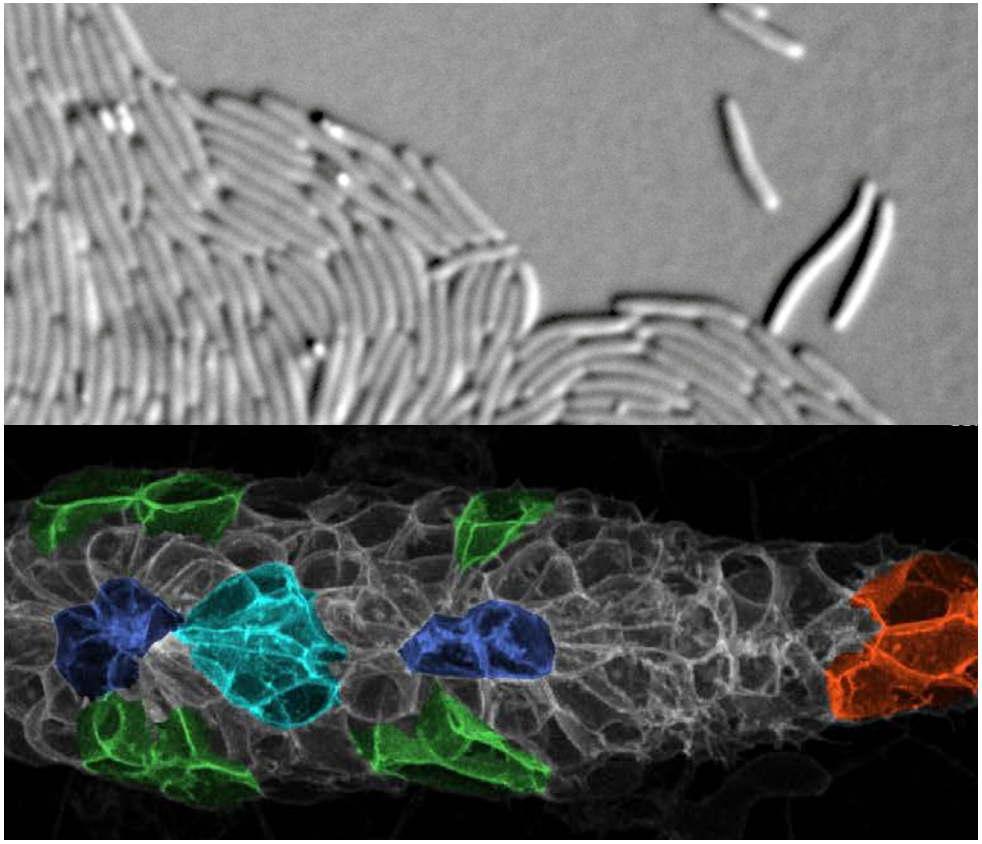
Cellular Motility



Course 4: Collective motility in development

Thomas Lecuit

chaire: Dynamiques du vivant

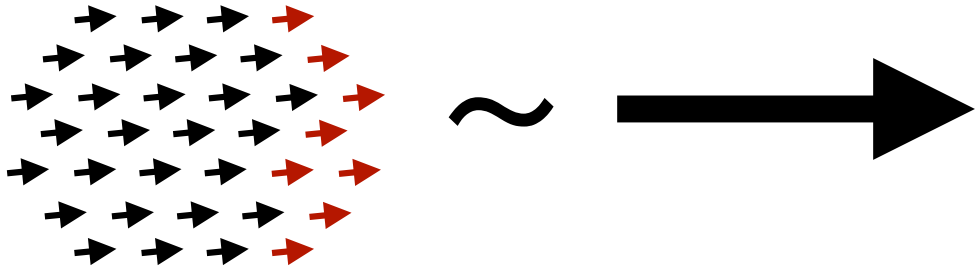
COLLÈGE DE FRANCE 1530

Case Studies of collective cell migration

- **Collective migration with leaders:**

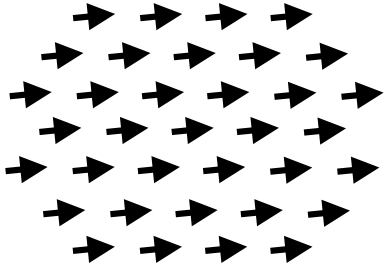
Case Study 1: Neural crest cell migration (*Xenopus*)

Case Study 2: Sensory organ primordium migration in fish lateral line (Zebrafish)



- **Collective migration without leaders:**

Case Study 3: Egg chamber rotation (*Drosophila*)



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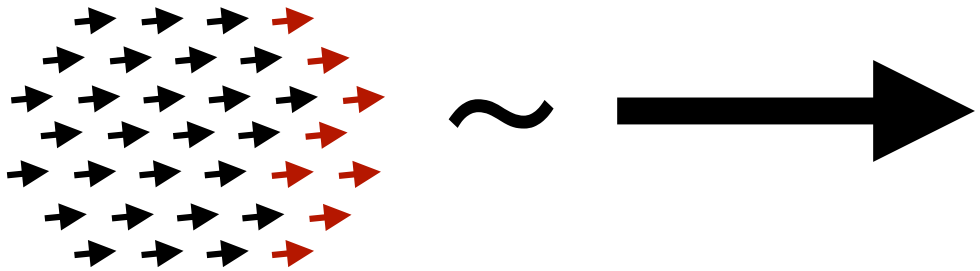

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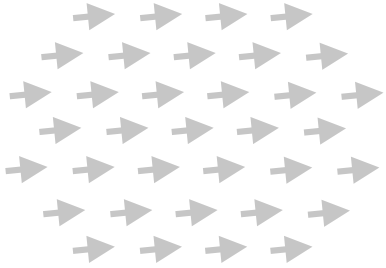
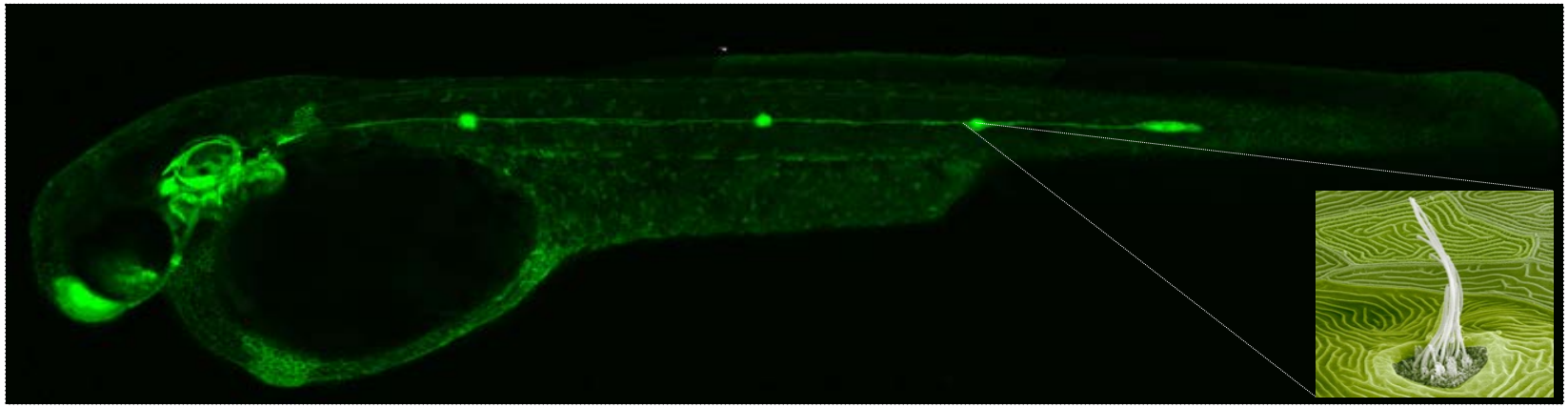
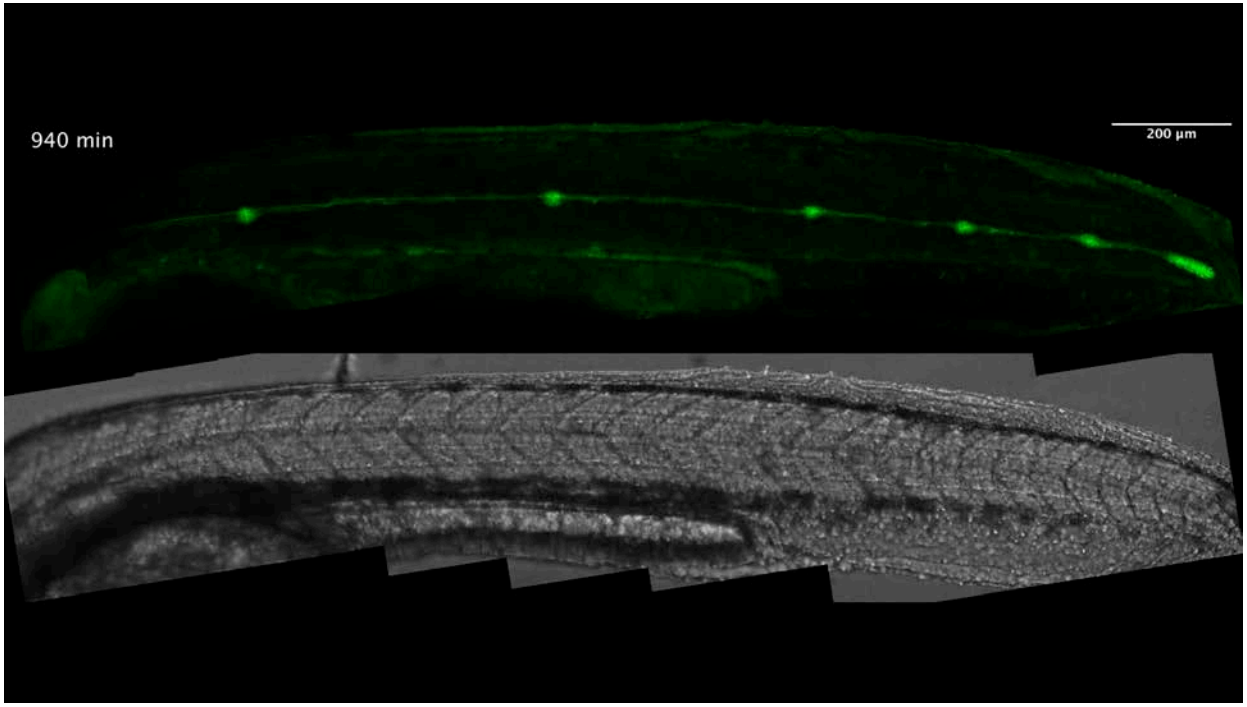


Collective migration in fish lateral line



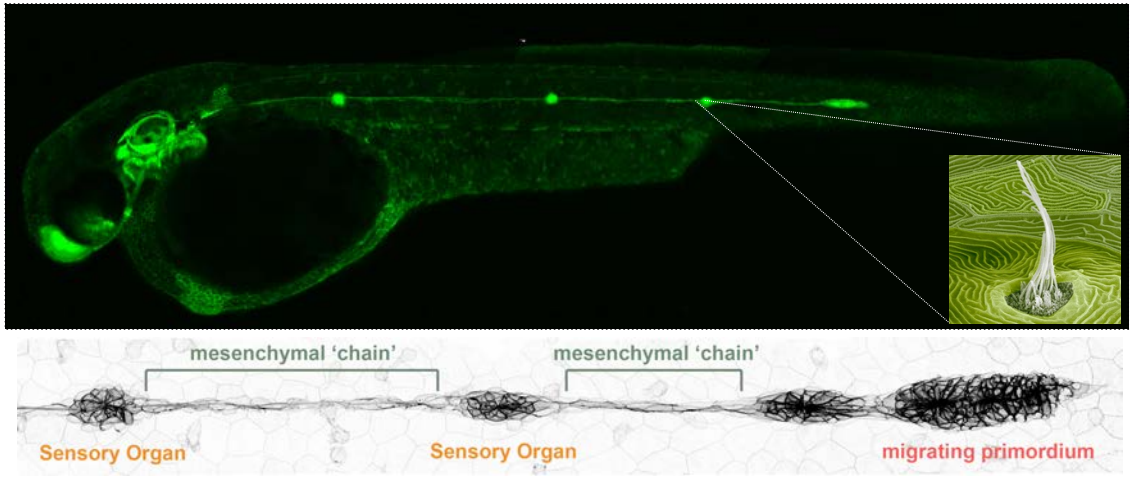


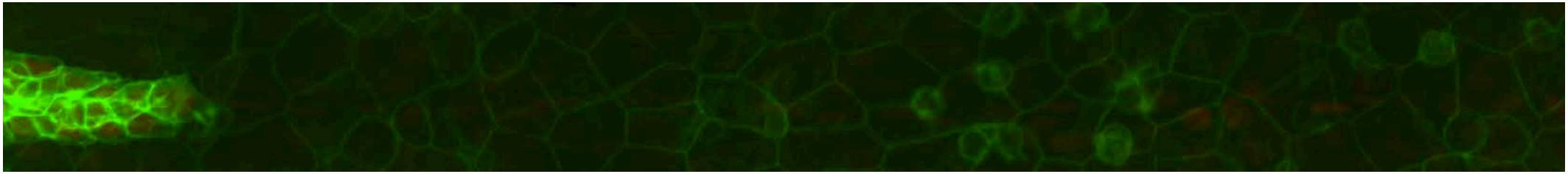
Speed ~1-2µm/min

Collective migration in fish lateral line

- Migration of the primordial of sensory organ

The lateral line is comprised of a series of mechanosensory hair cell organs (neuromasts) that are deposited throughout the skin by the posterior lateral line primordium (pLLP), a cohesive mass of more than 100 migrating cells.



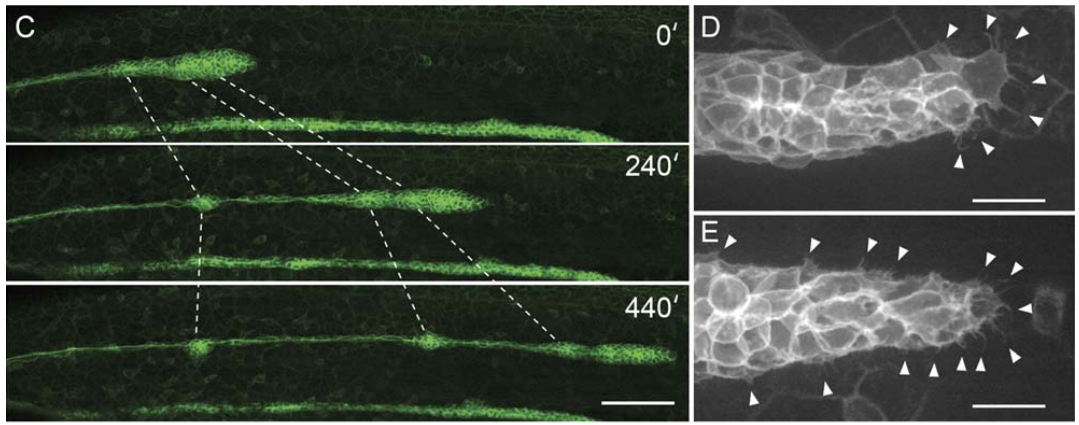


Speed ~1-2µm/min

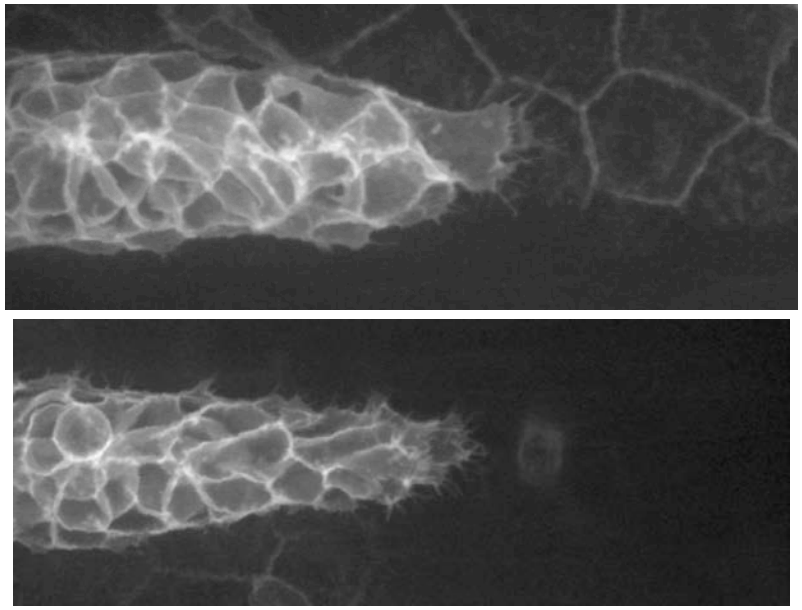
Darren Gilmour lab, Zürich

Collective migration in fish lateral line

- All cells in the primordium are motile



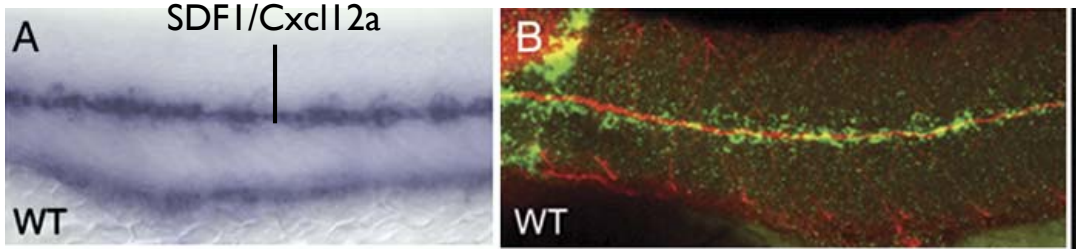
- All cells in the primordium, at the front but also in the bulk exhibit filopodia and therefore likely respond to guidance cues



Peter Haas and D. Gilmour, *Developmental Cell* 10, 673–680 (2006)

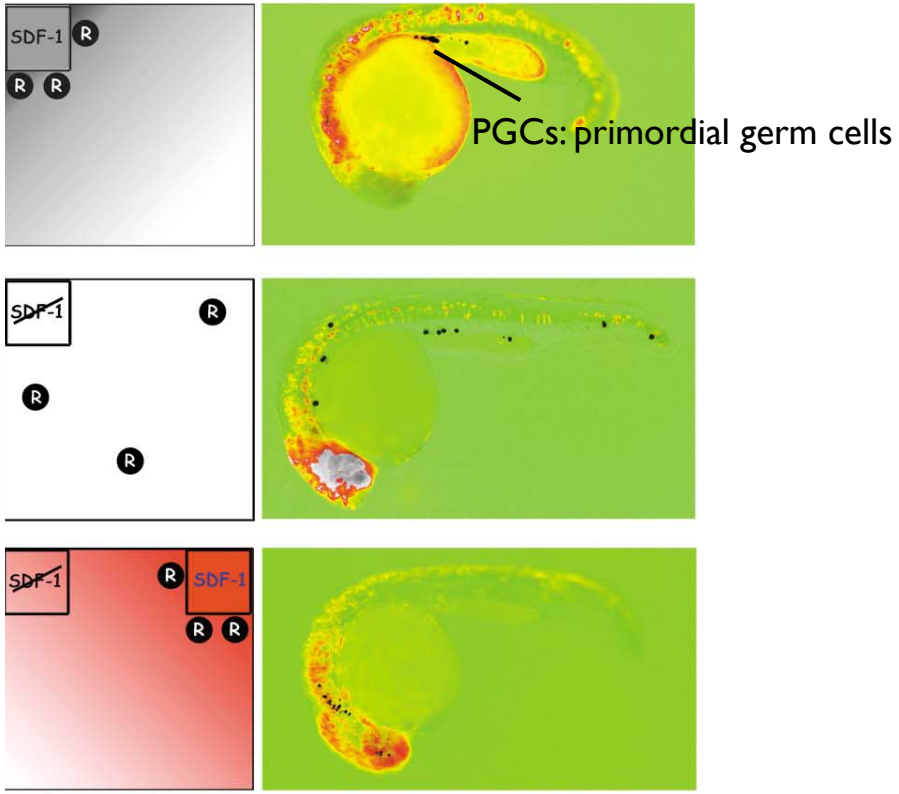
Collective migration in fish lateral line

- A chemoattractant is expressed in a track along the lateral line



Peter Haas and D. Gilmour, *Developmental Cell* 10, 673–680 (2006)

- The chemoattractant SDF1/Cxcl12a is expressed along the lateral line where the primordia migrate
- SDF1 is a potent chemoattractant in a variety of biological contexts (eg. leukocytes, neurons, primordial germ cells etc).
- SDF1 operates via its receptor CXCR4, a GPCR.
- SDF1 attracts primordial germ cells (PGCs) to specific locations in zebrafish

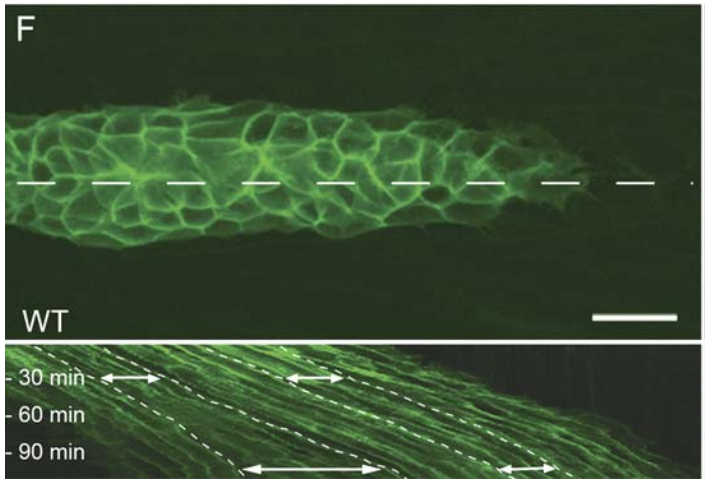


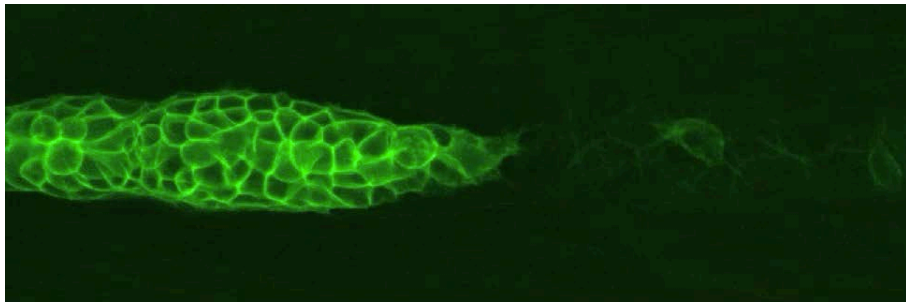
Doitsidou, M., et al. and Raz, E. (2002). *Cell* 111, 647–659.

