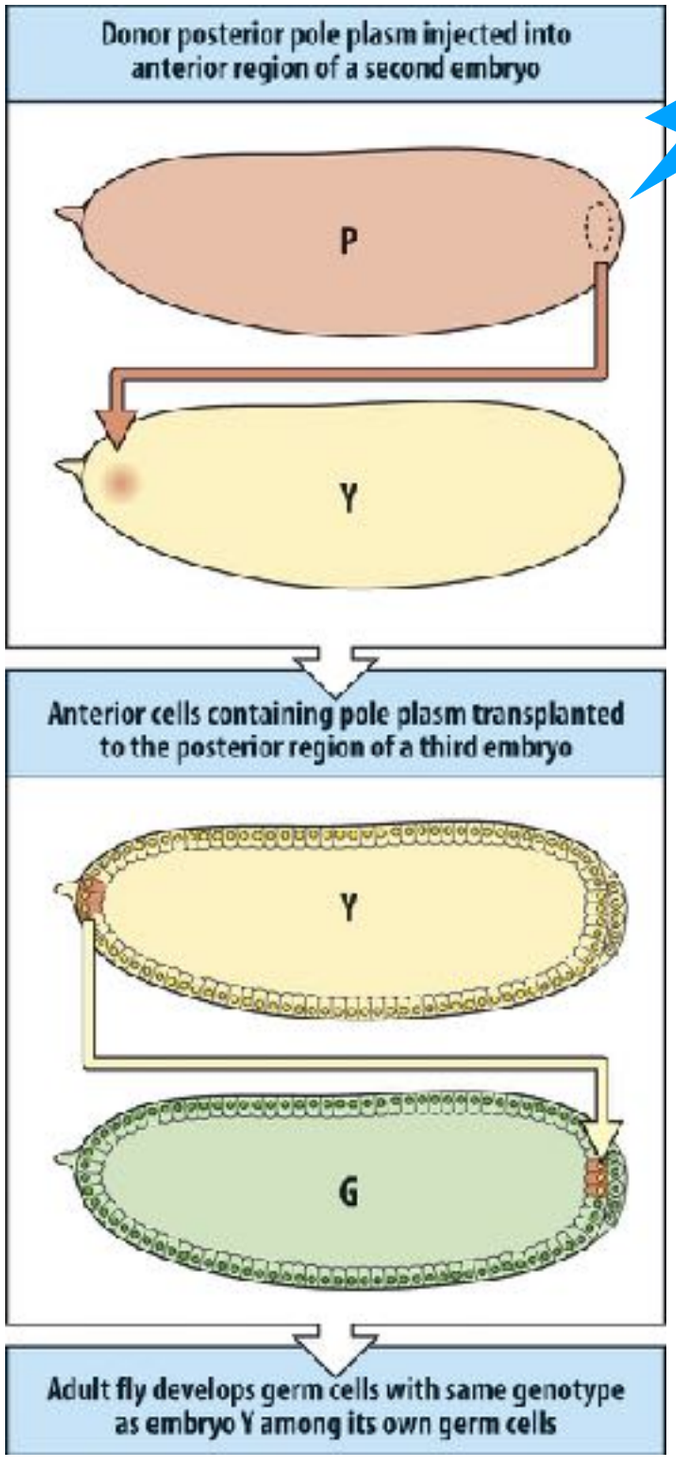
Germ cells - setting aside the next generation

- Specified outside the gonad
- Give rise to gametes - sperm and eggs
- Three roles:
  - Preservation of genetic integrity
  - Generation of genetic diversity (meiosis)
  - Transmission of genetic information
- Maintain pluripotency (immortal…)
- Sperm vs. egg determined by gonad

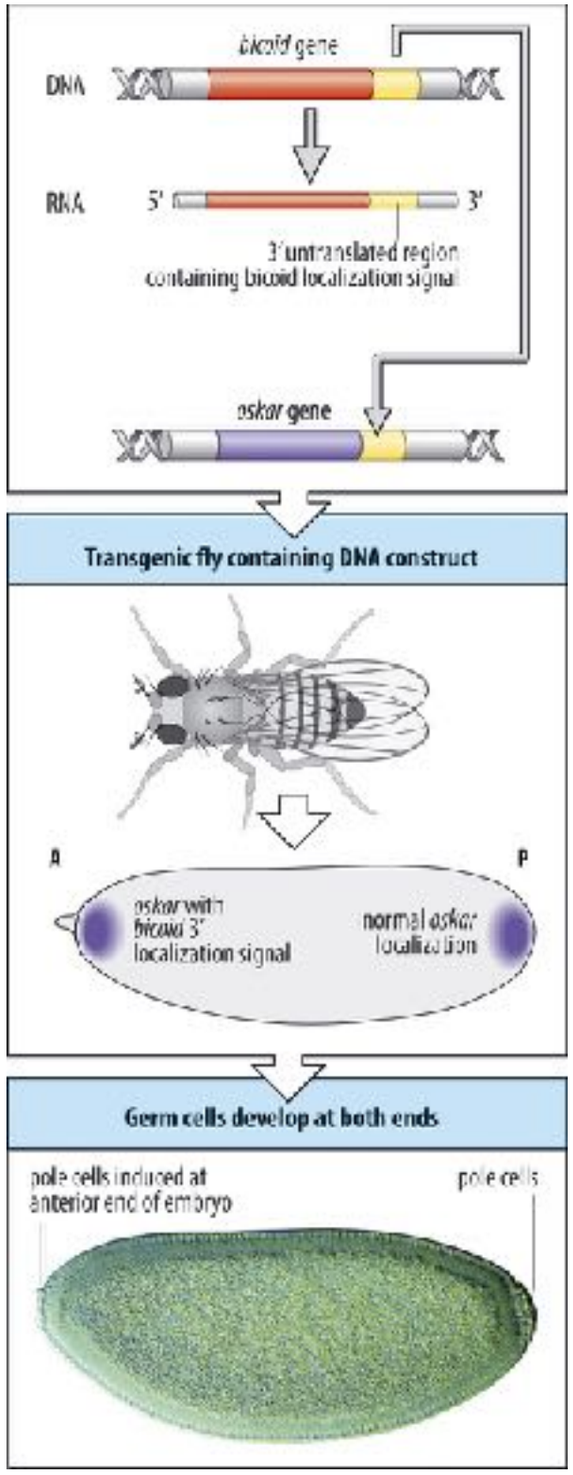
Case 1. Maternal determination of germ cells - germ plasm

- Localised in the early embryo
- RNA-binding proteins Vasa, Nanos, Oskar inihbit translation
- Cells that inherit germ plasm become germ cells
- May be distinct organelle…

Localised germ plasm - *D. melanogaster*



UV induced sterility



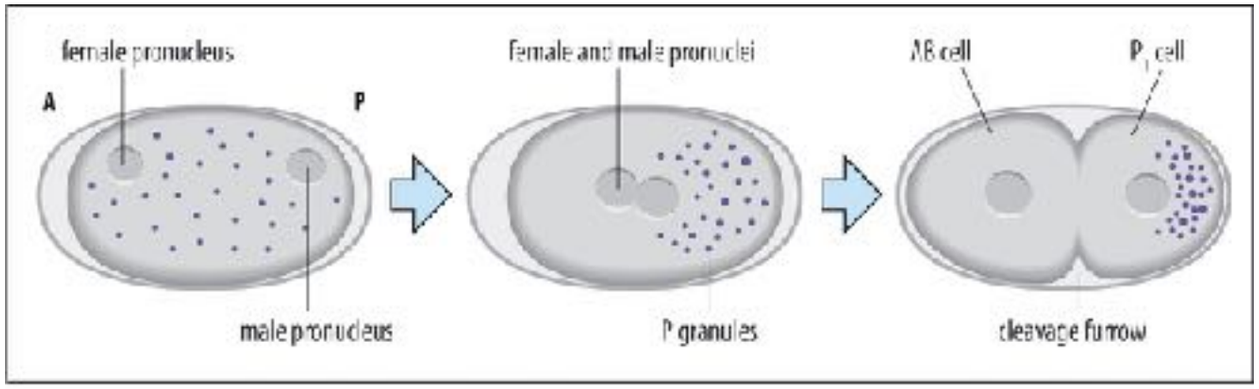
oskar flies are sterile

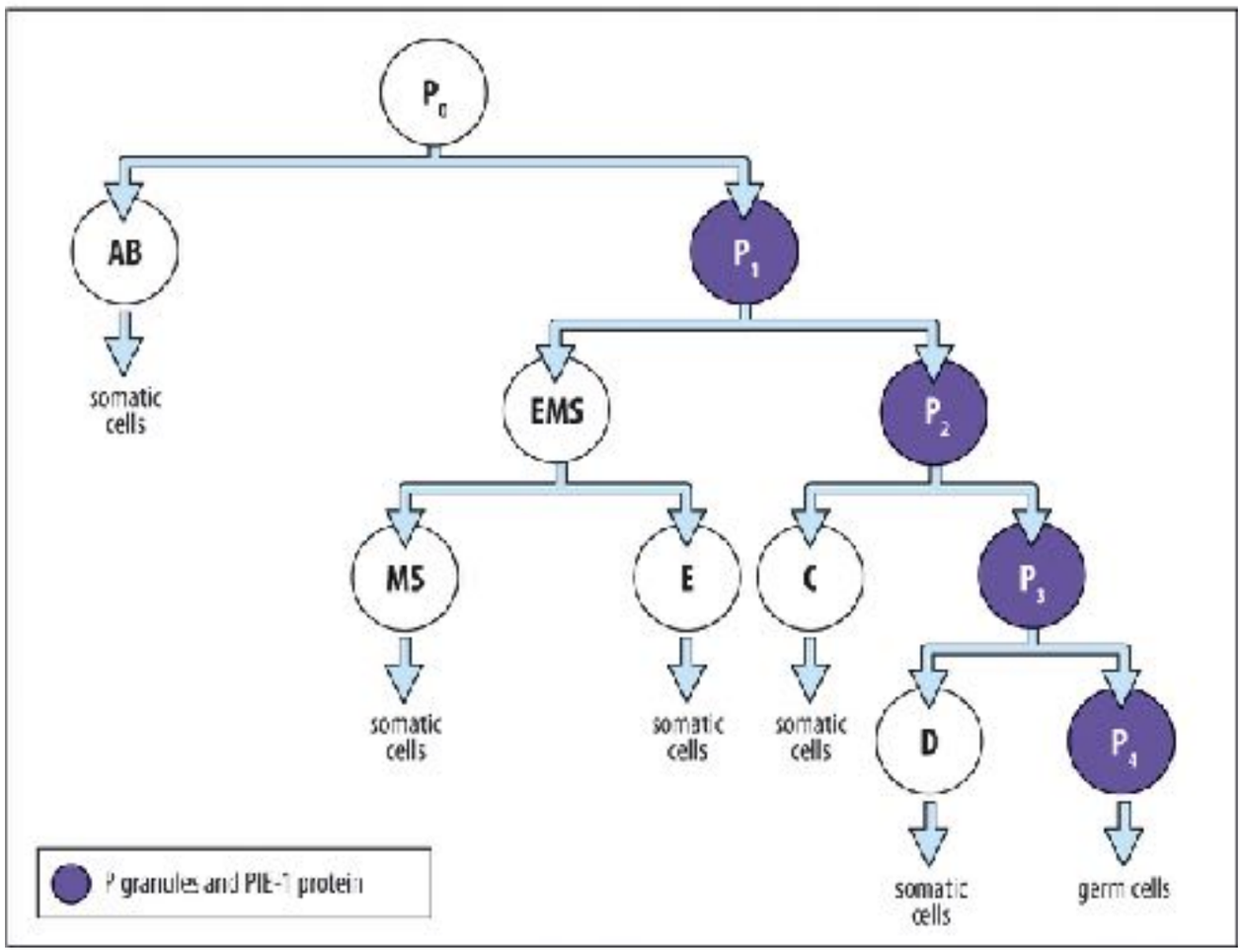
oskar necessary and sufficient for pole cells

Oskar RNA-binding protein nucleates pole granules

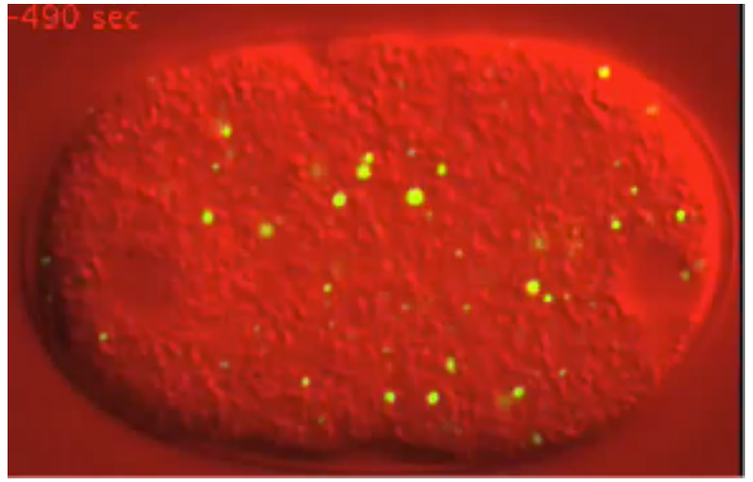
eLife 2018;7:e37949 doi: 10.7554/eLife.37949

Localisation of germ plasm - *C. elegans*

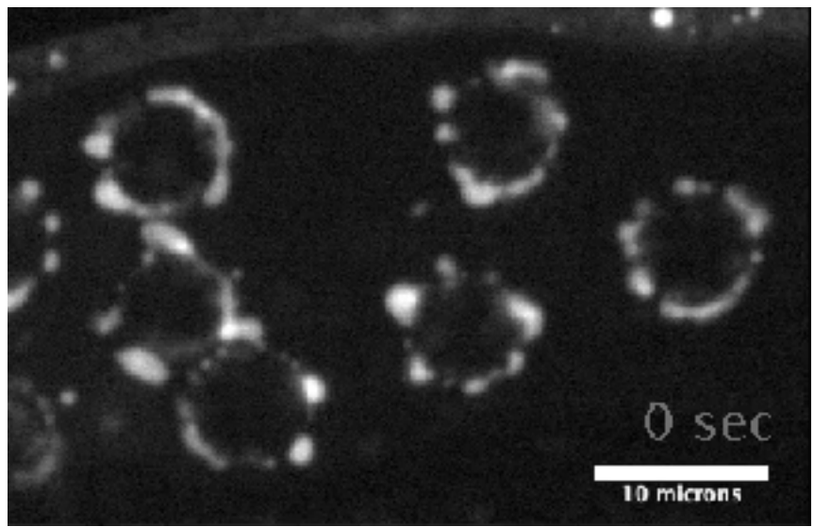




PIE-1 nuclear protein represses transcription - keeps cells silent during early somatic signaling