Collective migration in fish lateral line

- Polarized organisation of the primordium in response to chemoattractant

- The movement of cells in a wild type primordia is orderly.
- The movement of cells in a CXCR4b mutant is affected. Cells are intrinsically dynamic within the primordia but the movement is not directed towards the posterior
- The morphology of primordia is no longer polarized globally
- Overall the primordia fail to move directionally





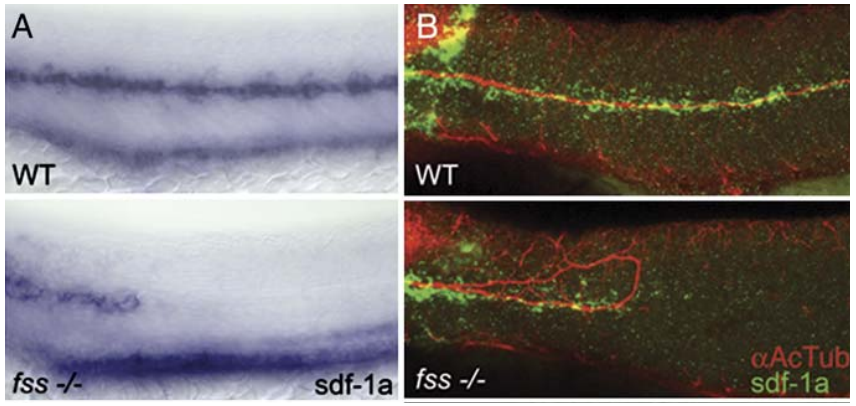
Intrinsic polarity

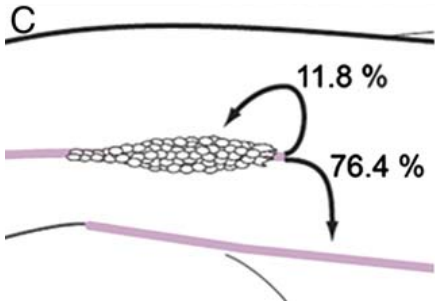
Peter Haas and D. Gilmour, *Developmental Cell* 10, 673–680 (2006)

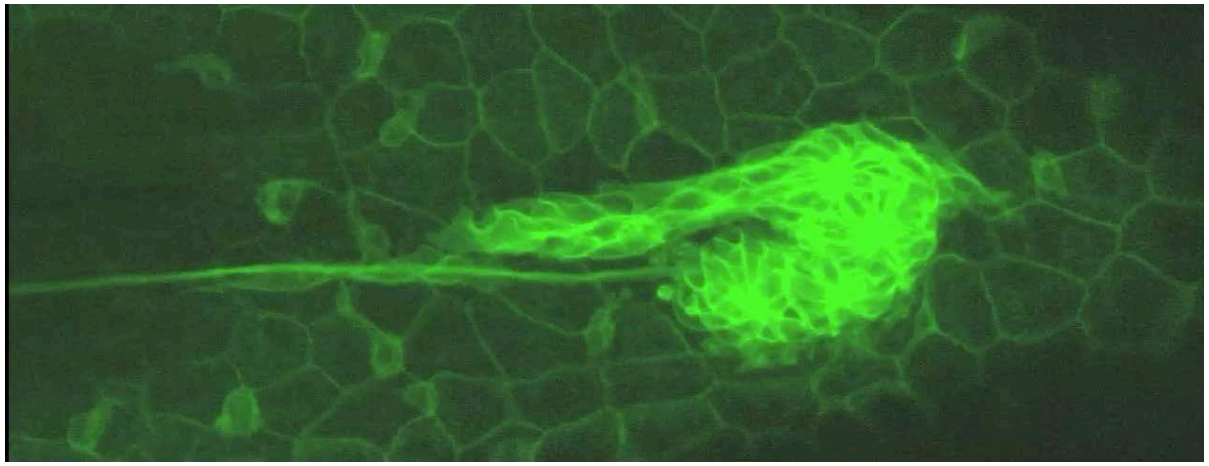
Collective migration in fish lateral line

- Structural polarity of cell cluster underlies directionality

- In a mutant where SDF1 expression is reduced to a shorter region, primordia often U-turn
- Primordia do not change polarity/direction: trailing cells do not become leader cells
- This suggests that primordia have an intrinsic global polarity



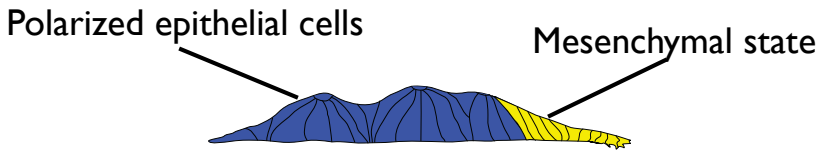




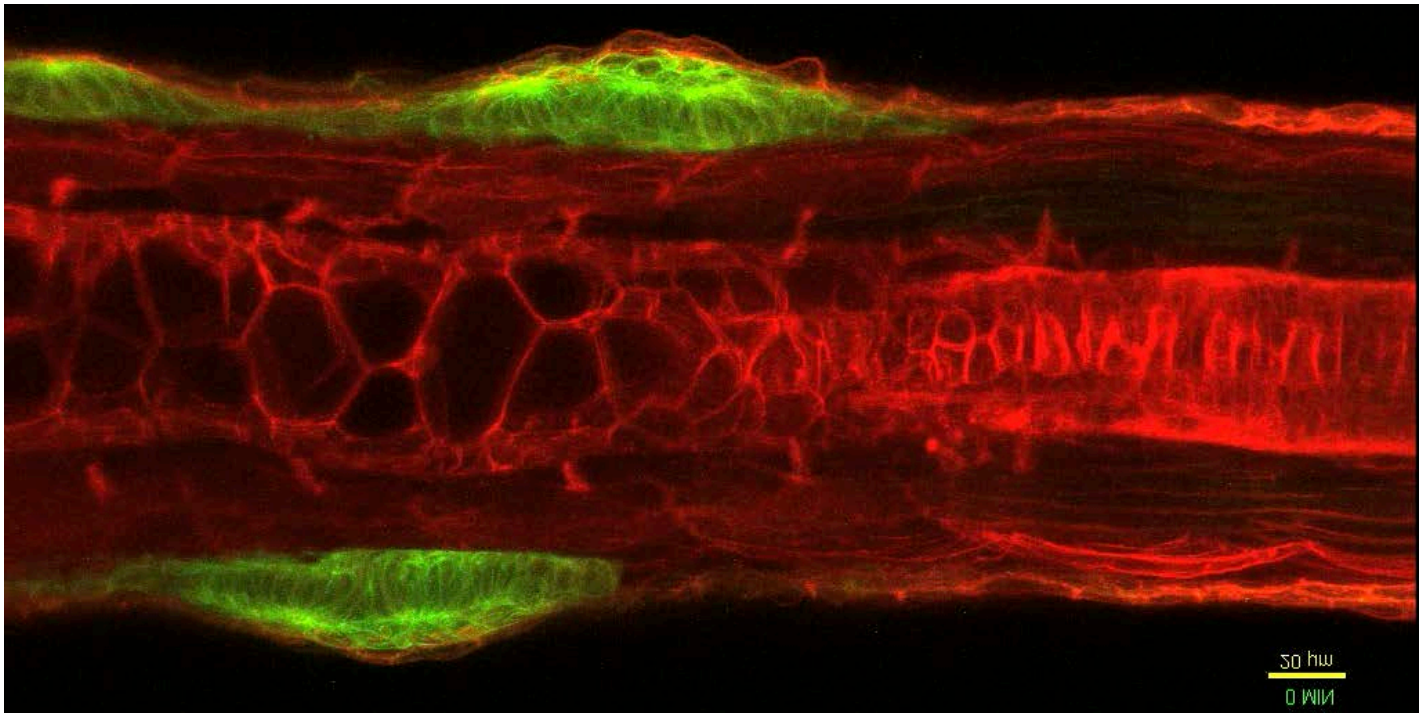
Peter Haas and D. Gilmour, *Developmental Cell* 10, 673–680 (2006)

Collective migration in fish lateral line

- Structural polarity of cell cluster underlies directionality



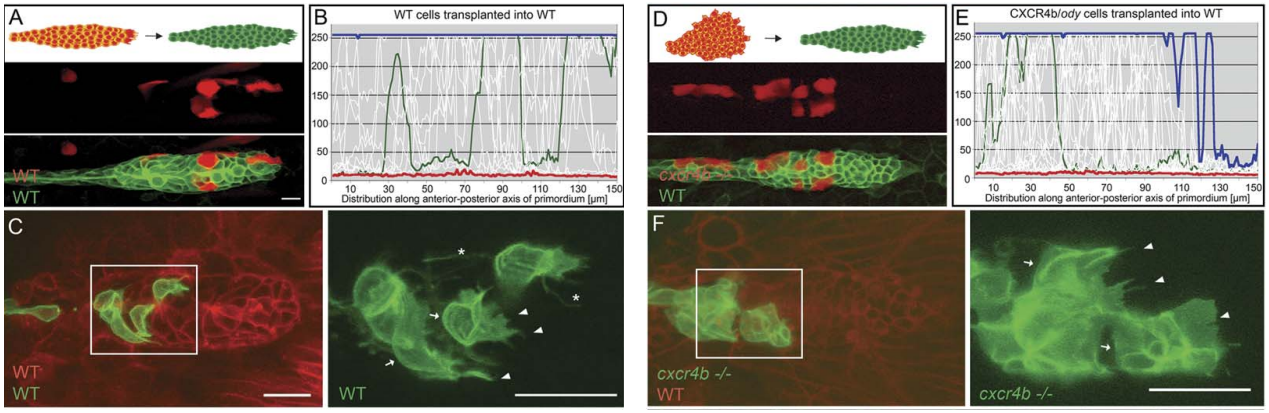
Side view

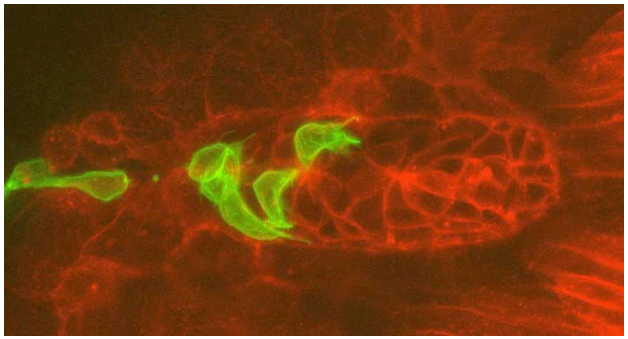


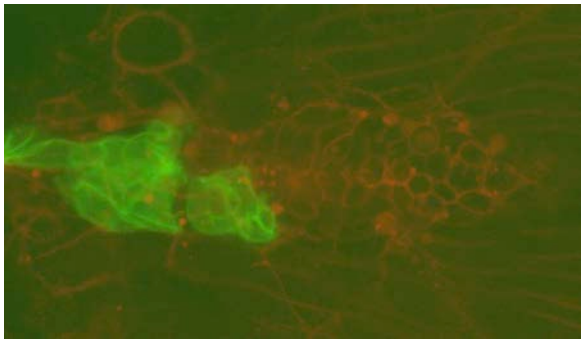
Collective migration in fish lateral line

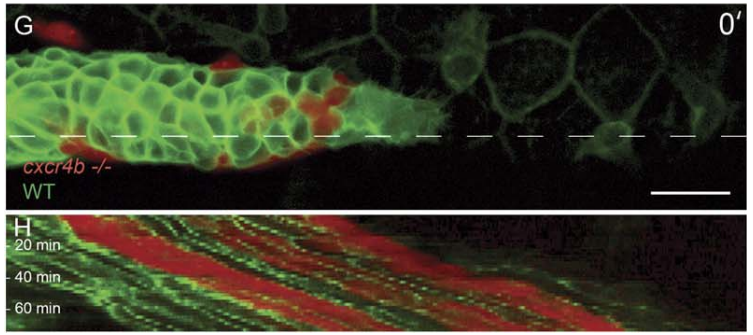
- Chemoattractant signaling is required at the leading edge of cluster

- Mosaic experiments of control cells into a control host primordium.
- When mutant cells are grafted into a wildtype host CXCR4 mutant cells can be co-opted into a host and move with the primodium.
- Wildtype and mutant cells adopt a polarized behavior with filopodia extended to the tip of primordium, independent of CXCR4
- They maintain their position within primordia and move directionally via interactions with neighbors independent of CXCR4 activity.
- Mutant cells never adopt an anterior most position in primordia suggesting they are excluded from leading position







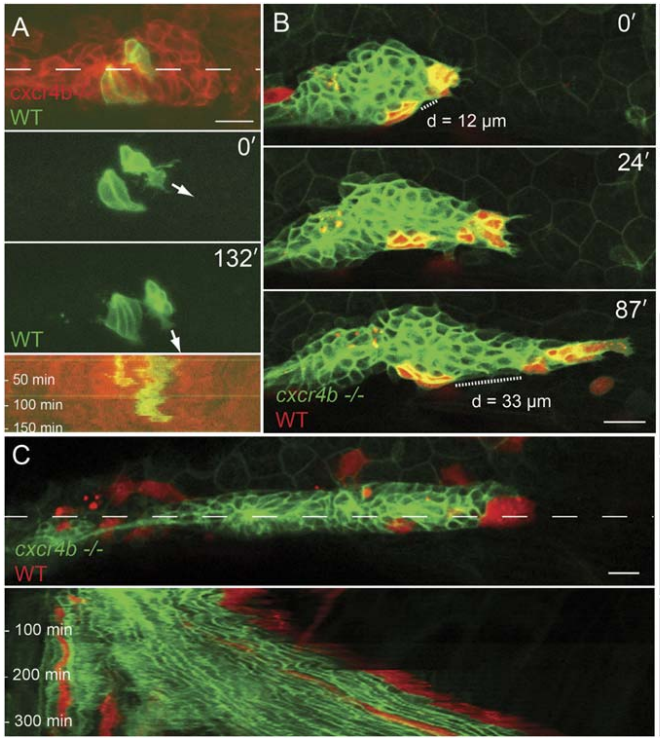


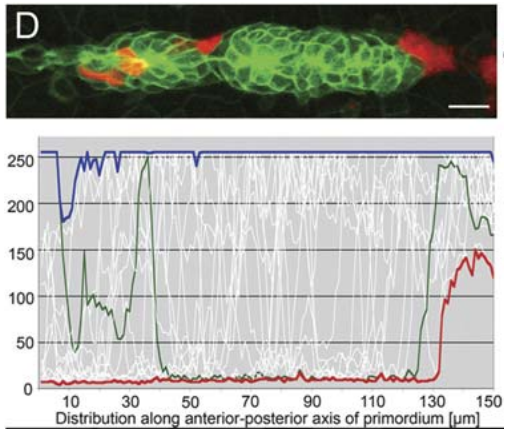
Peter Haas and D. Gilmour, *Developmental Cell* 10, 673–680 (2006)

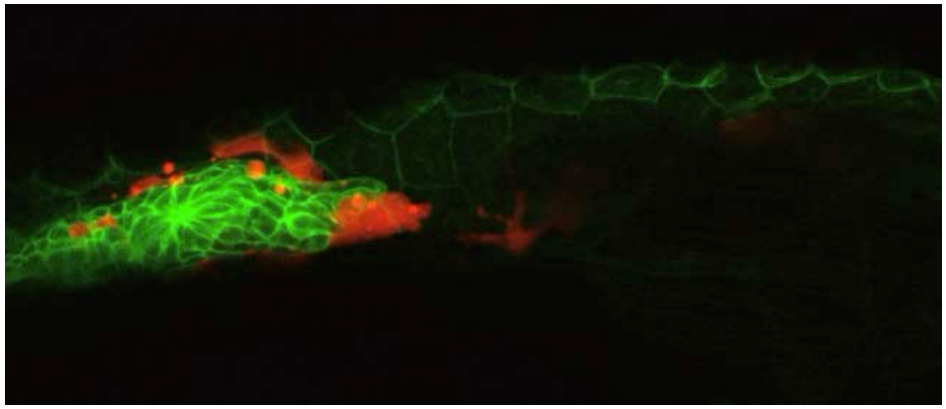
Collective migration in fish lateral line

- The leading edge functions as an organizing center for collective motility

- Leading edge organizing center in the primordium:
- Wildtype cells in a mutant primordium do not translocate to the front. They remain in a fixed position within the primordium. They are not attracted towards an SDF1 source per se.
- A few wild type cells can rescue a CXCR4 mutant primordium.
- They get to the leading edge via the tumbling at early stages of primordium development





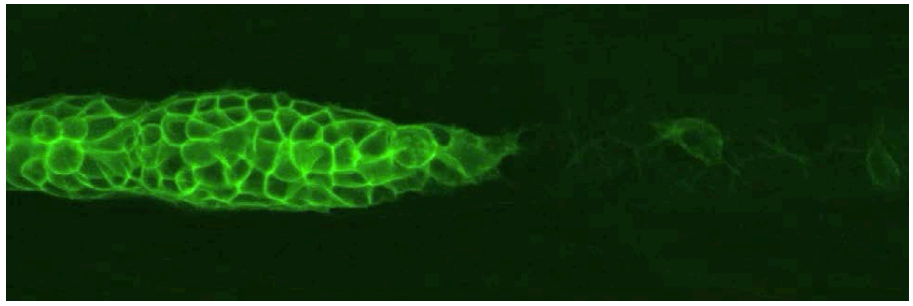


Peter Haas and D. Gilmour, *Developmental Cell* 10, 673–680 (2006)

Collective migration in fish lateral line

- **Conclusions:**
- The lateral line primordium is a cluster of 100 cells that moves directionally to the posterior
- Directionality requires the existence of a track of SDF1/Cxcl12a chemoattractant
- Chemoattractant sensing is required in the leading edge cells in the cluster
- Yet directionality of cluster cannot be determined by pre-patterned SDF1 chemical gradient per se: clusters can move in both directions on track.
- Directionality requires the global polarization of the cell cluster which is independent of chemoattractant signaling.