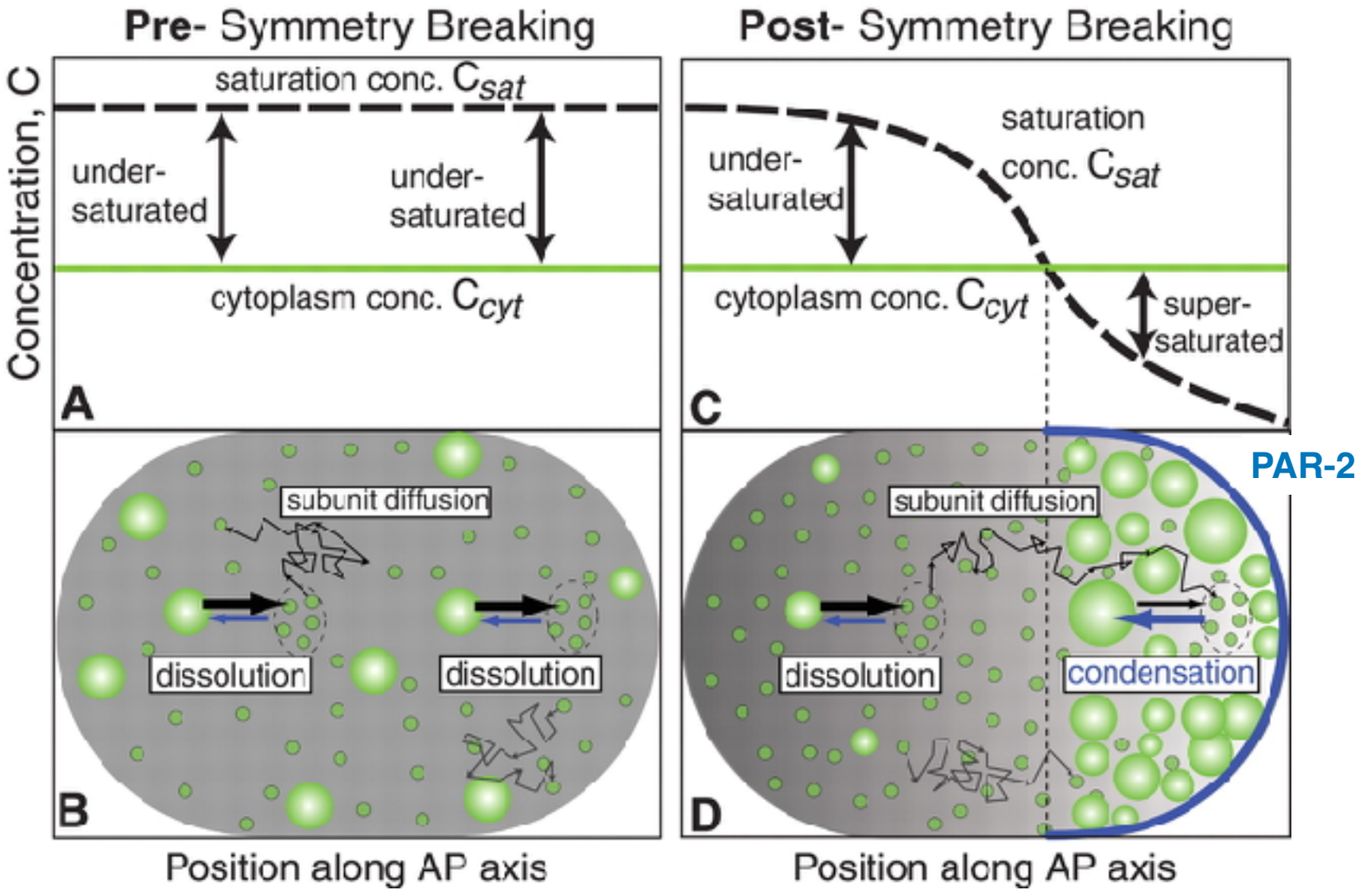
PGL-1-GFP



Syncytial germ cell nuclei in PGL-1-GFP adult

Science. 2009 Jun 26;324(5935):1729-32. doi: 10.1126/science.1172046.

Non-membrane bound organelles: liquid-liquid phase separation

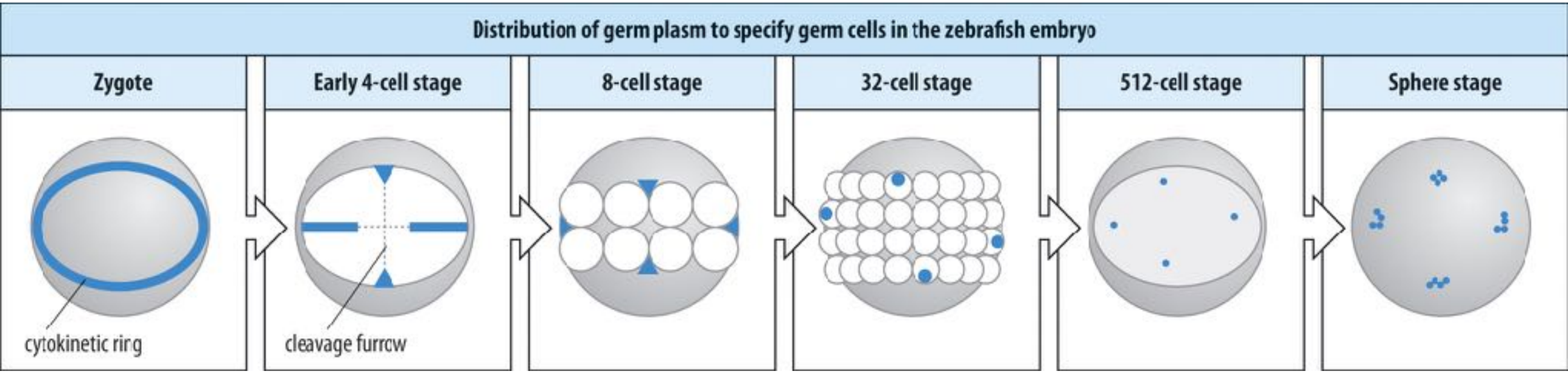


Properties

- RNA-protein, low complexity proteins
- Elevated local concentration
- Buffering of cytoplasm
- Regulation by e.g. phosphorylation

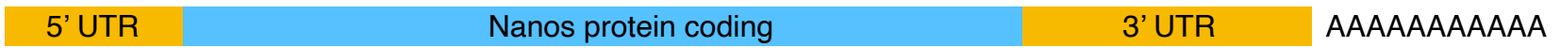
Science. 2009 Jun 26;324(5935):1729-32. doi: 10.1126/science.1172046.

Localisation of germ plasm in zebrafish

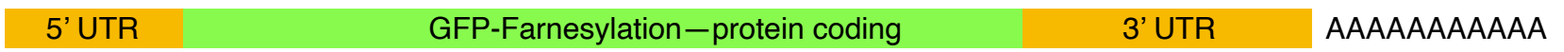


vasa mRNA

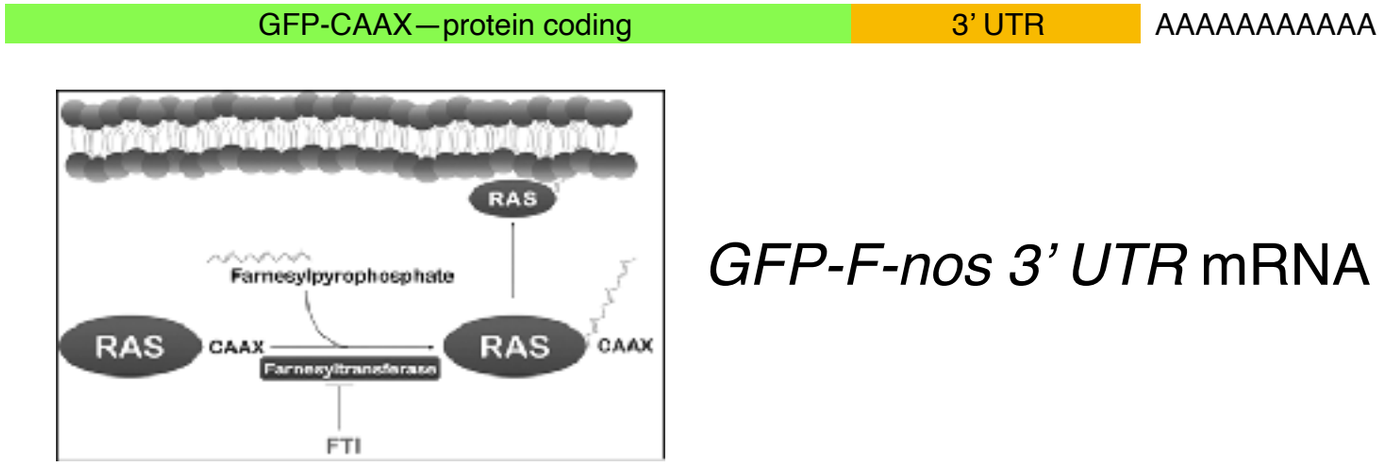
nanos mRNA



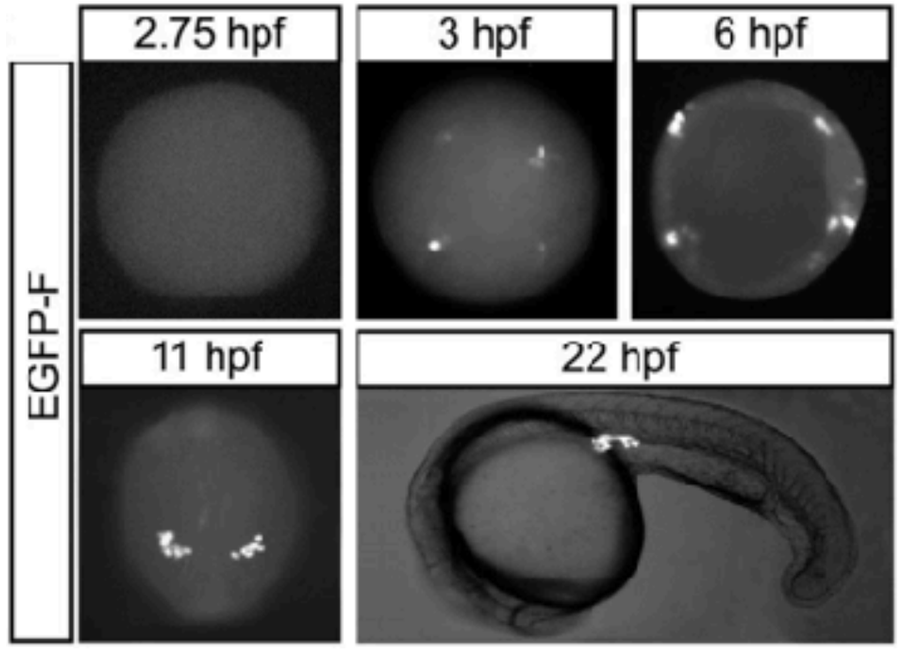
GFP-F-nos 3' UTR mRNA

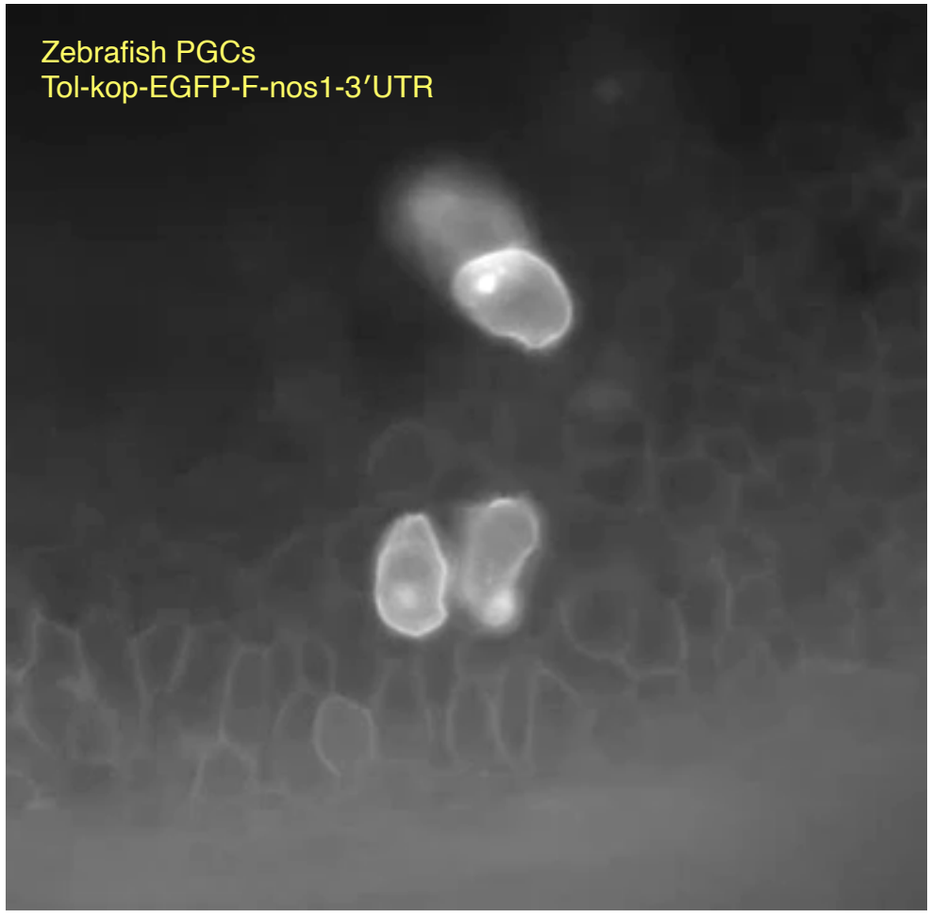


Labeling the PGCs in zebrafish

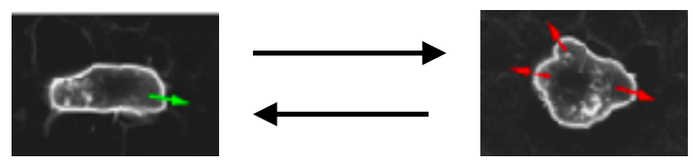