Top view



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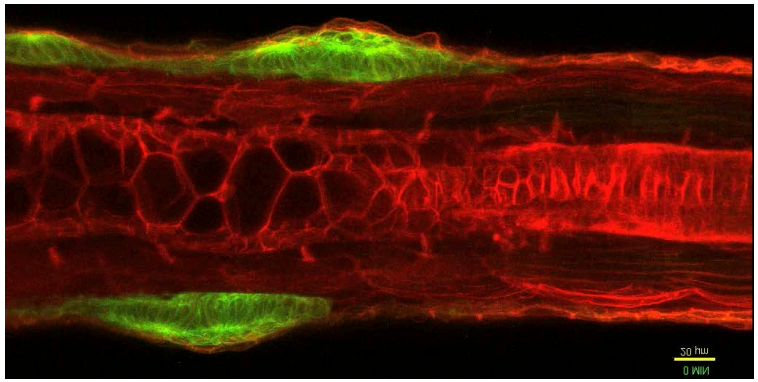


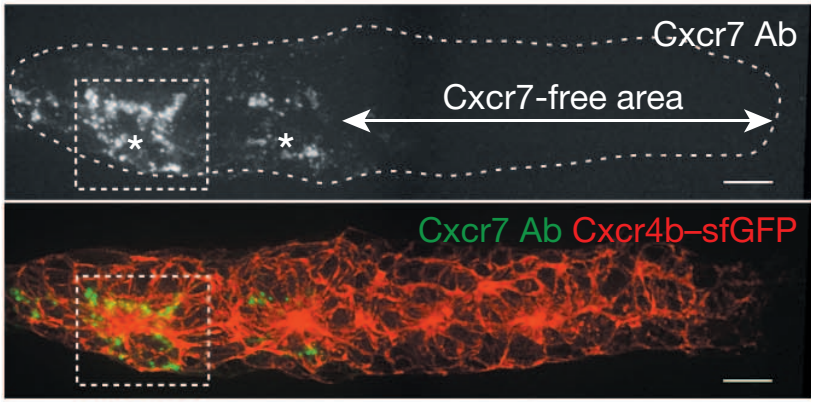
Peter Haas and D. Gilmour, *Developmental Cell* 10, 673–680 (2006)

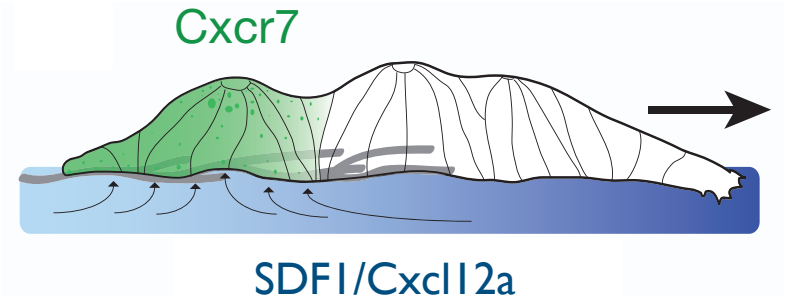
Collective migration in fish lateral line

Hypothesis :

- Cluster motility requires self-generated gradient of chemoattractant
- Depends on intrinsic polarity of cell cluster
- For instance internalisation of SDF1/Cxcl12a at the rear by CXCR7 which works as a sink?

See also L. Tweedy et al., and R. Insall. *Science* 369, 1075 (2020)





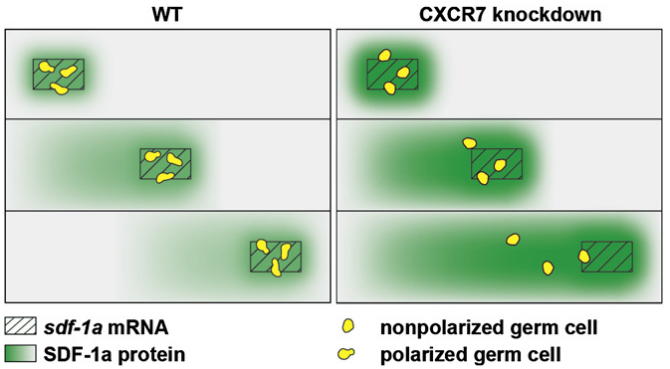
Experiments: E. Dona et al. and D. Gilmour. *Nature.* 503(7475):285-9 (2013)

Modeling: S. Streichan et al, D Gilmour and L. Hufnagel. *Phys. Biol.* 8 045004 (8pp) (2011)

Collective migration in fish lateral line

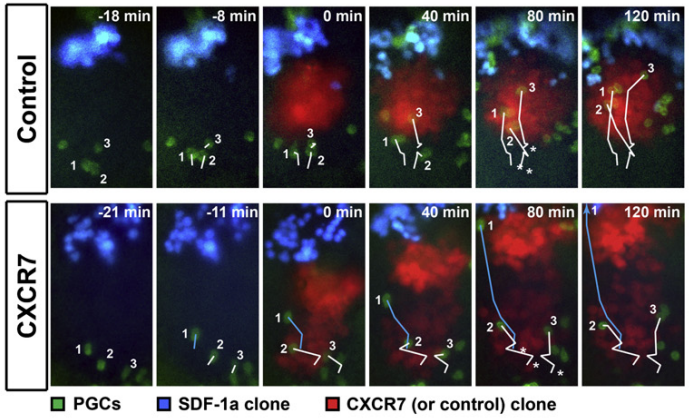
- A chemoattractant sink via receptor endocytosis

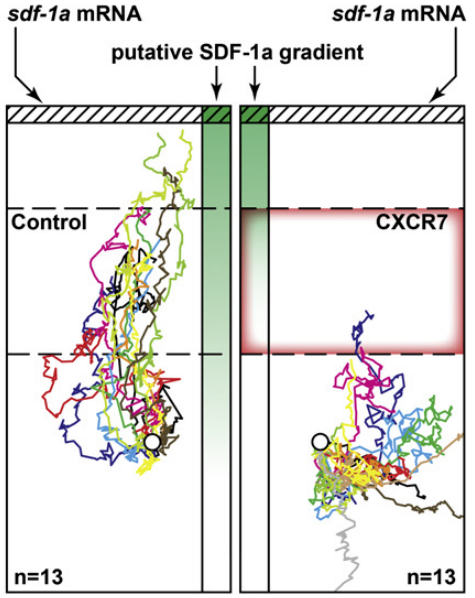
- Primordial Germ cells (PGCs) are guided by an SDF1a gradient that arises from moving source of SDF1 and endocytic activity of CXCR7 by PGCs
- CXCR7 works as a chemoattractant sink.



- Overexpression of CXCR7 in the soma blunts the SDF1 gradient and affects PGC migration

SDF1 clone in SDF1 mutant



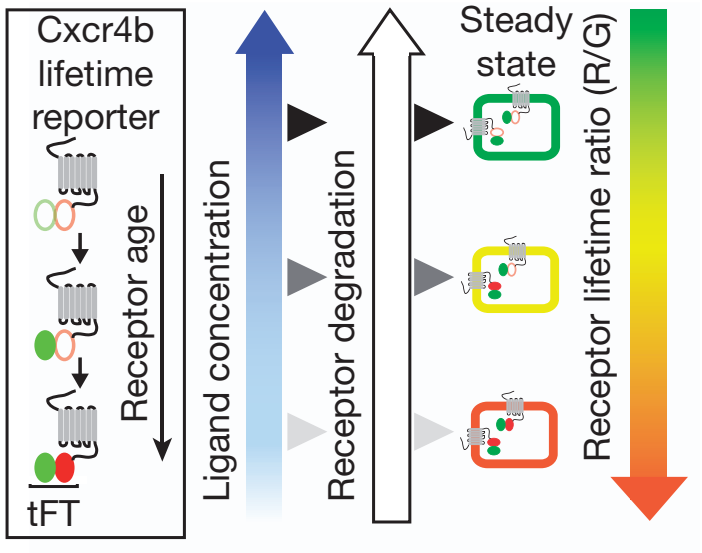


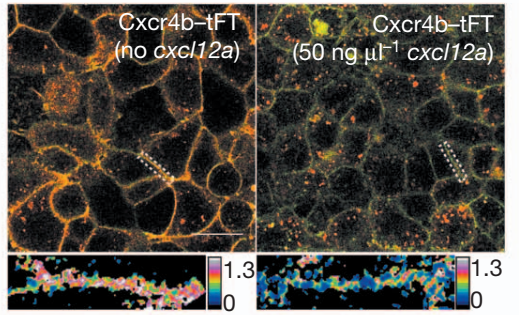
B.Boldajipour et al. and E. Raz. *Cell 132*, 463–473 (2008)

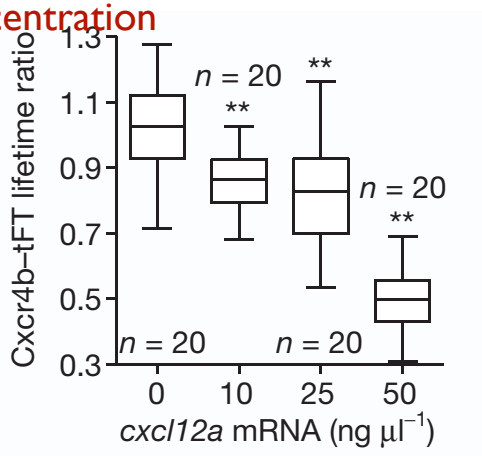
Collective migration in fish lateral line

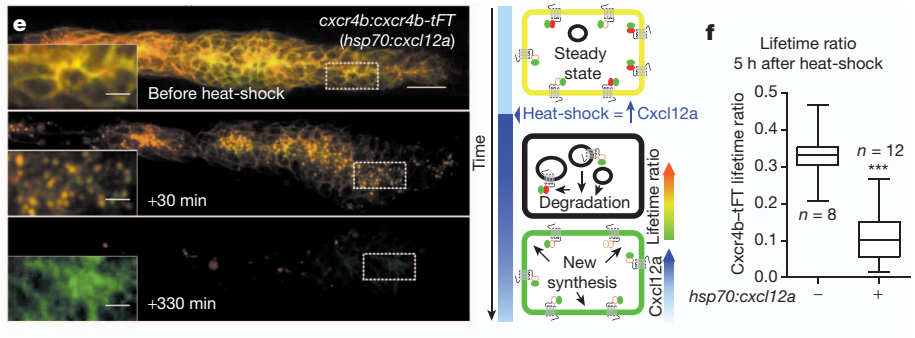
- Probing chemoattractant receptor lifetime at the cell surface

- Assay to monitor surface CXCR4a lifetime and indirectly SDF1/Cxcl12a gradient: based on fusion in tandem with fast maturing GFP and slow maturing RFP.
- Rationale: high concentration of chemoattractant induces receptor internationalisation and lowers surface receptor lifetime
- CXCR4 receptor lifetime ratio depends on SDF1/Cxcl12a ligand concentration







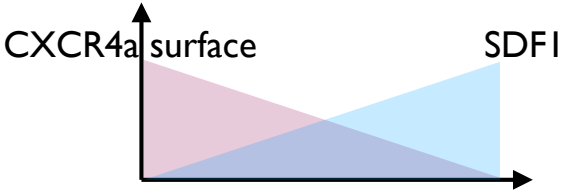


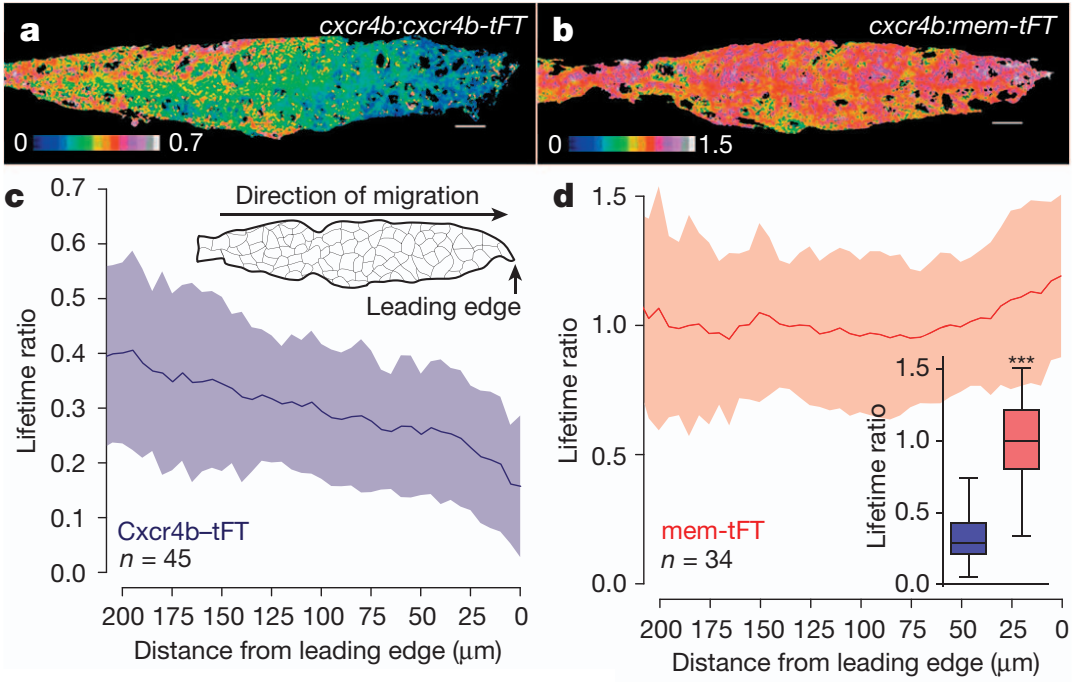
E. Dona et al. and D. Gilmour. *Nature*. 503(7475):285-9 (2013)

Collective migration in fish lateral line

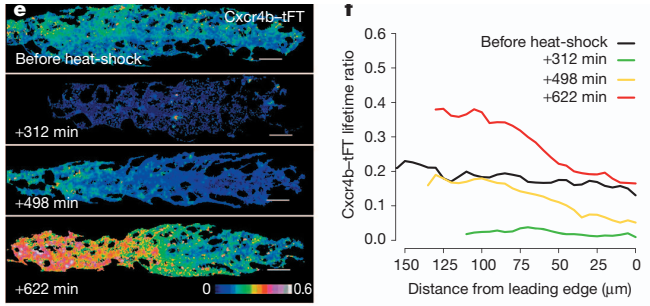
- Opposite gradient of ligand and receptor lifetime in primordium

- CXCR4 lifetime ratio is present in a gradient from anterior to posterior and reflects an opposite SDF1/Cxcl12a gradient





- A pulse of Cxcl12a expression abrogates CXCR4 lifetime gradient.
- The gradient then reforms spontaneously.

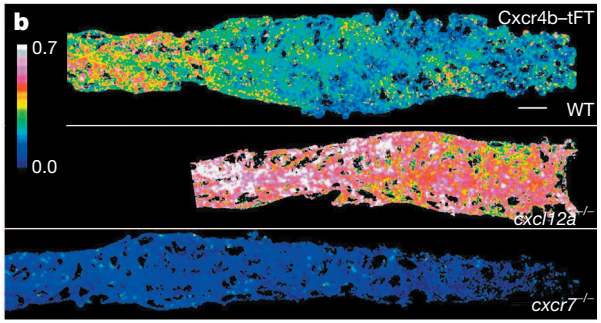


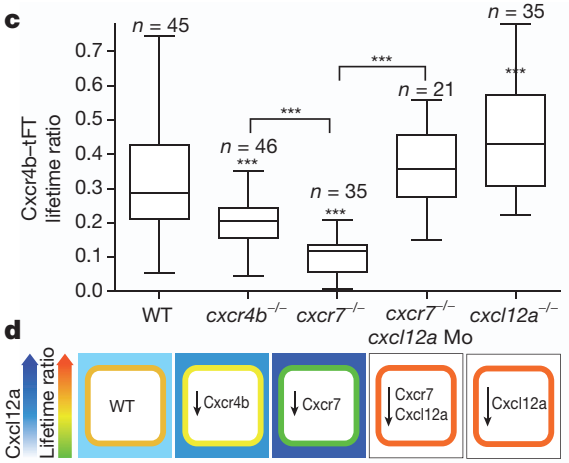
E. Dona et al. and D. Gilmour. *Nature*. 503(7475):285-9 (2013)

Collective migration in fish lateral line

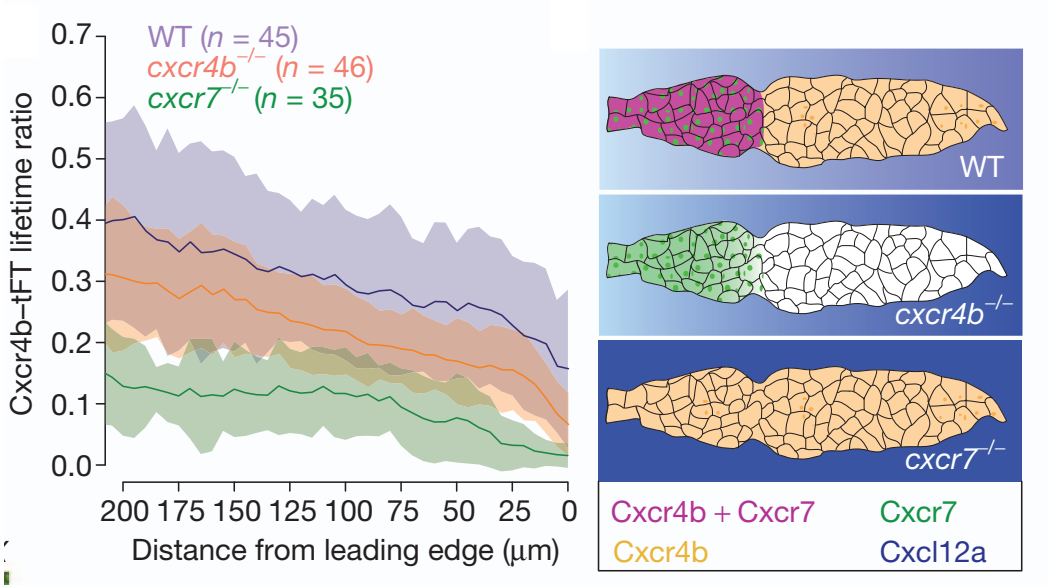
- Receptor antagonism in primordium underlies self-generated ligand gradient

- Interplay between CXCR4 and 7:
- In a CXCR7 mutant, CXCR4 ratio is lower because the receptor is less present at the surface because 1) more ligand is present and 2) ligand dependent internalisation is enhanced





- Overexpression of CXCR7 blocks emergence of self-generated ligand concentration gradient.

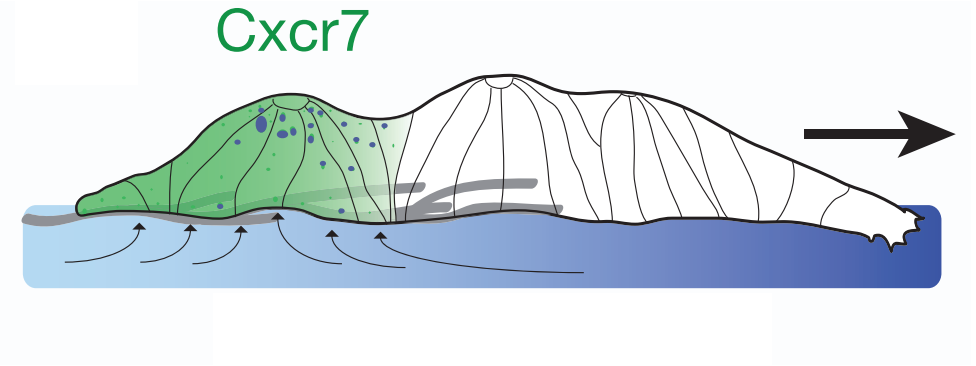


E. Dona et al. and D. Gilmour. *Nature*. 503(7475):285-9 (2013)

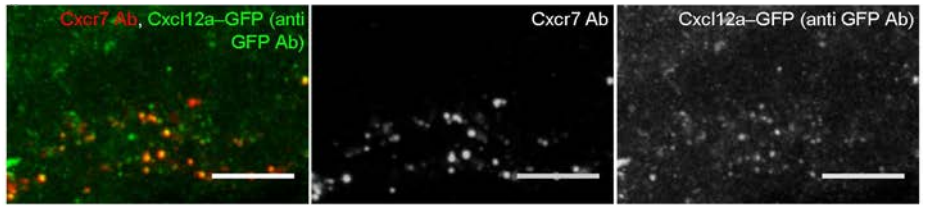
Collective migration in fish lateral line

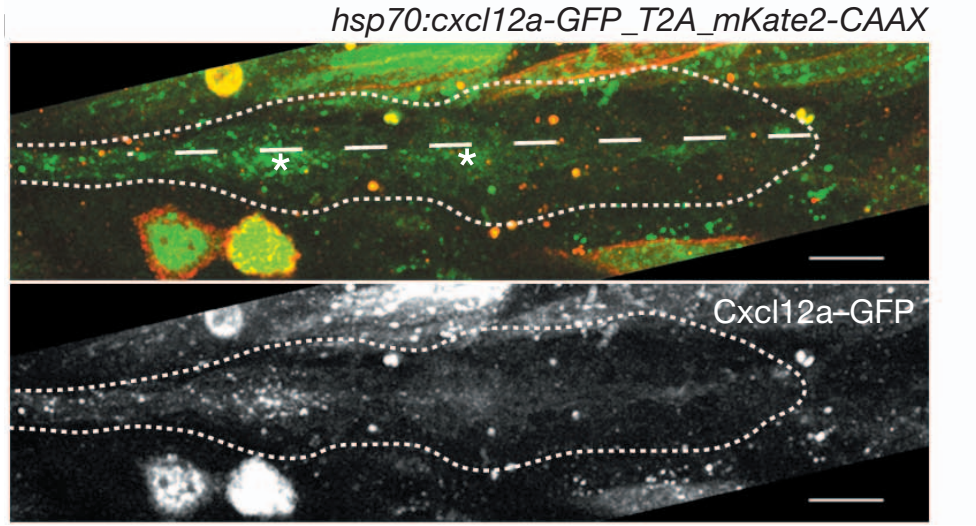
- Internalisation of ligand by CXCR7

- Internalisation of CXCR7 and its ligand SDF1/Cxcl12a



- The chemoattractant SDF1/ Cxcl12a is present in a gradient.



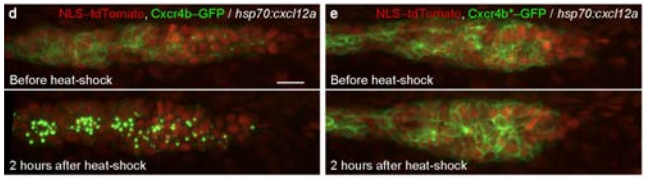


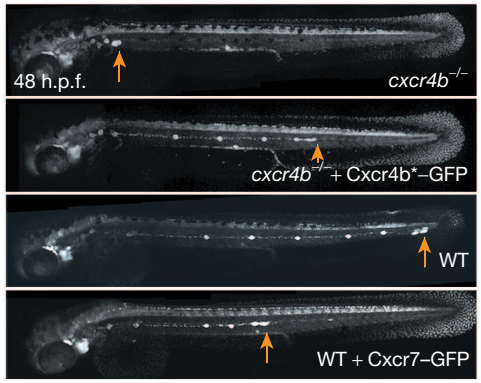
E. Dona et al. and D. Gilmour. *Nature*. 503(7475):285-9 (2013)

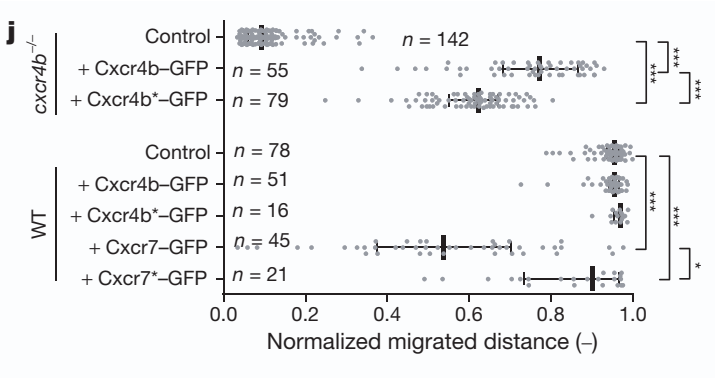
Collective migration in fish lateral line

- CXCR7 endocytosis is necessary and sufficient for primodium motility

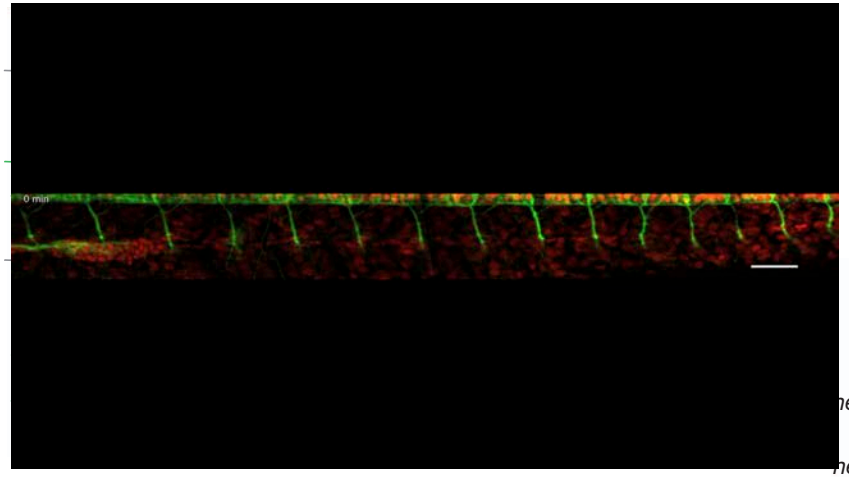
- CXCR7 endocytosis is required for collective motility
- Use of endocytosis deficient CXCR4 and 7 receptors.
- CXCR4 endocytosis is dispensable.

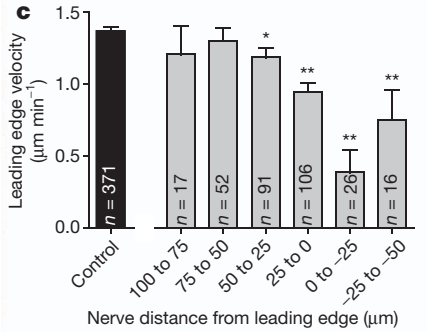


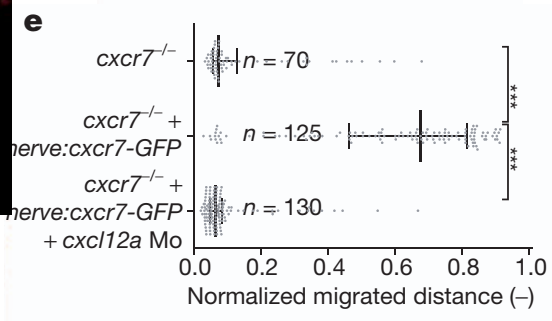




- Expression of CXCR7 in the nerve cells can rescue CXCR7 mutation in the primordium.
- CXCR7 expression in posterior of cluster is sufficient to drive collective motility



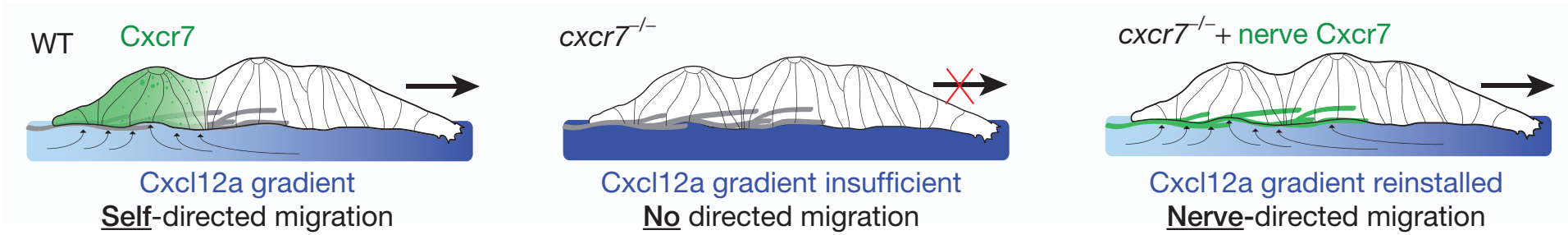




E. Dona et al. and D. Gilmour. *Nature*. 503(7475):285-9 (2013)

Collective migration in fish lateral line

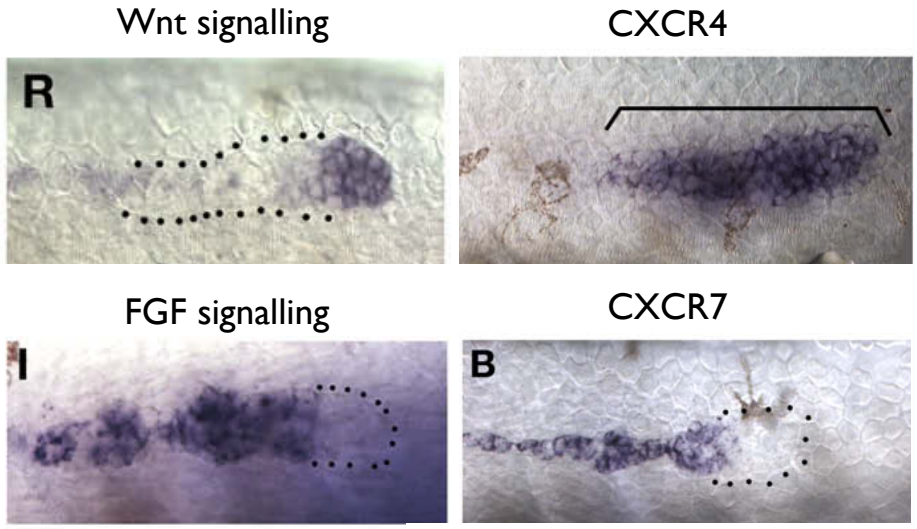
- Summary

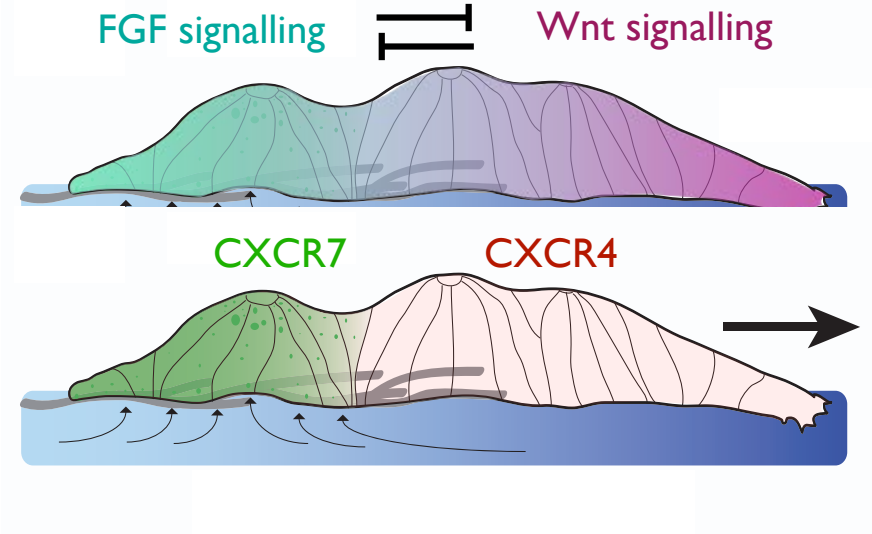


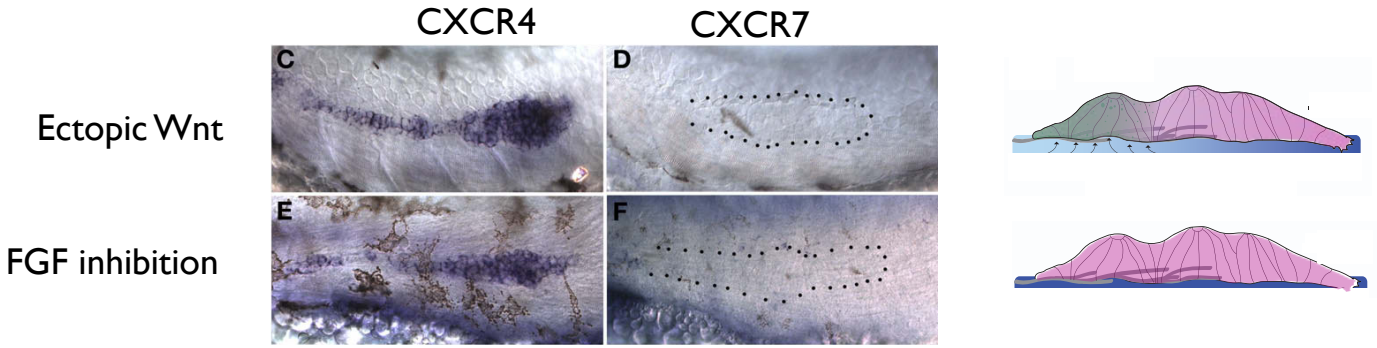
E. Dona et al. and D. Gilmour. *Nature.* 503(7475):285-9 (2013)

Collective migration in fish lateral line

- Intrinsic polarity of the primordium guides directionality of cell cluster





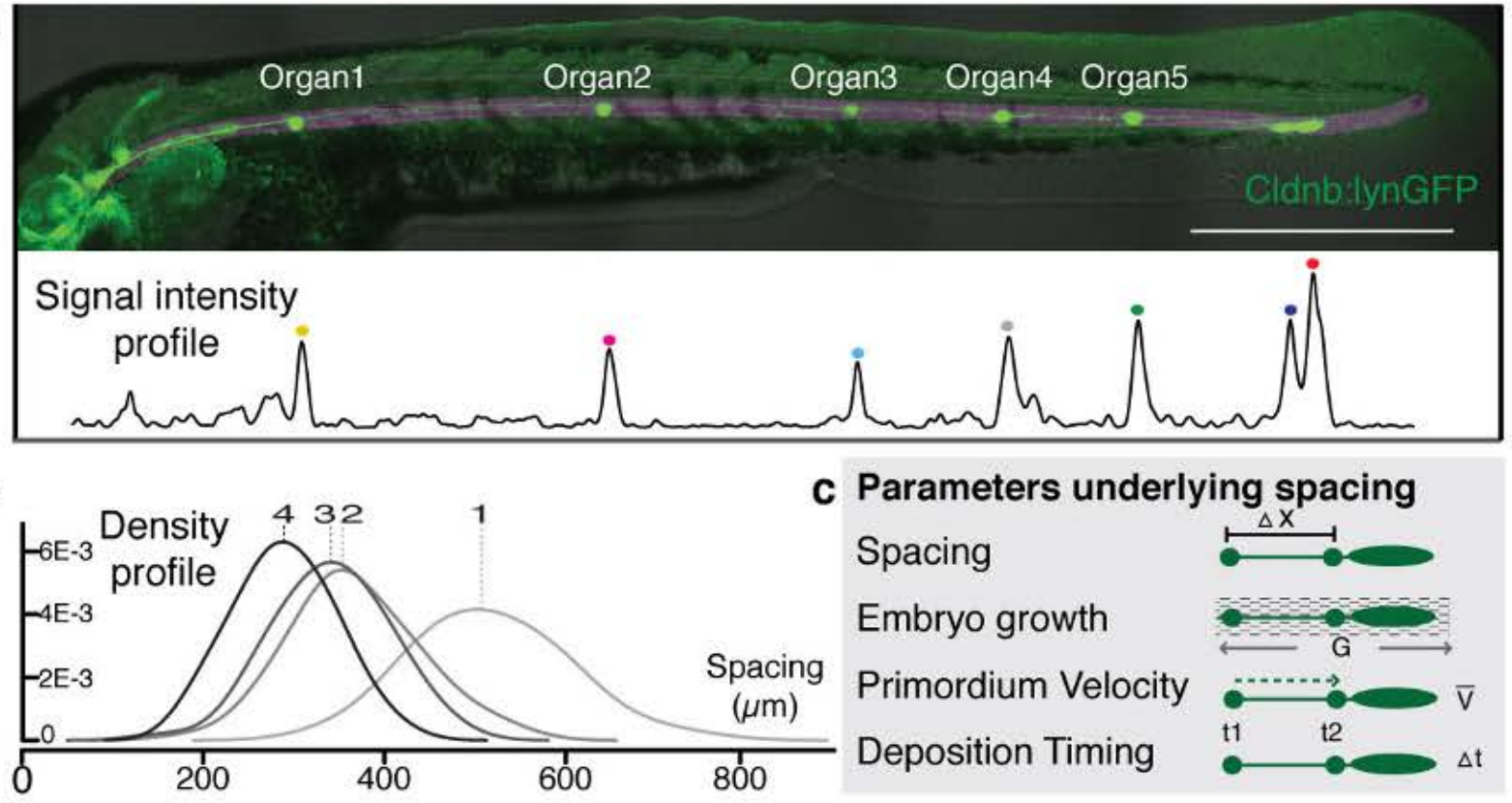


A. Aman and T. Piotrowski. *Developmental Cell* 15, 749–761 (2008)

Collective migration in fish lateral line

- Organ deposition and cluster motility

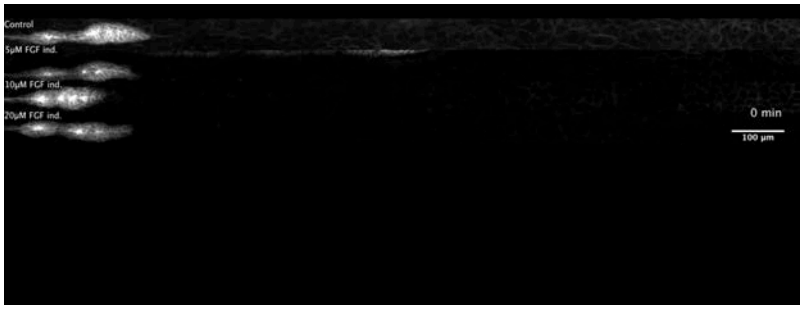
- Organs are deposited sequentially at the rear of the primordium

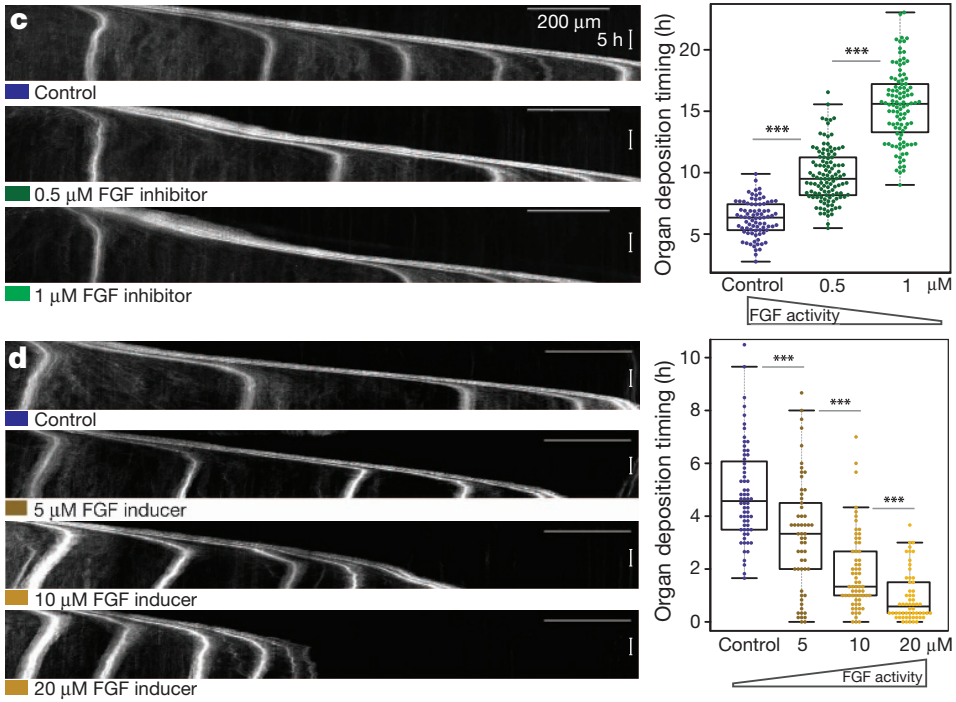


Collective migration in fish lateral line

- Organ deposition at rear of organ is tuned by FGF signaling

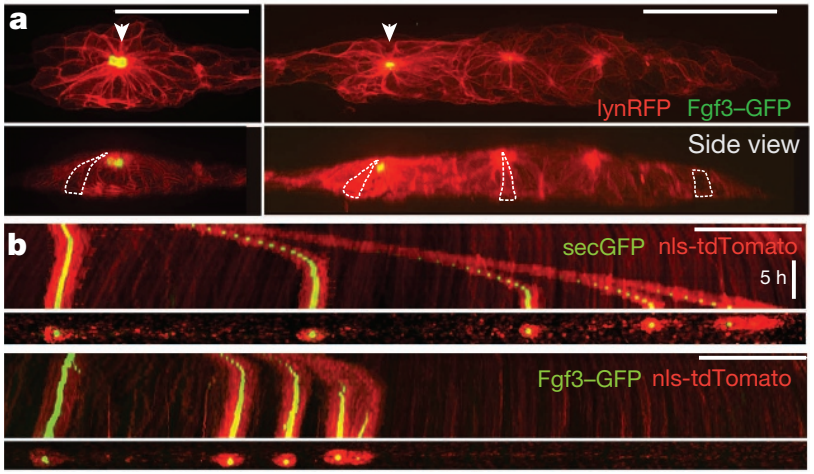
- FGF signaling tunes the timing of organ deposition
- Reduced FGF slows down organ deposition
- Increased FGF accelerates organ deposition