GFP-F-nos 3' UTR mRNA



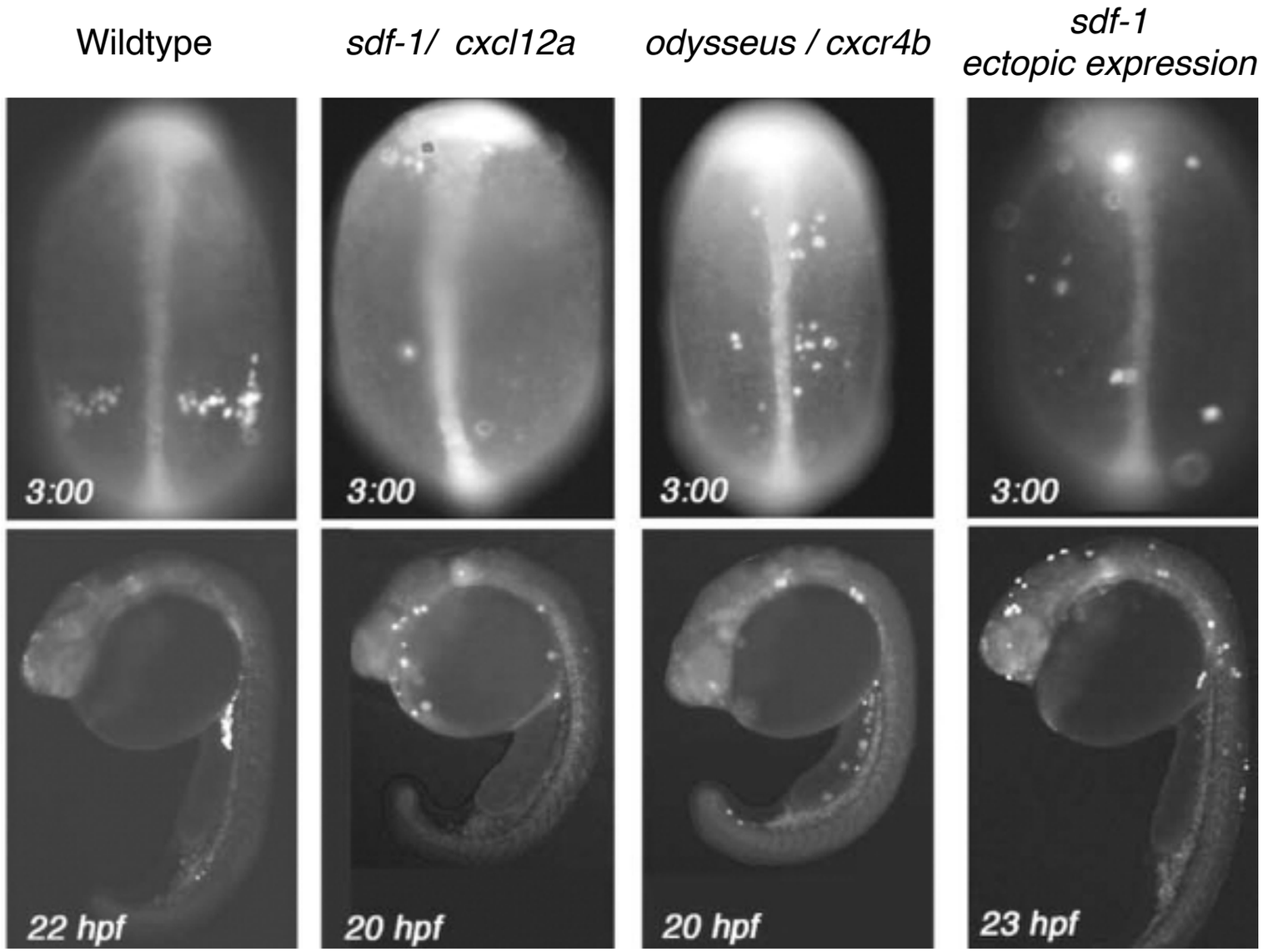


- PGCs can polarize
- Move by stabilising bleb-based protrusions
- "Run and tumble"
- Require E-cadherin for adhesion
- ~30 PGCs arrive in the gonad region



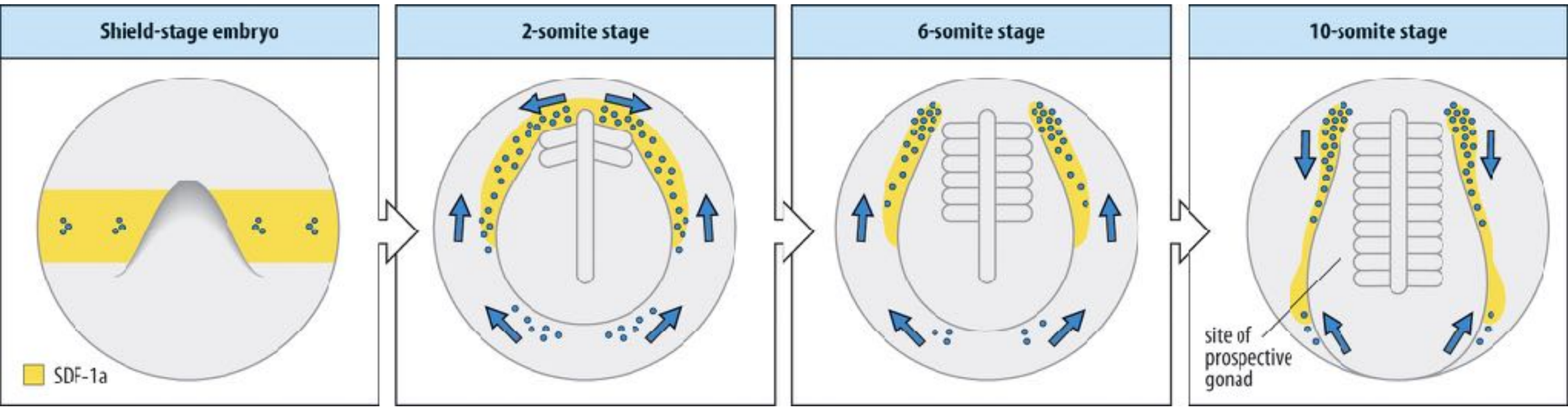
Journal of Cell Science 118, 4027-4038, doi:10.1242/jcs.02522

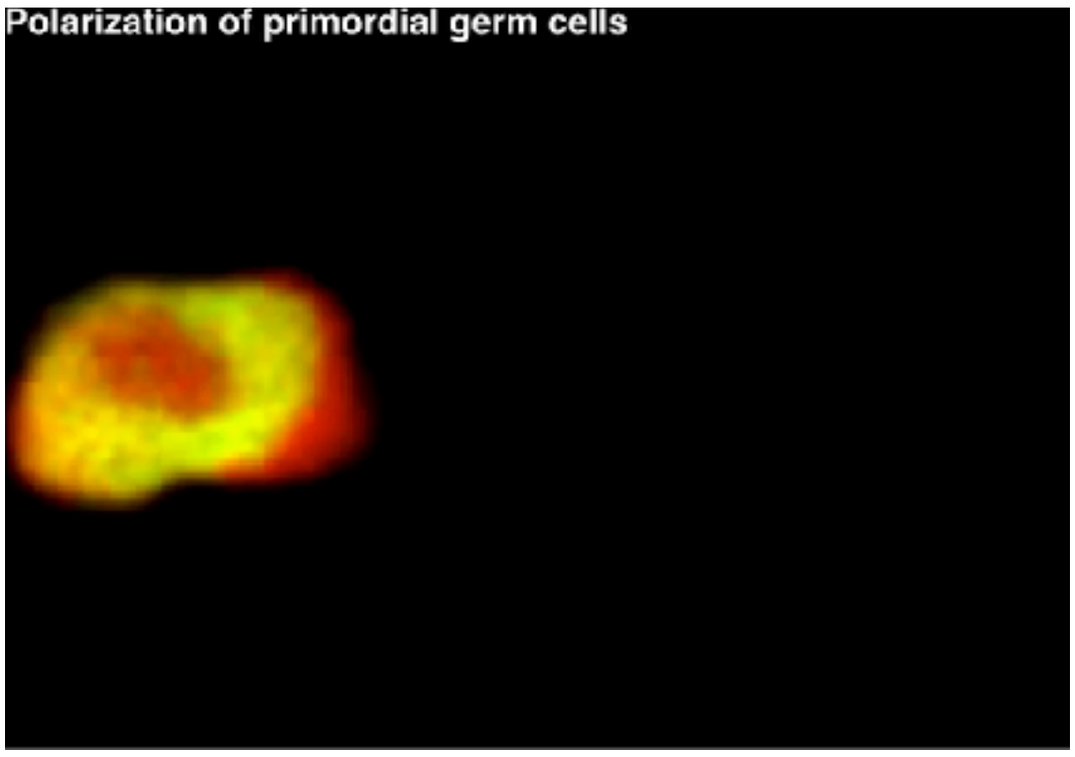
Mutants with ectopic PGCs



odysseus / cxcr4b expressed in PGCs

Finding the gonads: SDF-1 is attractive

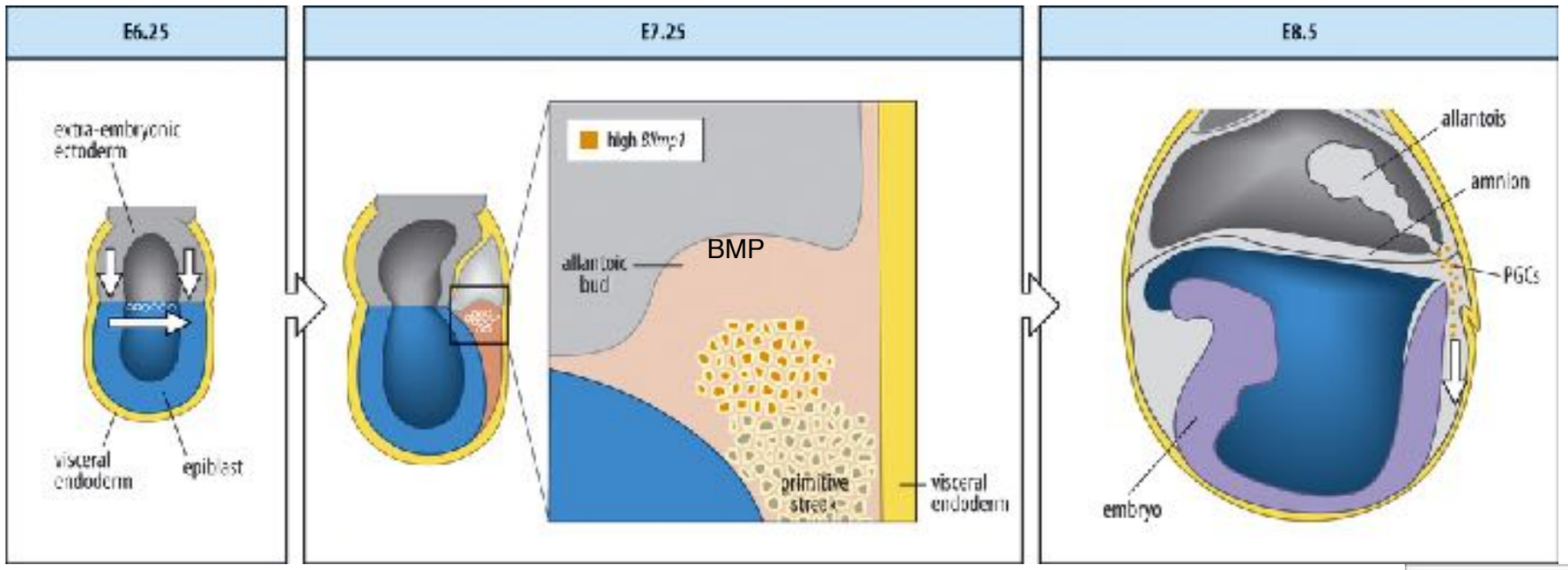




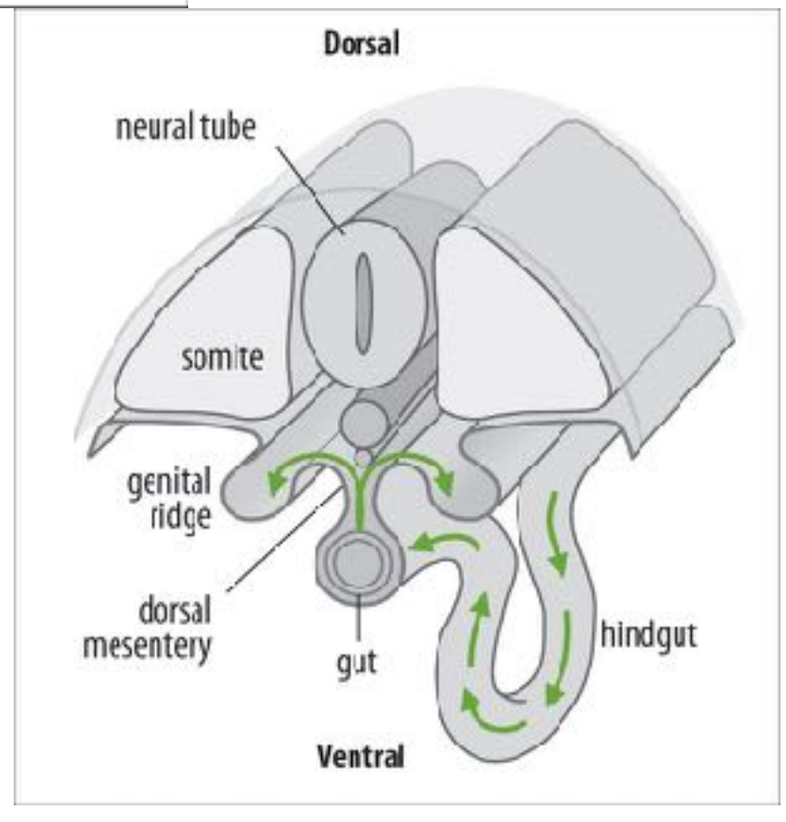
PGCs move towards SDF-1 expressing cells