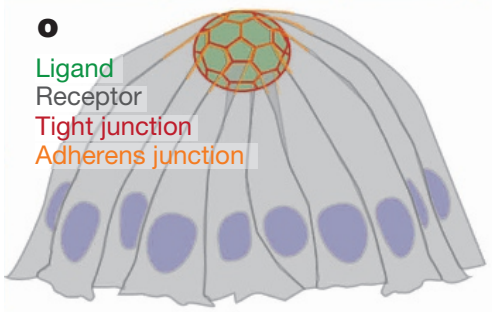


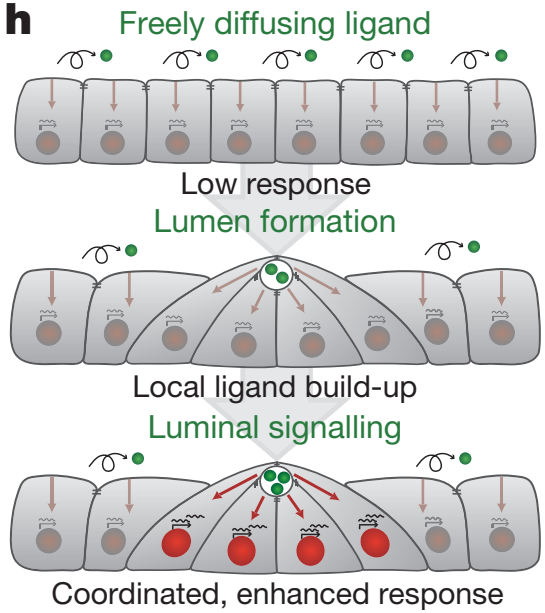


Collective migration in fish lateral line

- FGF is present in lumen of posterior cell cluster



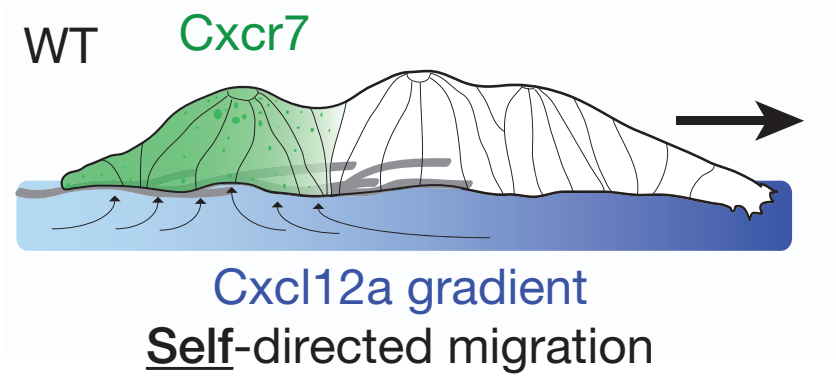


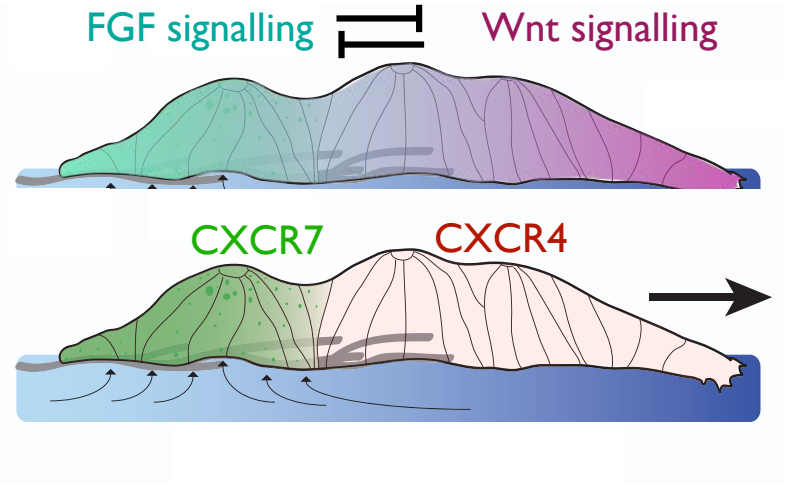


Collective migration in fish lateral line

- **Conclusions:**
- Chemoattractant sensing is required in the leading edge cells in the cluster
- Directionality of cluster is not determined by pre-patterned SDF1 chemical gradient per se
- Directionality requires the global polarization of the cell cluster which is independent of chemoattractant signaling.

- Directionality imparted by intrinsic structural polarization of cell cluster:
  - This is partly self-organized via local SDF1 gradient formation
  - But also partly pre-patterned by FGF/Wnt dependent regulation of CXCR7 expression.





Case Studies of collective cell migration

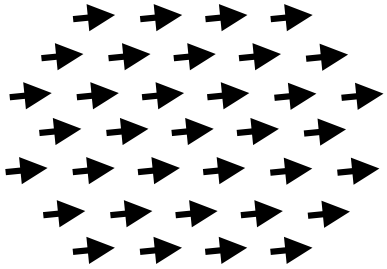
- Collective migration with leaders:

Case Study 1: Neural crest cell migration (*Xenopus*)

Case Study 2: Sensory organ primordium migration in fish lateral line (Zebrafish)

- Collective migration without leaders:

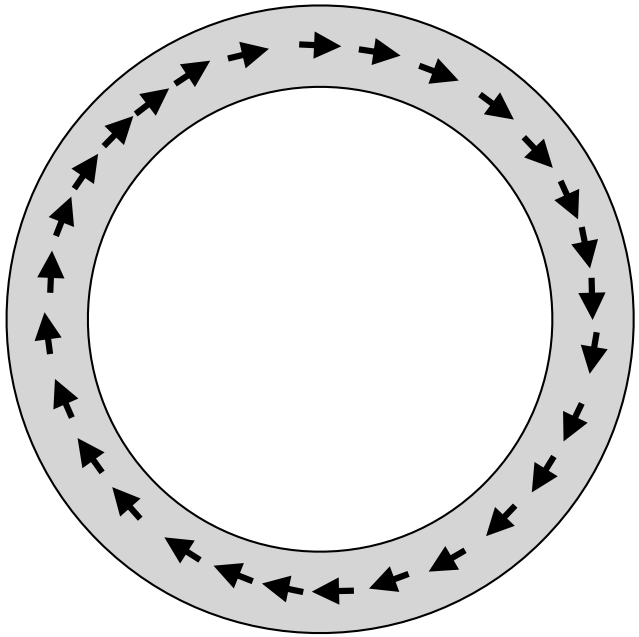
Case Study 3: Egg chamber rotation (*Drosophila*)



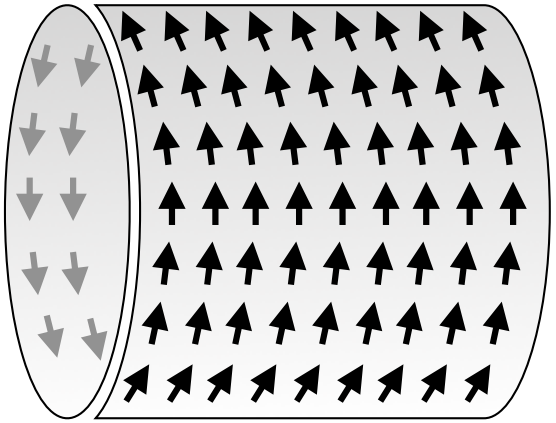
Collective motility without free boundary

- Tissue rotation

2D



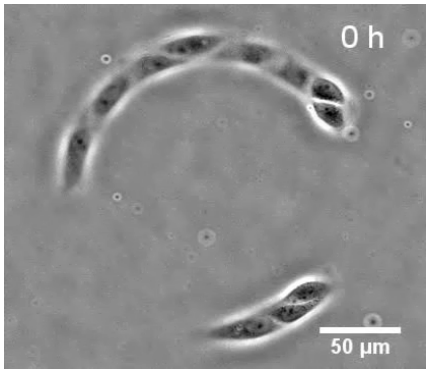
3D

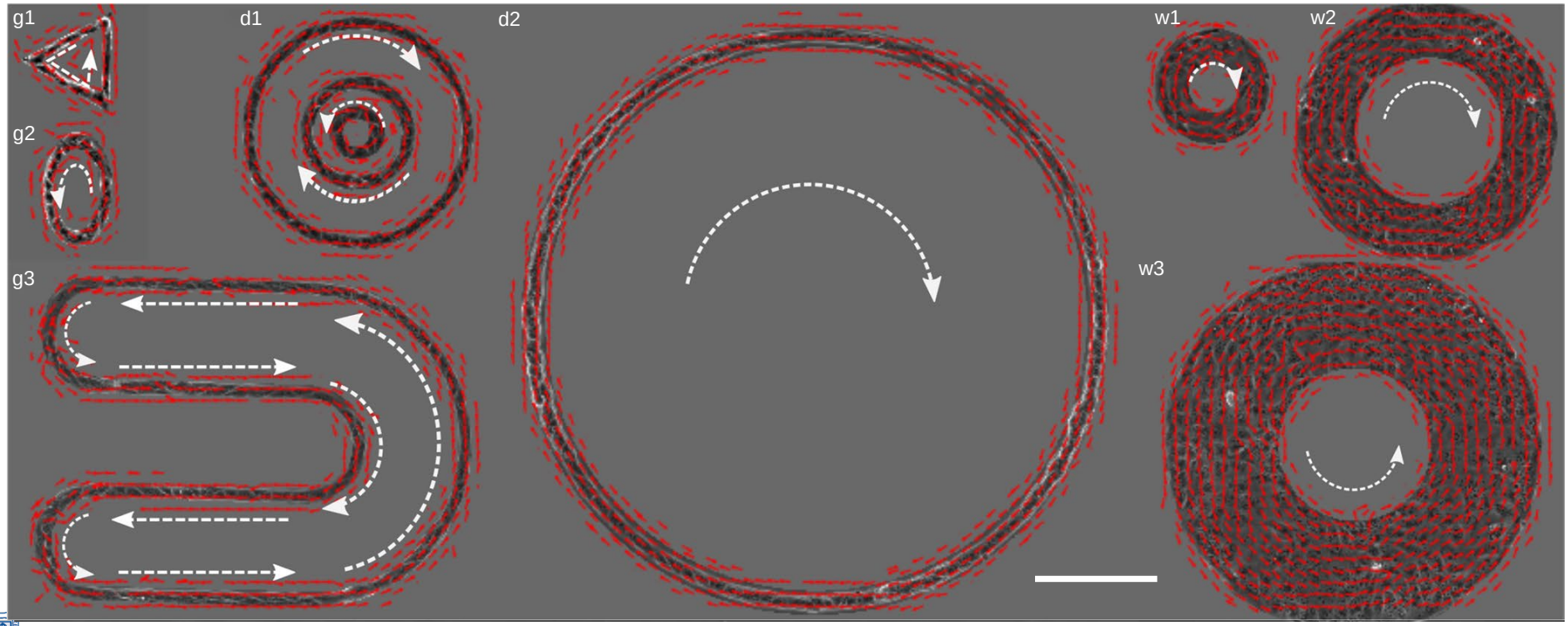


Collective motility without free boundary

Tissue rotation in 2D

- MDCK cells on a ring of Fibronectin
- Emergence of global order at confluence in a variety of geometric patterned substrates
- Tissue rotation is arbitrarily clockwise or anticlockwise





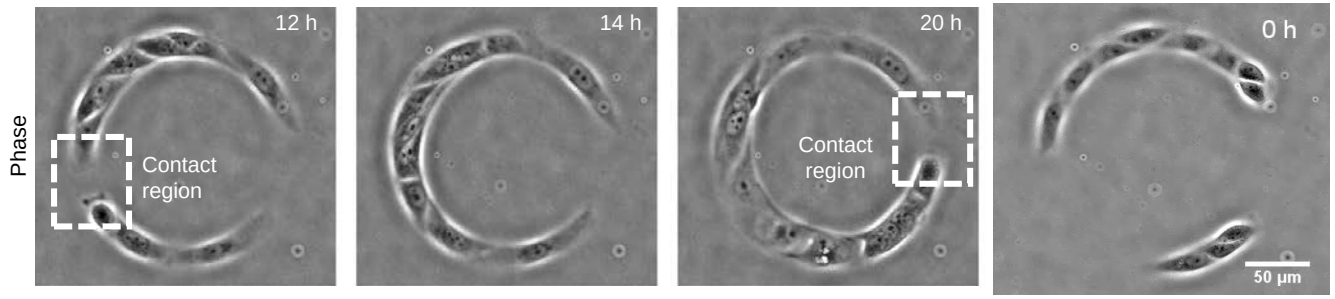
S. Jain, et al. and B. Ladoux, *Nat. Phys.* 16, 802–809 (2020).

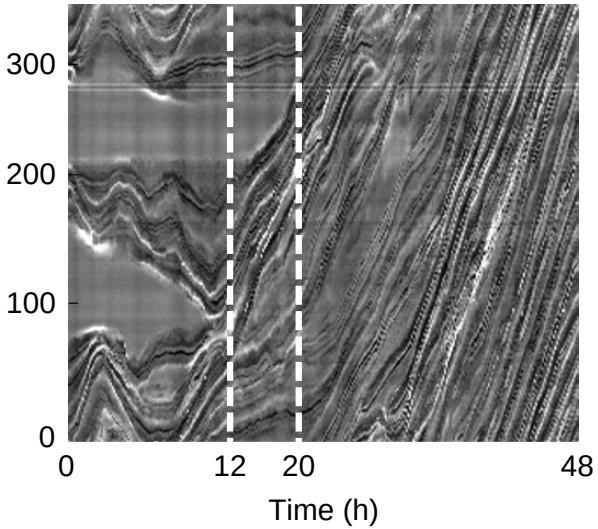
Collective motility without free boundary

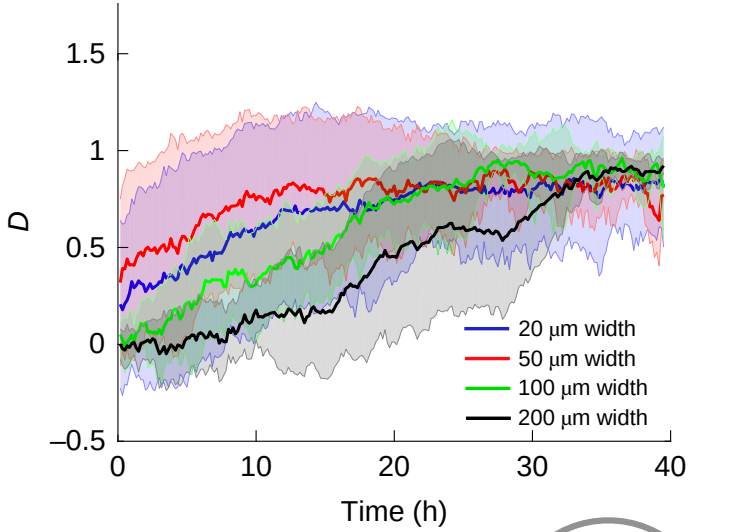
• Tissue rotation in 2D

- Emergence of global alignement of cell velocities

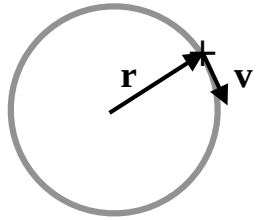
- Trains of MDCK cells with CW or CCW rotation collide head to head
- Global alignement of velocity following collision of cell trains
- Coordination parameter D measures the degree of alignement of velocities (+1 if CW, -1 if CCW and 0 if random motion of cells)







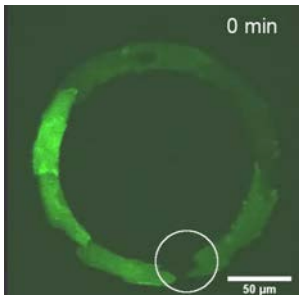
$$\mathbf{D} = \frac{1}{n}\sum \frac{\mathbf{r}}{|\mathbf{r}|} \quad \frac{\mathbf{v}}{|\mathbf{v}|}$$



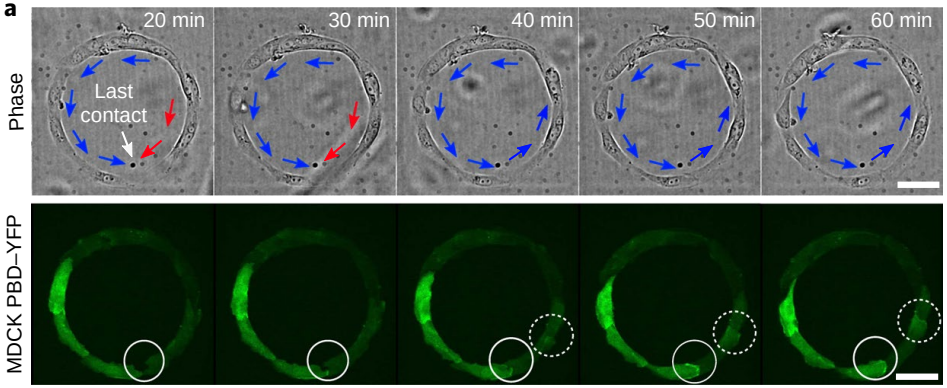
S. Jain, et al. and B. Ladoux, *Nat. Phys.* 16, 802–809 (2020).

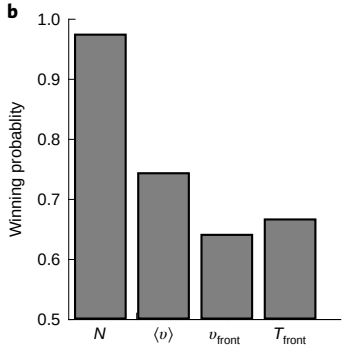
Collective motility without free boundary

• Tissue rotation in 2D



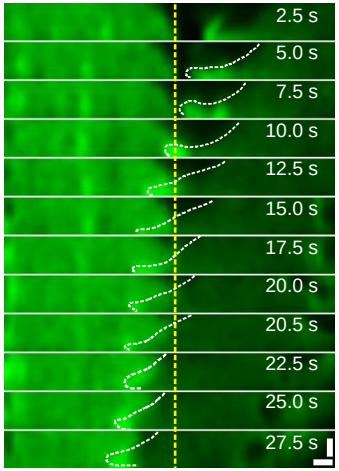
- Cells have an intrinsic polarity and repolarize at contact sites

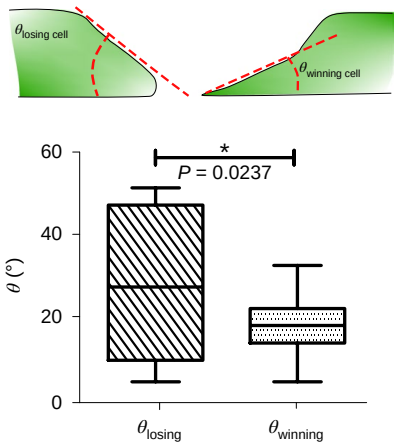


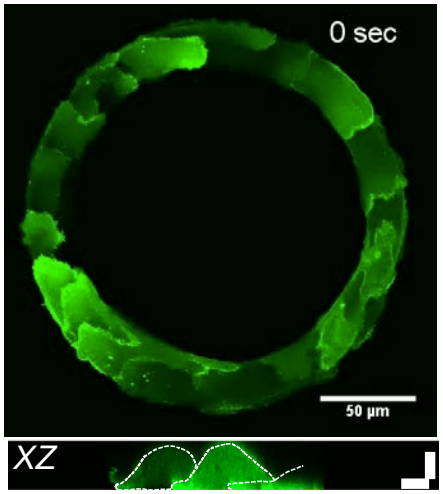


- Front-Back polarity is assessed with RacGTP sensor (PDB-YFP)
- Cells have an intrinsic polarity

- Following collision, cells repolarize to yield global order
- The longer, faster moving cell train tends to keep its polarity
- A cryptic lamelipode forms at cell contacts. Cells with largest lamelipodes tend to maintain their polarity following contacts
- Stochastic distribution of polarities gives rise to global polarity





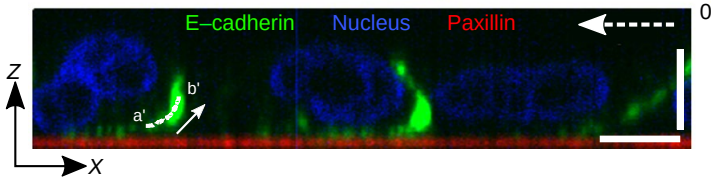


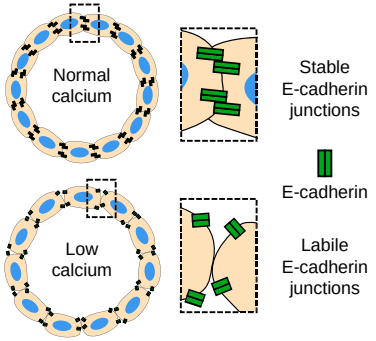
S. Jain, et al. and B. Ladoux, *Nat. Phys.* 16, 802–809 (2020).

Collective motility without free boundary

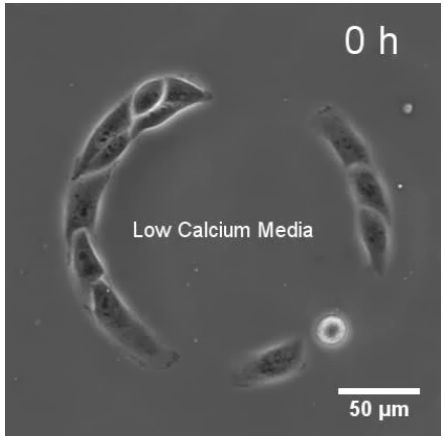
• Tissue rotation in 2D

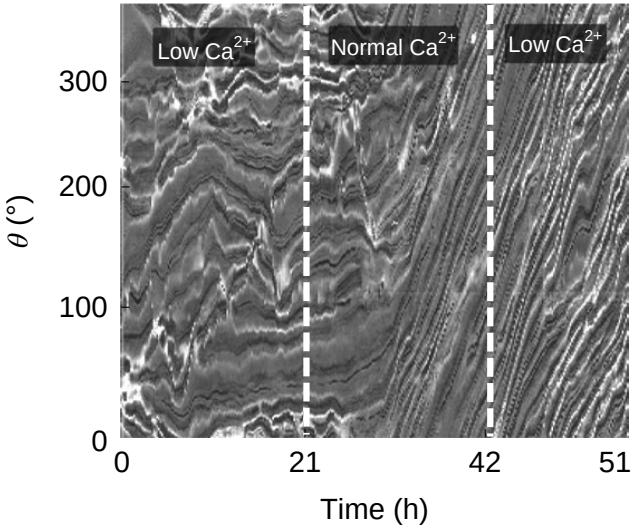
- Cell-cell adhesion is required for the emergence of global order but not for maintenance
  - E-cadherin is polarized and mediates cell cell contacts
  - Low calcium is used to disrupt E-cadherin adhesion

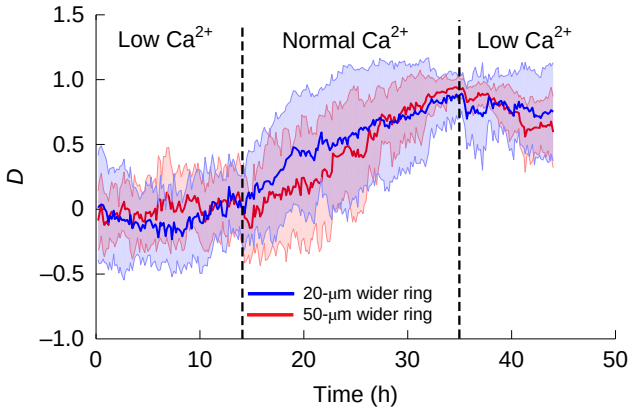




- Without cell-cell adhesion (low calcium or alpha-catenin KD), cells keep random polarity and fail to re-polarize following contacts







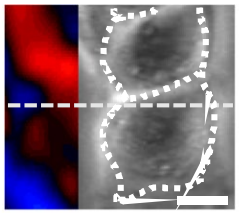
S. Jain, et al. and B. Ladoux, *Nat. Phys.* 16, 802–809 (2020).

Collective motility without free boundary

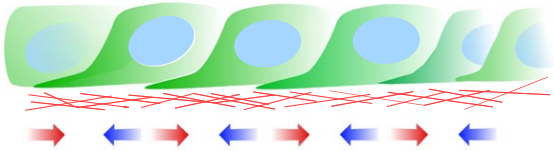
Tissue rotation in 2D

- Cells exhibit local force dipole characteristic of intrinsic motility
- There is no evidence of global intercellular coupling and physical ordering when velocity alignement emerges

- Traction force microscopy: force dipoles at the single cell scale.

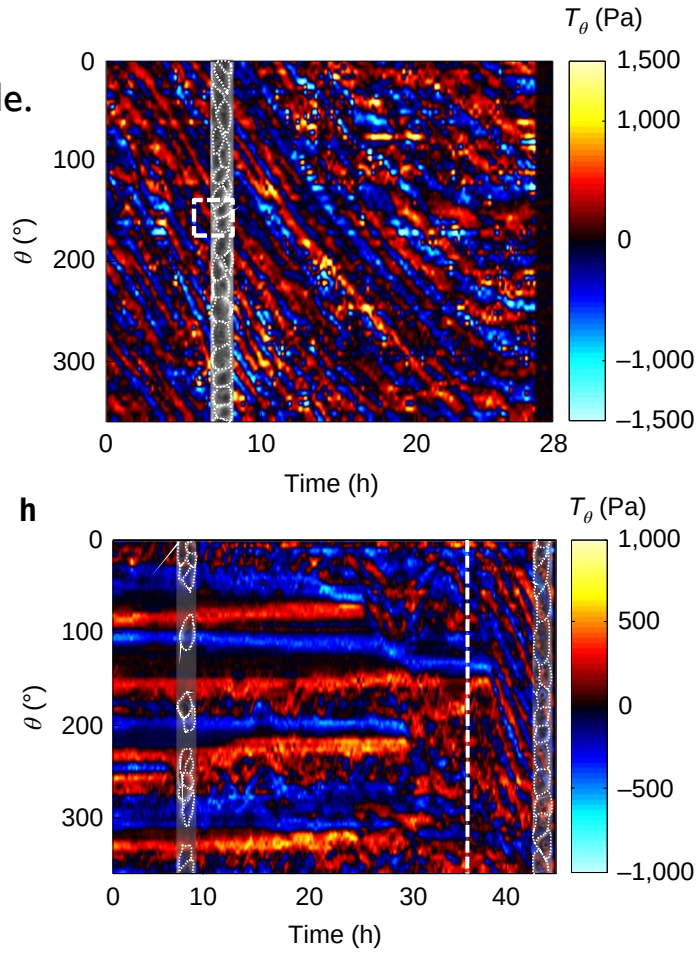


Traction force distribution at single-cell level



- Small cell clusters show collective force dipole characteristic of intercellular mechanical coupling via adhesion proteins.

- But, at confluence, following velocity alignement, force dipoles are local, at the single cell scale.

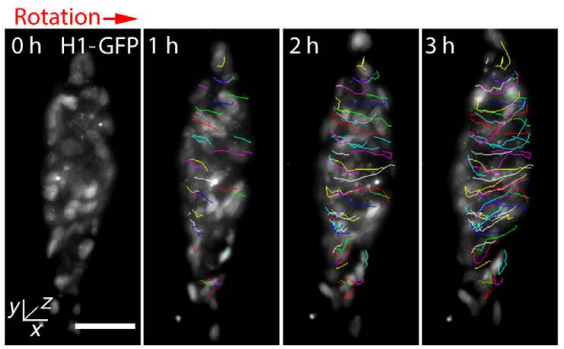


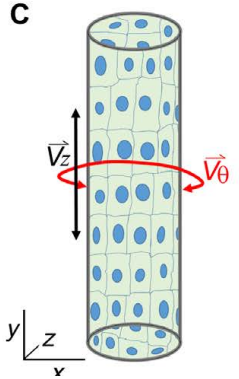
S. Jain, et al. and B. Ladoux, *Nat. Phys.* 16, 802–809 (2020).

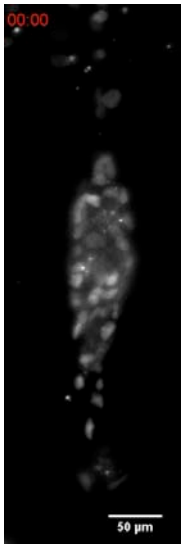
Collective motility without free boundary

• Tissue rotation in 3D

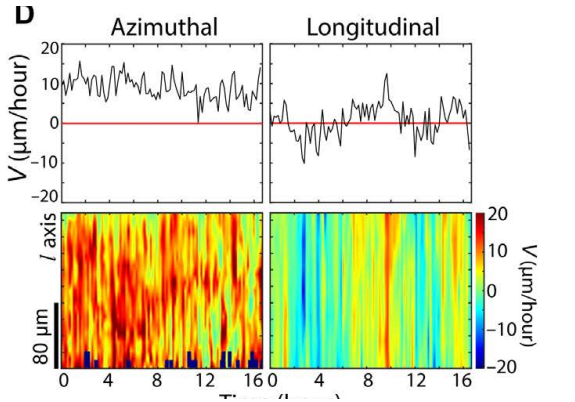
- Emergence of tissue rotation on a concave curved surface

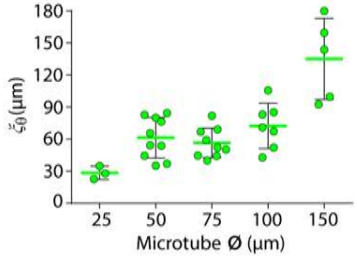


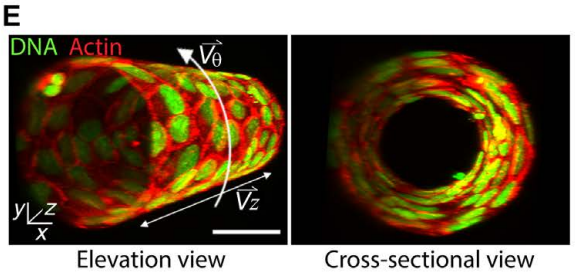


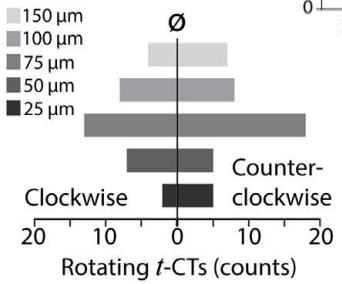


- Velocity is azimuthal, CW or CCW.
- Rotation is found over a wide range of tube diameter. Above 150µm, there is no longer rotation. This may reflect the velocity correlation length scale in MDCK cells ~200µm, on flat unconfined surfaces.
- On curved surfaces, this correlation length ξ_θ increases with tube diameter









A. Glentis *et al.*, and B. Ladoux. *Sci. Adv.* **8**, eabn5406 (2022)

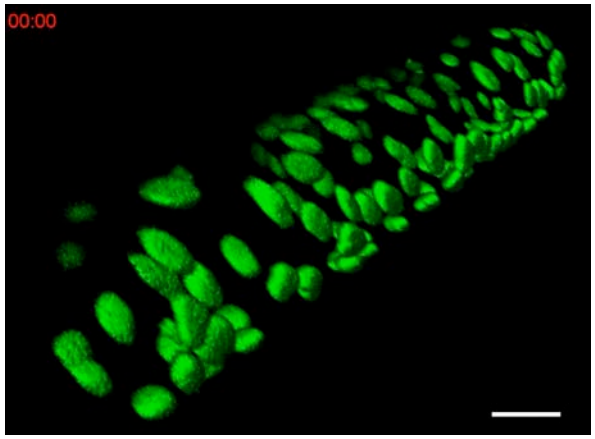
Collective motility without free boundary

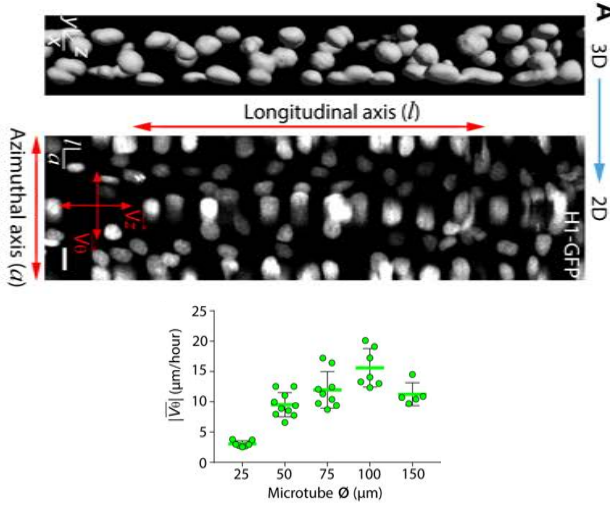
Tissue rotation in 3D

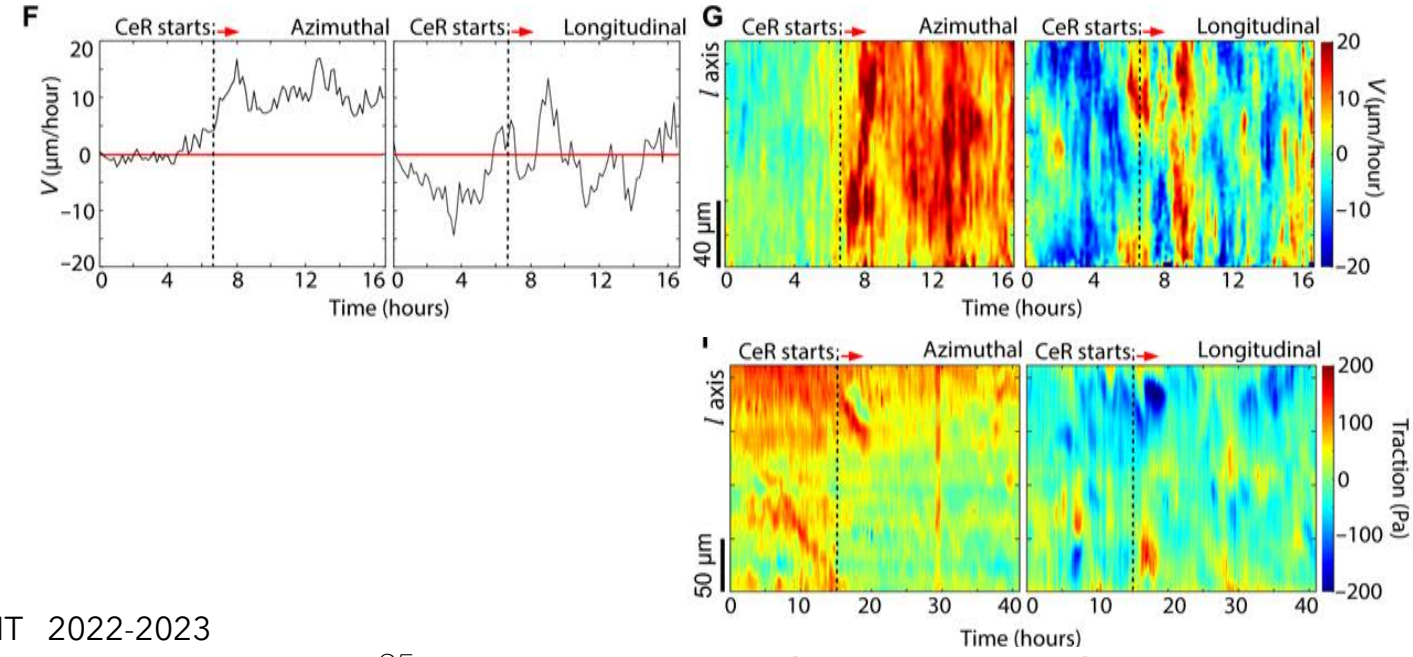
- Emergence of tissue rotation on a concave curved surface

- In a first phase, cell motility is random
- Rotation emerges after 2h with global alignement of velocity, clockwise or counterclockwise

- This is associated with a global reduction in traction forces







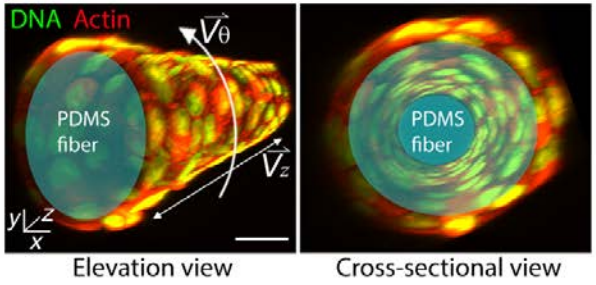
A. Glentis *et al.*, and B. Ladoux. *Sci. Adv.* **8**, eabn5406 (2022)

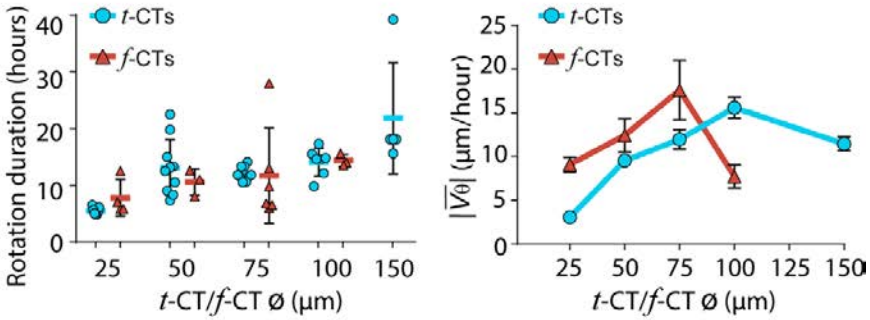
Collective motility without free boundary