Transplant of SDF-1-expressing cells

Case 2 - somatic specification mouse PGCs



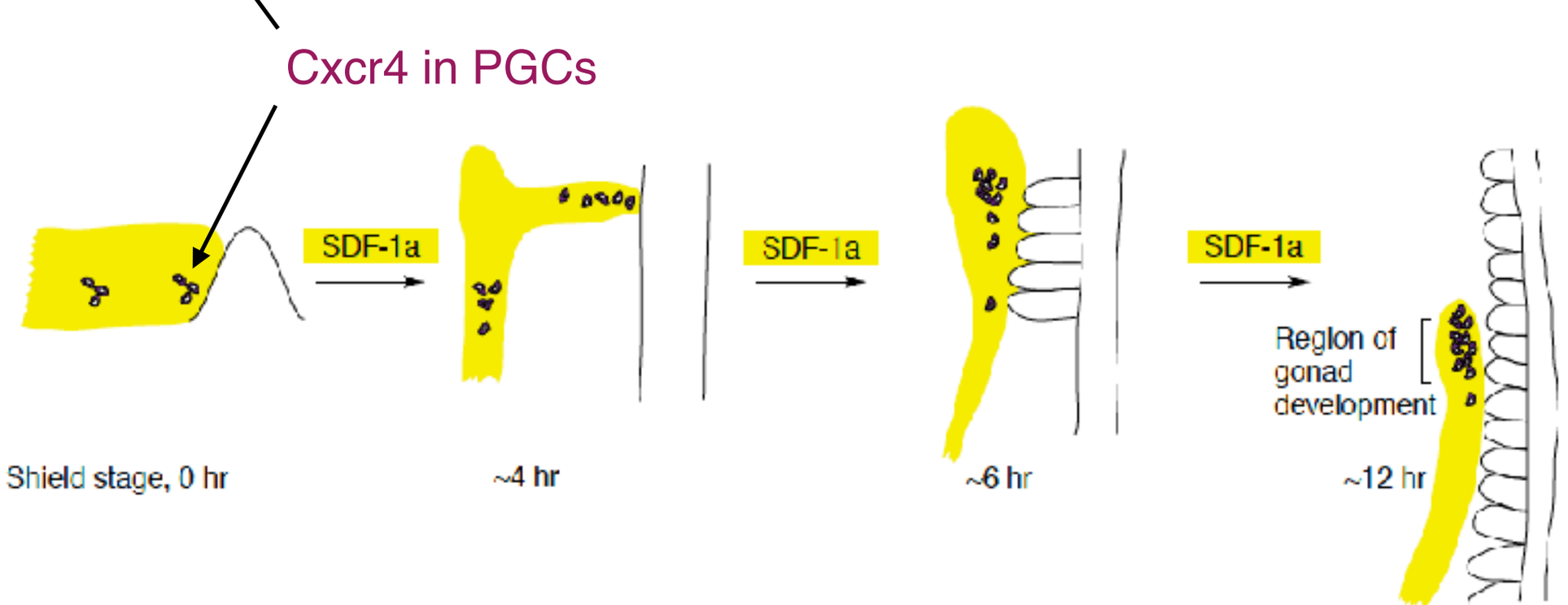
- ~ 40 Blimp1-positive cells at posterior of primitive streak
- Induced by BMP signals
- Migrate into hindgut
- Exit gut into genital ridge