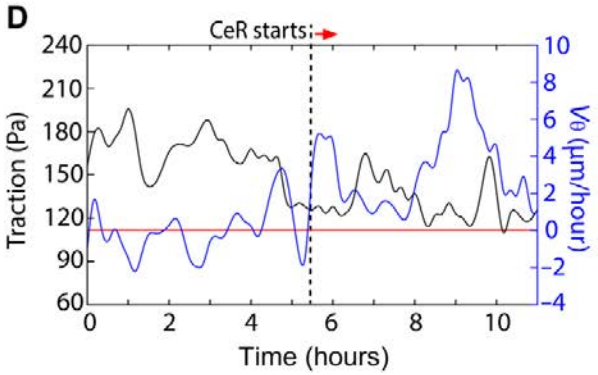
• Tissue rotation in 3D

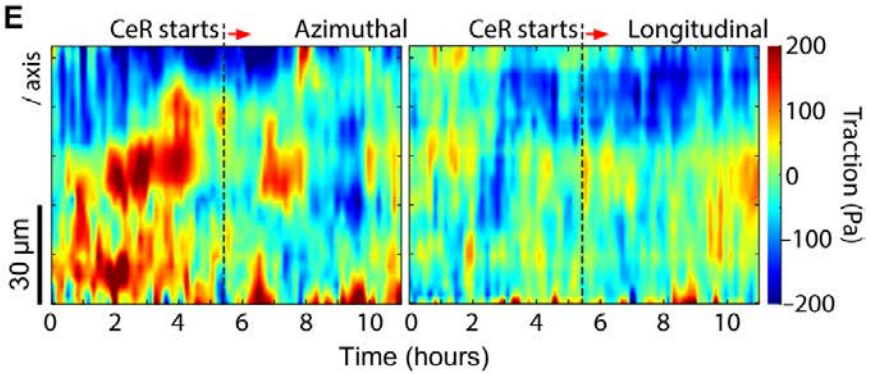
- Emergence of tissue rotation on a convexe surface

t-CT: tubular curved tissue
f-CT: convexe tissue on fiber







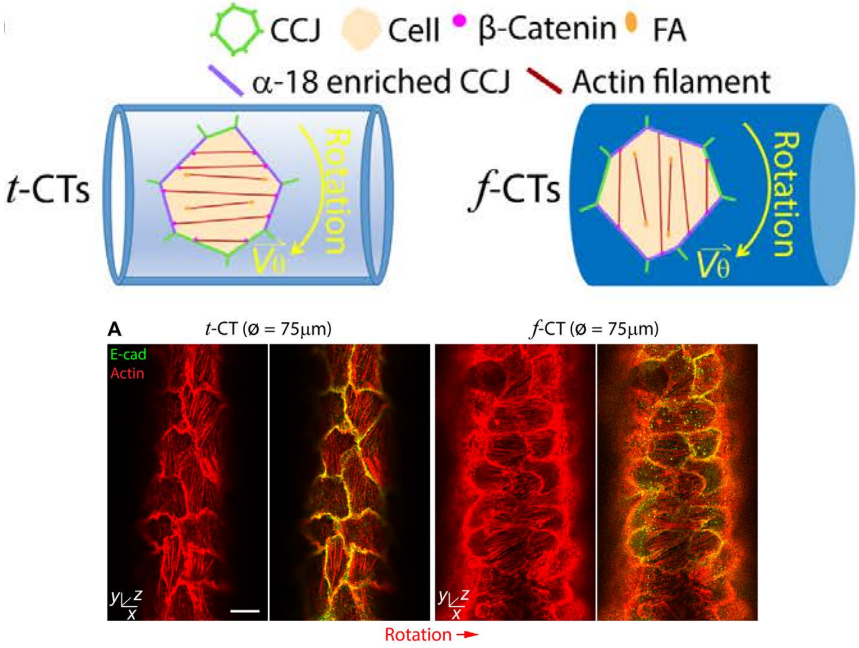


A. Glentis *et al.*, and B. Ladoux. *Sci. Adv.* **8**, eabn5406 (2022)

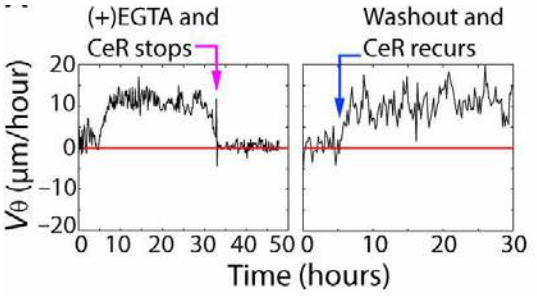
Collective motility without free boundary

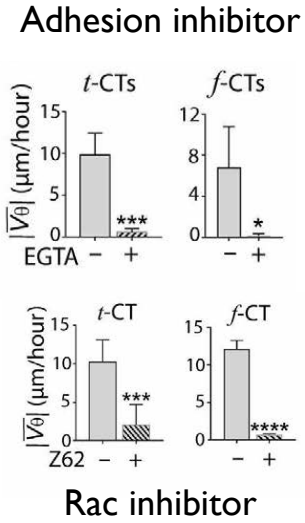
• Tissue rotation in 3D

- Cells exhibit orthogonal cell polarity in concave and convexed curvatures
- Rotation requires cell adhesion, and cell polarization (Rac1)



t-CT: tubular curved tissue
f-CT: convexe tissue on fiber



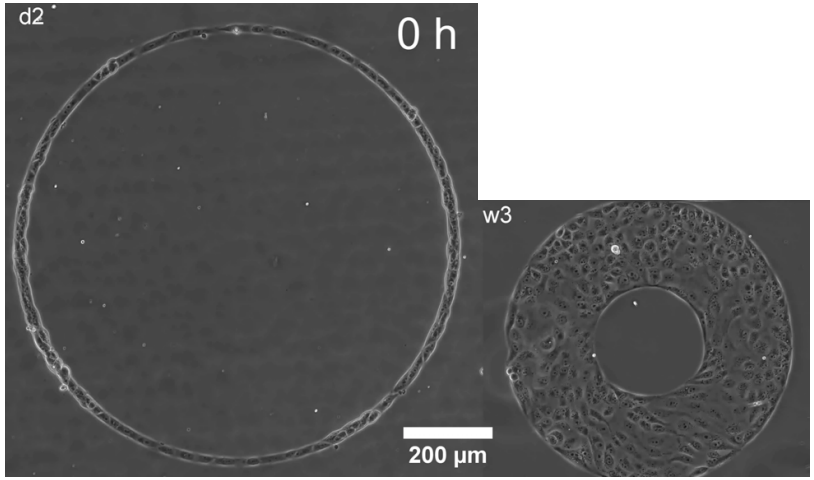


A. Glentis *et al.*, and B. Ladoux. *Sci. Adv.* **8**, eabn5406 (2022)

Collective motility without free boundary

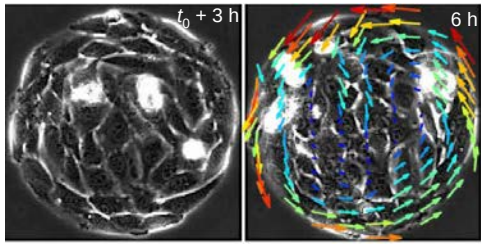
Tissue rotation in 2D and 3D: conclusions

- Intrinsic capacity to break symmetry at cellular scale
- Cell interactions reorganize local polarities and lead to local ordering
- Global ordering emerges at high density when all cells interact.
- This involves coupling between curvature, velocity and polarity (the mechanisms are not understood, phenomenological model)
- There is no need for long range ordering (by mechanochemical gradients, eg, chemotactic cues or durotactic signals).
- Yet such long range cues could potentially increase robustness or velocity alignments (ie. Increase the velocity and polarity correlation lengths).



Collective motility without free boundary

- Topological defects in polarity field is linked to chiral symmetry breaking



P. Guillemat et al. K. Kruse and A. Roux.
Nature Materials. 21: 588–597 (2022)

Cultured myoblasts

Nematic order parameters

- Nematic tensor order (in 2D)

$$Q_{ij} = \langle u_i u_j \rangle - \frac{1}{2}\delta_{ij}$$ (=0 for disordered state)

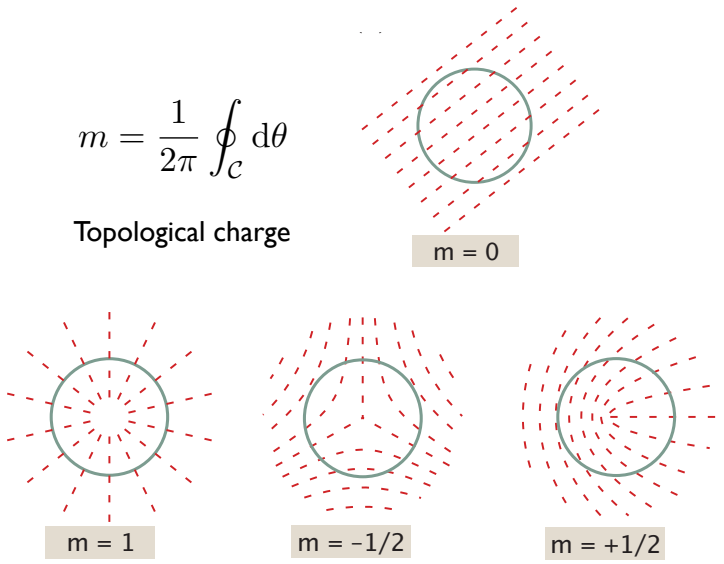
2nd statistical moment

- Scalar order $S = 1 - \langle \delta\theta^2 \rangle$ $\theta_i = \bar{\theta} + \delta\theta_i$

Topological charge in a tissue

$$m = \frac{1}{2\pi}\oint_C \mathrm{d}\theta$$

Topological charge

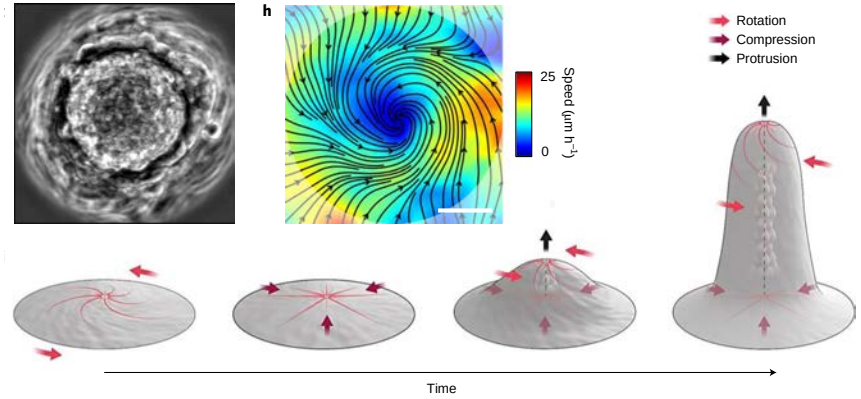


Christina Hueschen and Rob Phillips. The restless cell, *in press*

Collective motility without free boundary

- Topological defects in polarity field is linked to chiral symmetry breaking

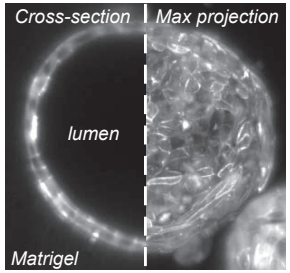
- Integer topological defects organize stresses driving tissue morphogenesis

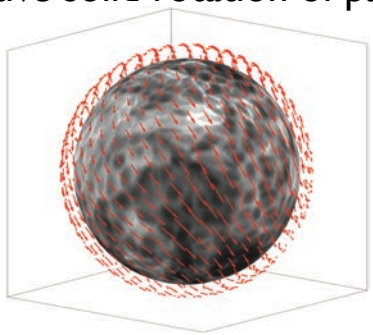


P. Guillemat et al. K. Kruse and A. Roux.
Nature Materials. 21: 588–597 (2022)

- Asters and spirals form around integer topological defects in cultured myoblasts
- Stresses accumulate at integer topological defects
- Mounds and spirals in 3D emerge

- Emergent chirality in active solid rotation of pancreas spheres



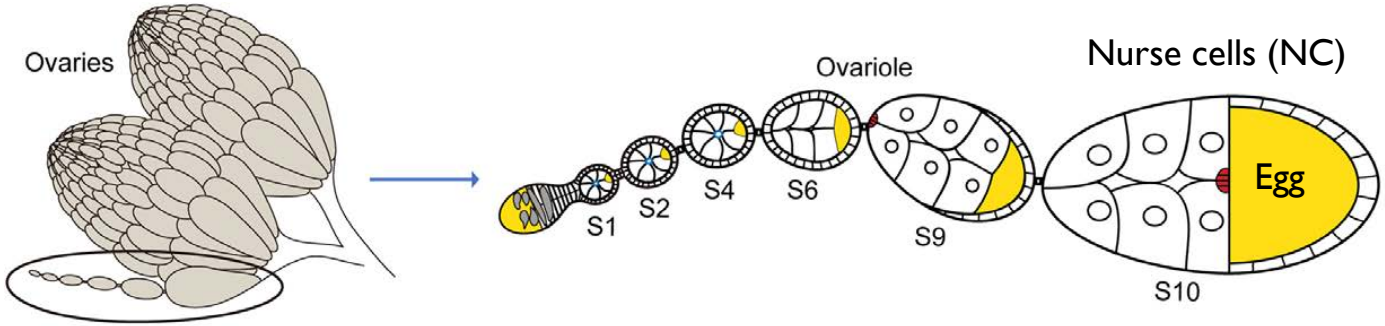


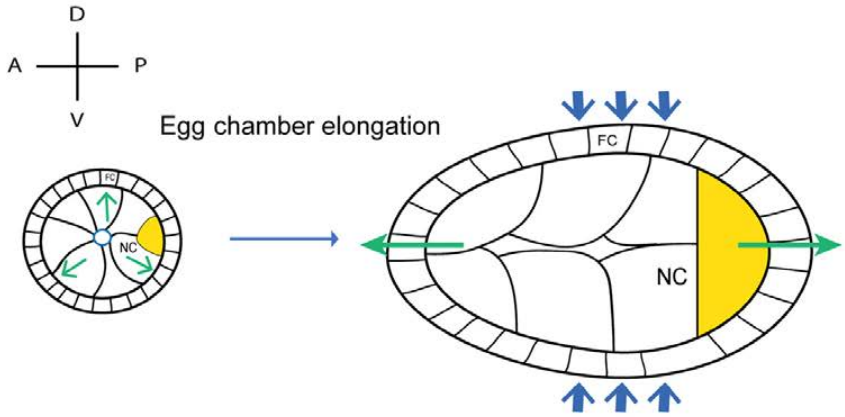
Tzer Han Tan et al, A. Grapin-Botton and F. Jülicher. *biorxiv*
https://doi.org/10.1101/2022.09.29.510101

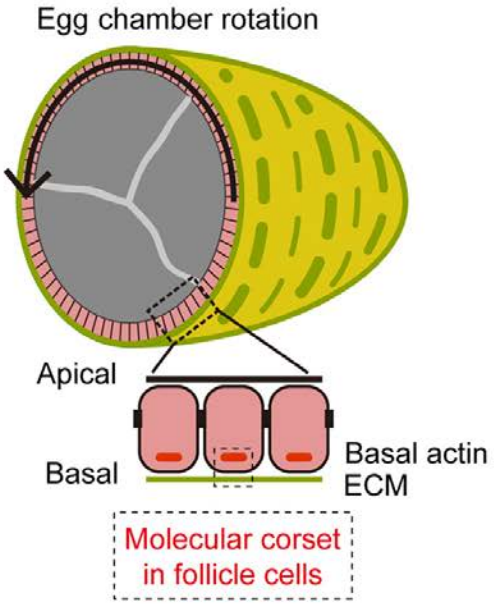
Collective motility and Tissue rotation in vivo

- Egg chamber morphogenesis in *Drosophila*

- The egg grows and elongates.
- Egg elongation requires active remodeling by the surrounding epithelium



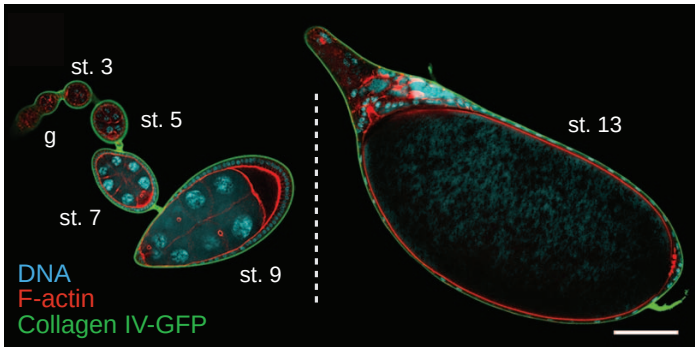


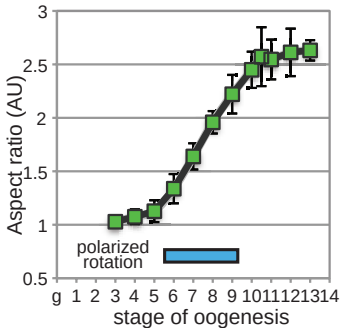


Popkova A, Rauzi M and Wang X. Front. *Cell Dev. Biol.* 9:645235. doi: 10.3389/fcell.2021.645235 (20

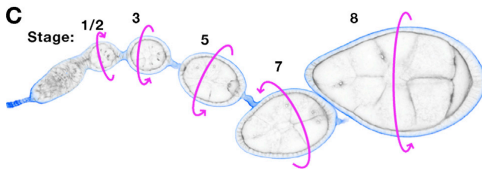
Collective motility and Tissue rotation in vivo

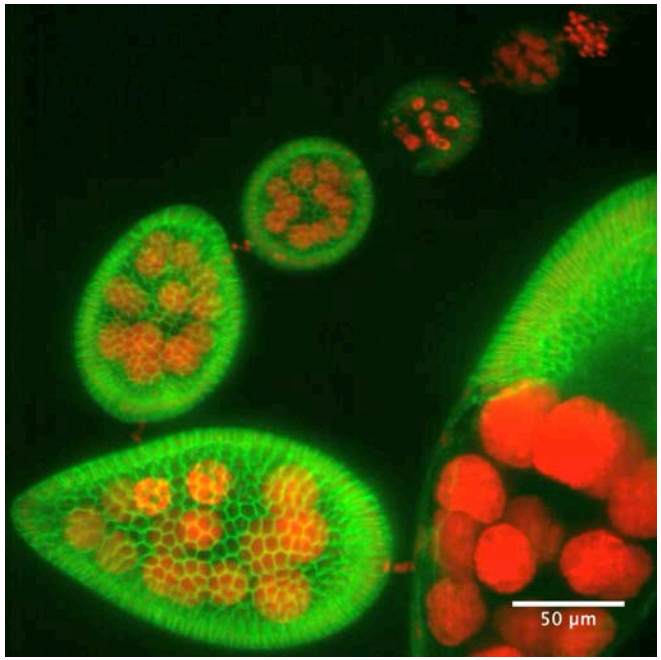
- Egg chamber rotation occurs simultaneously with elongation

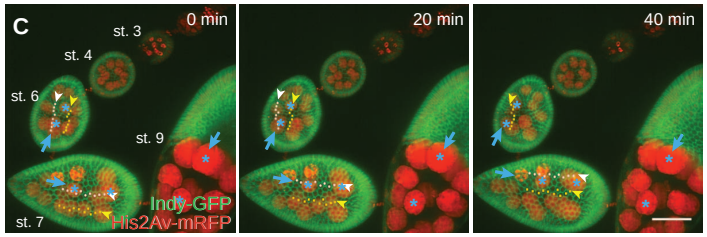




- Egg chamber rotation has no predetermined orientation
- The follicular epithelium rotates together with the egg and nurse cells



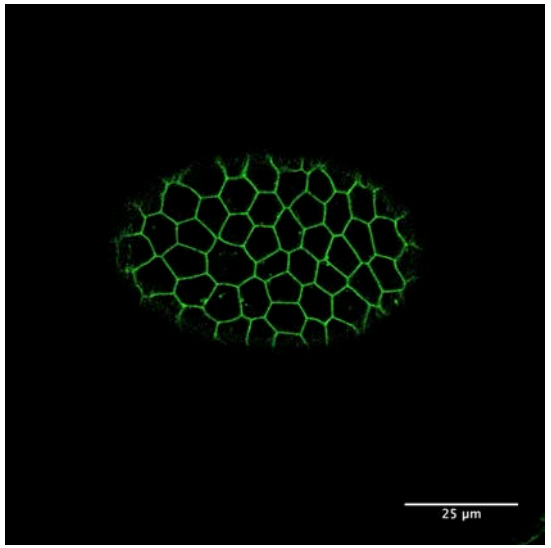




Saori L. Haigo and David Bilder
Science 331, 1071 (2011)