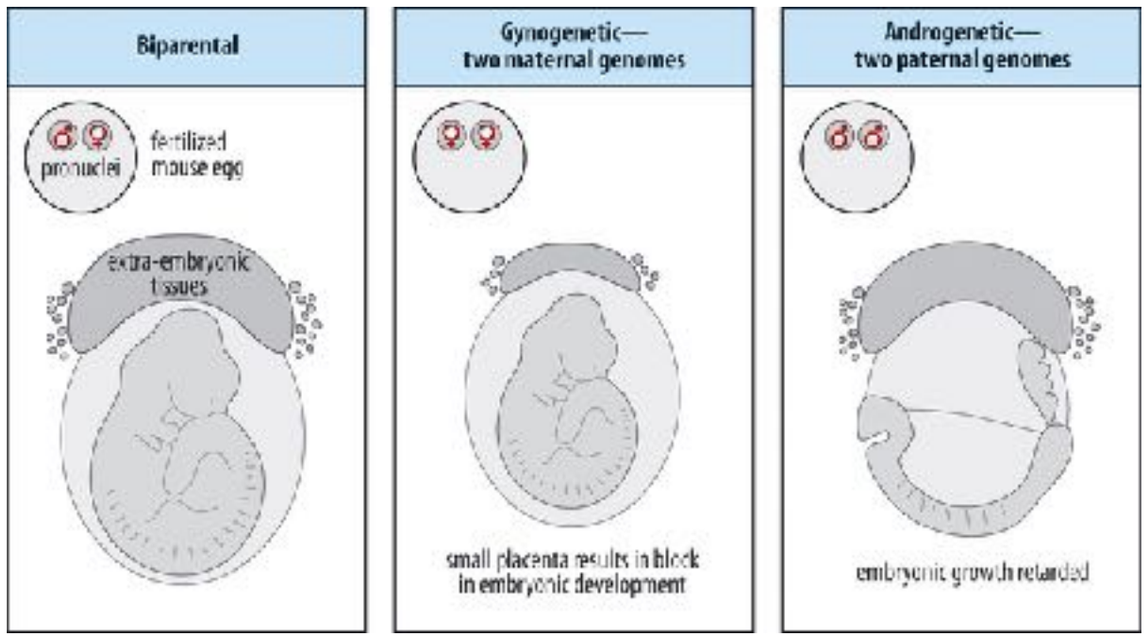
Conservation of guidance mechanisms

Mouse

Zebrafish

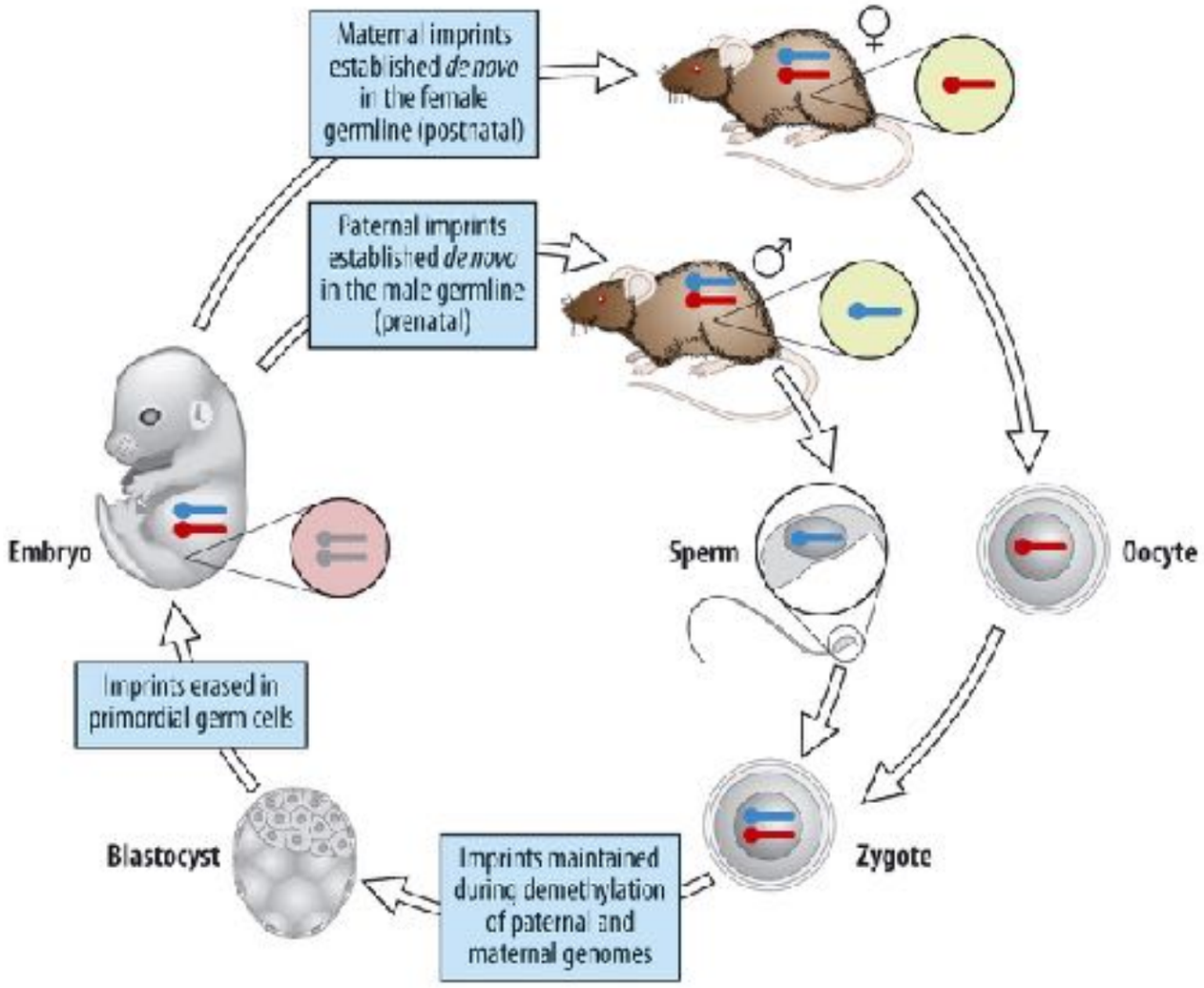


Mammalian gene imprinting - life cycle



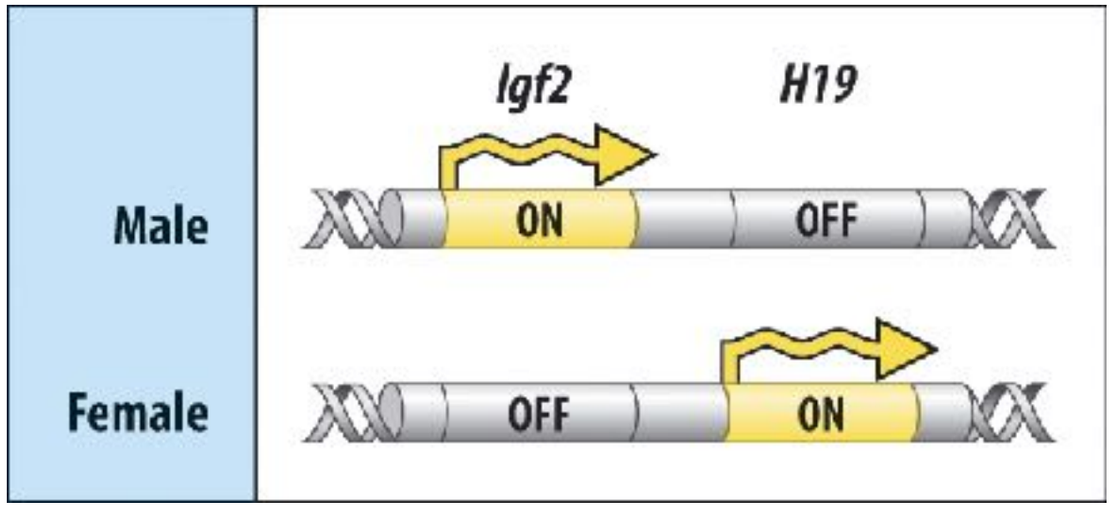
Male and female genomes are not equivalently expressed

A memory of being in sperm or egg



Imprinted genes are “re-set” each generation

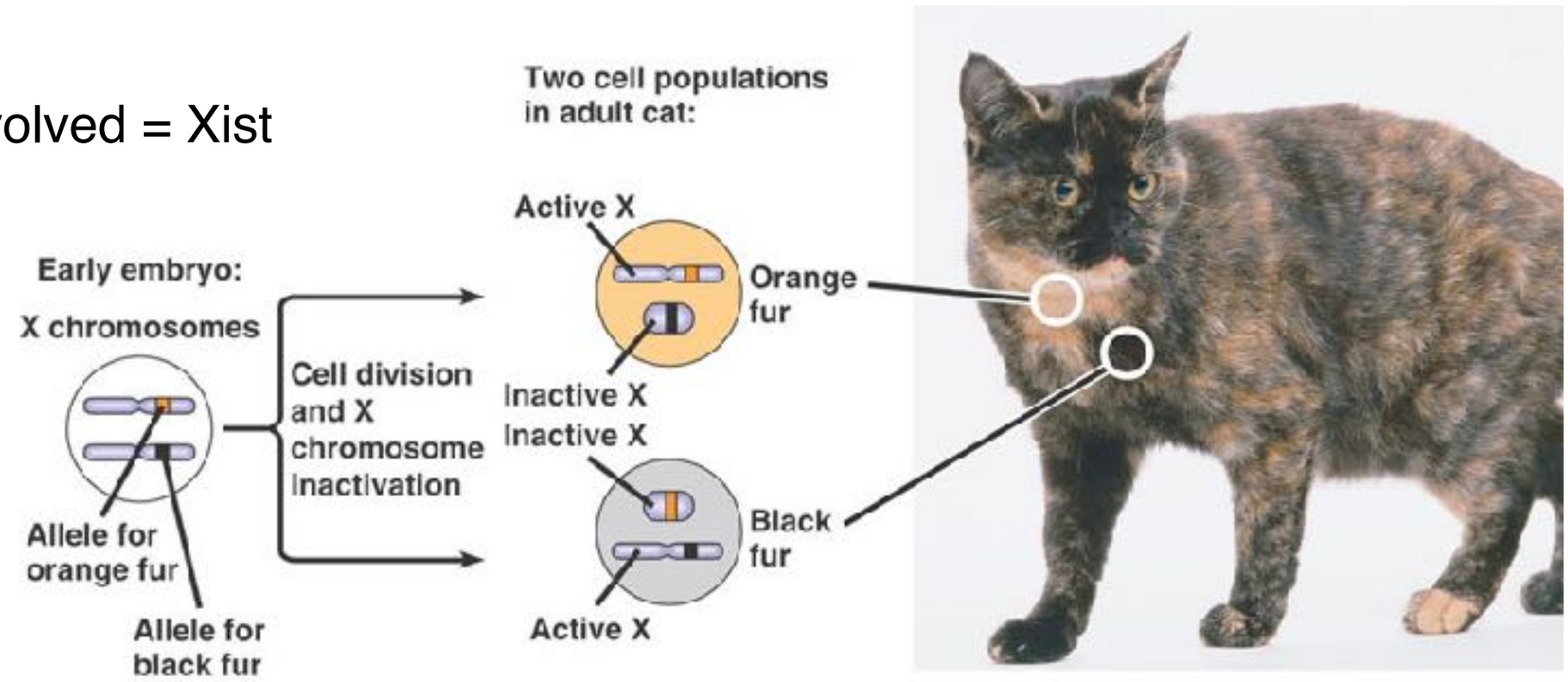
Mammalian gene imprinting - genetics



- 80+ imprinted genes known
- DNA methylation invovled
- Many are non-coding RNAs - H19
- IGF2 paternal mutant embryos are small
- Beckwith Wiedemann babies are big
- Parental-conflict theory

X-chromosome inactivation

- Early, stable
- Noncoding RNA involved = Xist



Summary

- Germ plasm specifies germ cells in many organisms
- RNA binding proteins may have structural and translational function
- CXCR signaling system drives long-range migration of germ cells to gonads
- Germ cells remain bipotent, and harbor pluripotency
- Germ cells wipe most epigenetics

Questions?