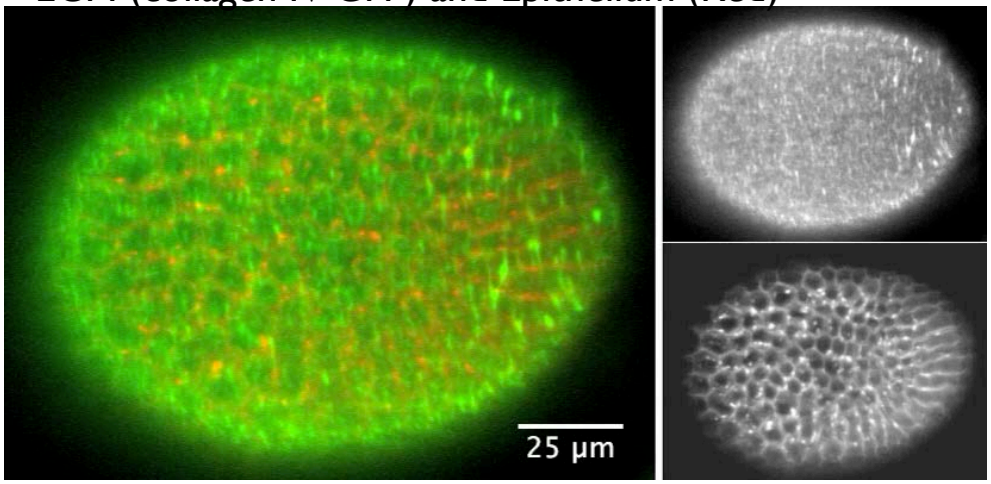
Collective motility and Tissue rotation in vivo

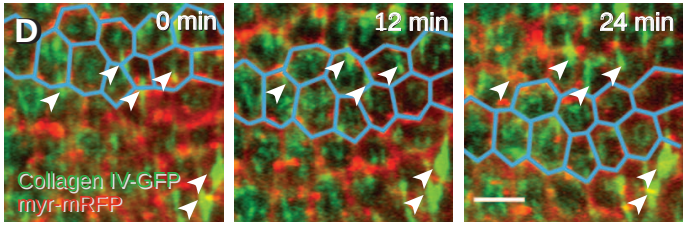
- The follicular epithelium rotates but the outer extracellular matrix layer composed of Collagen IV is a static substratum



Epithelium rotation

ECM (collagen IV-GFP) and Epithelium (Red)





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Collective motility and Tissue rotation in vivo

- Integrin adhesion and ECM are required for tissue rotation

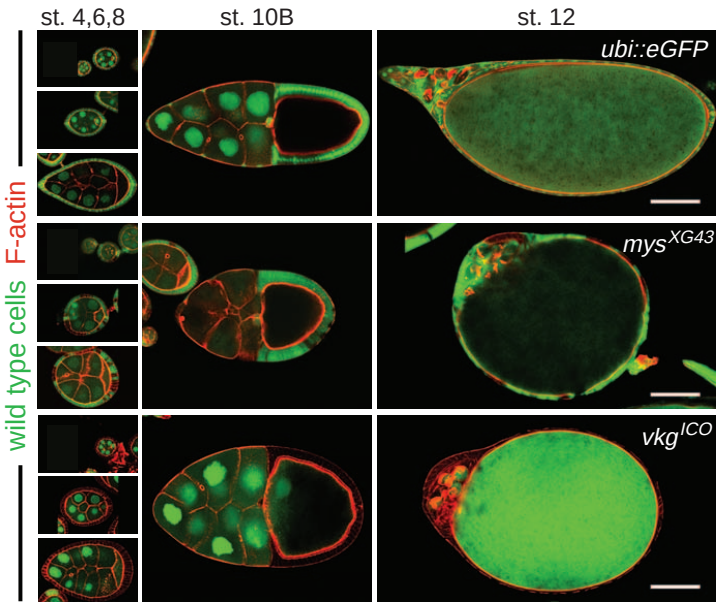
- Integrins and Collagen-IV are both required for:
  - — Egg chamber Elongation
  - — And Rotation

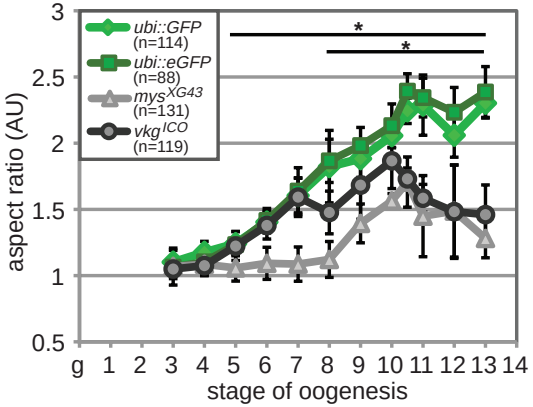
mys: gene encoding ß-integrin

vkg: gene encoding Collagen-IV

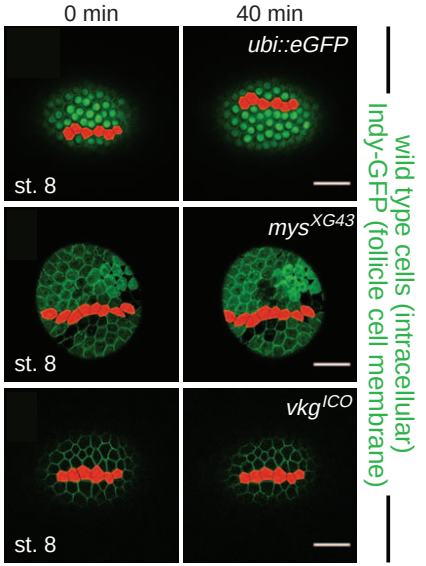
Similar defects are observed following collagenase treatment

Egg chamber *Elongation*





Egg chamber *Rotation*



percentage (%), by stage	stage	5	6	7	8
ubi::GFP (n=19)	↕	**71.4**	**100**	**100**	**100**
	⇄	0	0	0	0
	–	28.6	0	0	0
ubi::eGFP (n=30)	↕	**83**	**100**	**100**	**100**
	⇄	0	0	0	0
	–	17	0	0	0
mysXG43 (n=18)	↕	25	0	14	0
	⇄	25	33	**43**	25
	–	**50**	**67**	**43**	**75**
vkgICO (n=19)	↕	**100**	**50**	**57**	12.5
	⇄	0	**50**	0	12.5
	–	0	0	43	**75**

↕ polarized rotation
⇄ off-axis rotation
– no rotation

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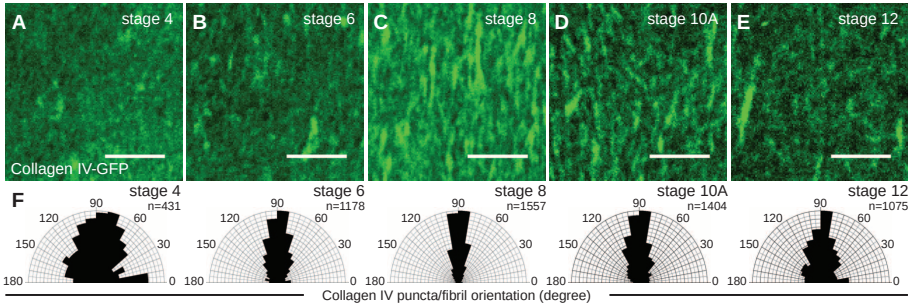
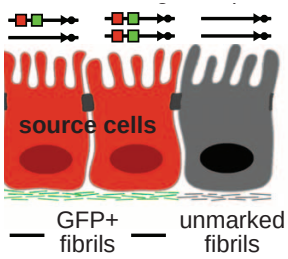
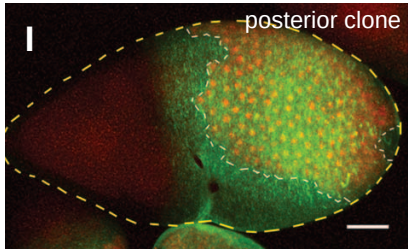
Collective motility and Tissue rotation in vivo

- Tissue rotation orients the secreted ECM in a circumferential molecular corset
  - Collagen-IV forms polarized fibrils around the circumference of rotating egg chamber

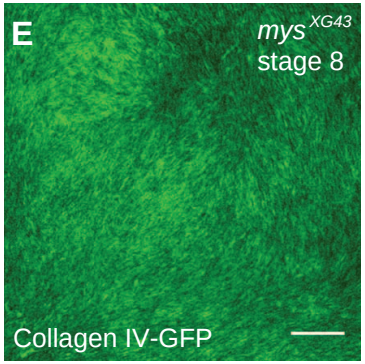


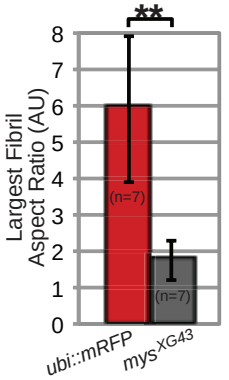
  - Collagen is deposited by the rotating tissue

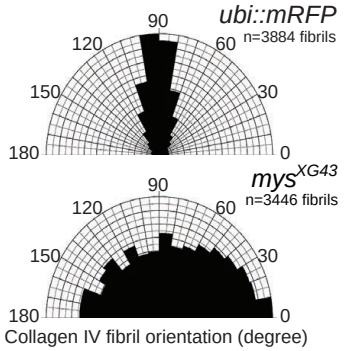




  - When Integrins are absent and tissue rotation blocked, the collagen fibrils are no longer polarized.







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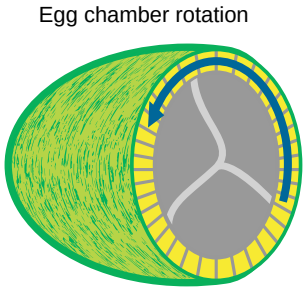
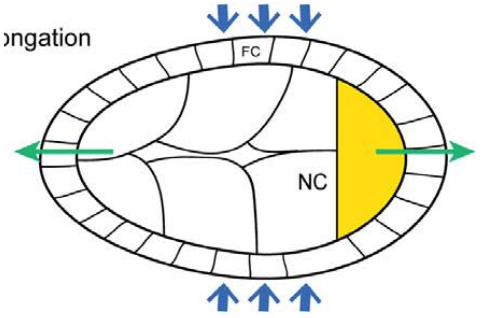
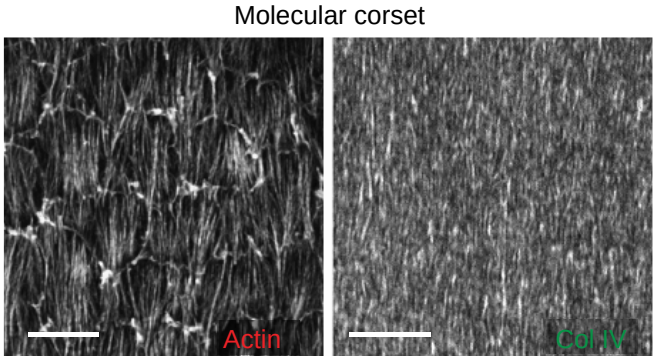
Collective motility and Tissue rotation in vivo

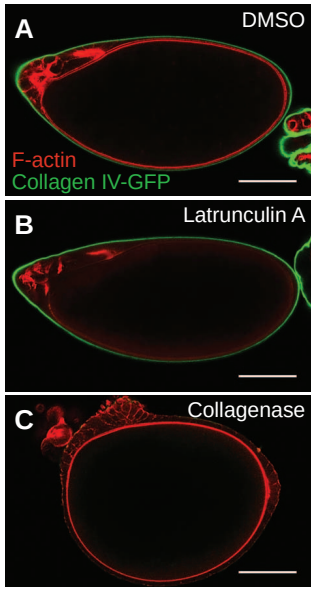
- Hypothesis: A molecular corset constrains egg growth along the antero-posterior axis

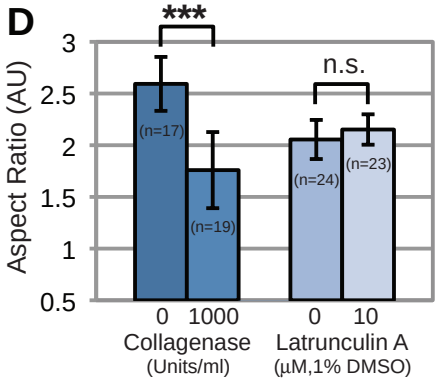






- The corset comprises actin filaments and Collagen IV, yet actin is dispensable for egg elongation, but Collagen is required

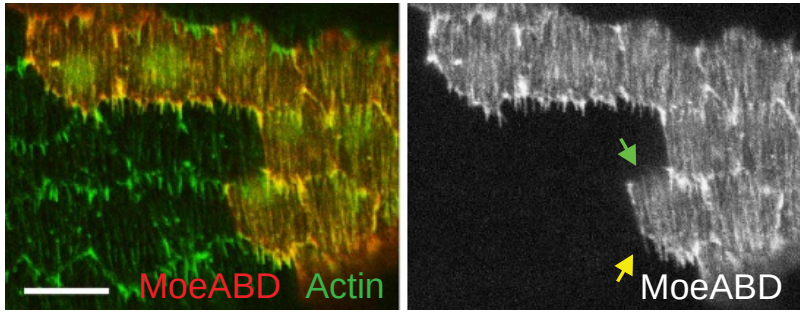




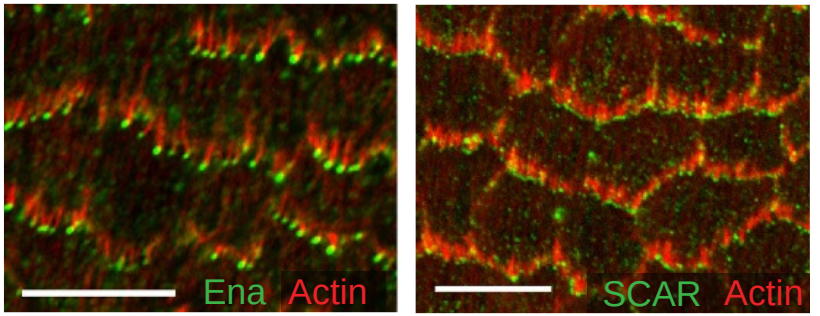
Collective motility and Tissue rotation in vivo

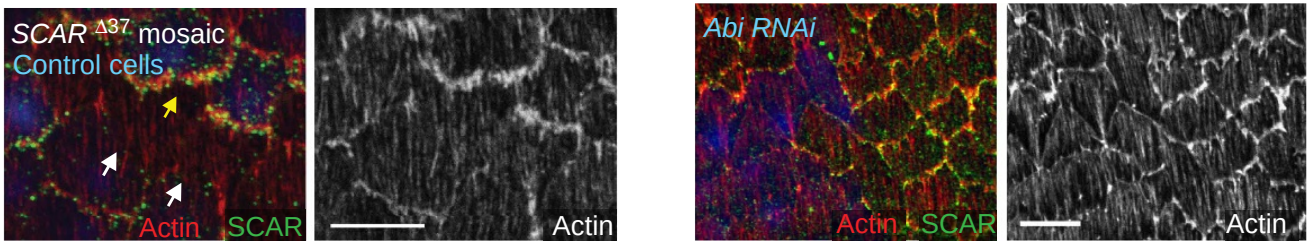
- Question: What drives collective motility during tissue rotation?

- The basal surface of follicle epithelial cells have protrusions at their leading edge: filopodia and lamelipodia



- Ena marks the tip of filopodia
- SCAR (regulator of Arp2/3 and branched actin nucleation) is concentrated at lamelipodia.
- SCAR and Abi, control actin nucleation at the leading edge.



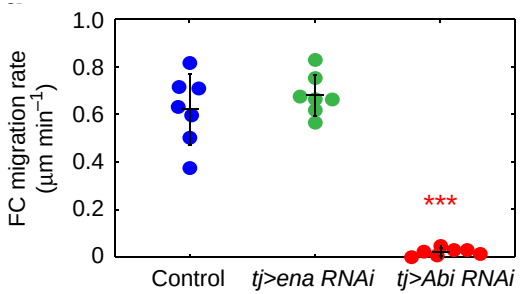


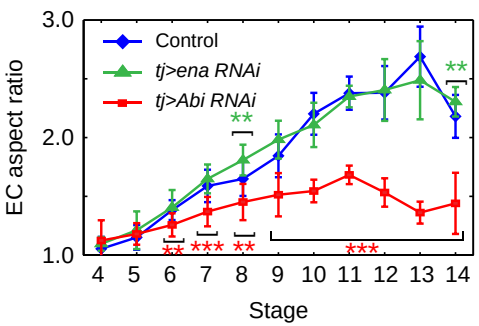
M. Cetera et al. and S. Horne-Badovinac. *Nature Communications.* 5:5511 (2014) (DOI: 10.1038/ncomms6511)

Collective motility and Tissue rotation in vivo

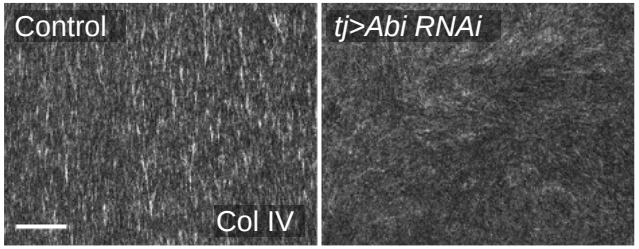
- Branched actin nucleation at the leading edge is required for tissue rotation and global tissue polarization

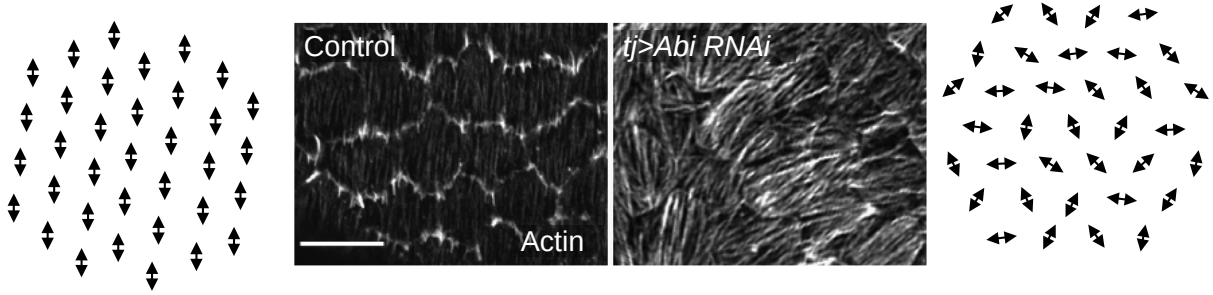
- SCAR and Abi are both required for migration of follicle epithelial cells and tissue rotation
- And for tissue elongation
- ENA and filopodia are dispensible for migration and elongation.





- In the absence of lamelipodia (Abi KD), follicle epithelial cells have an intrinsic axial organisation but fail to coordinate the emergence of a global polarity at the tissue level.
- Collagen IV is no longer globally polarized.



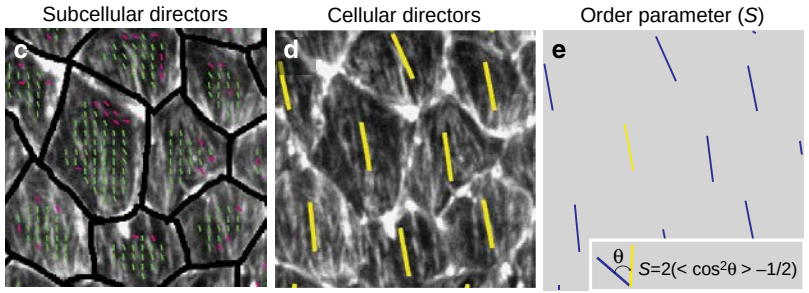


M. Cetera et al. and S. Horne-Badovinac. *Nature Communications.* 5:5511 (2014) (DOI: 10.1038/ncomms6511)

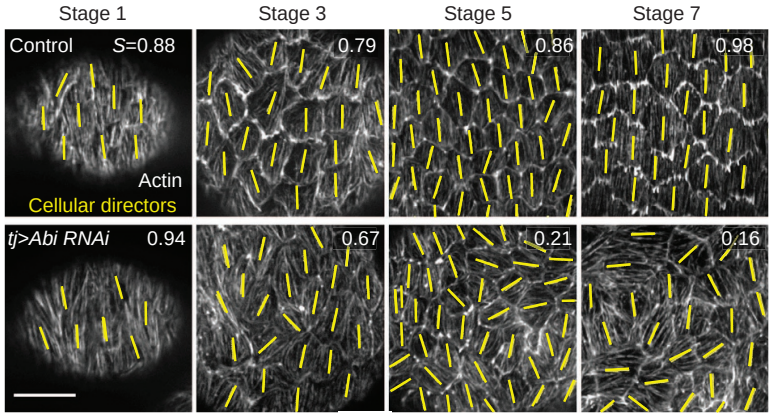
Collective motility and Tissue rotation in vivo

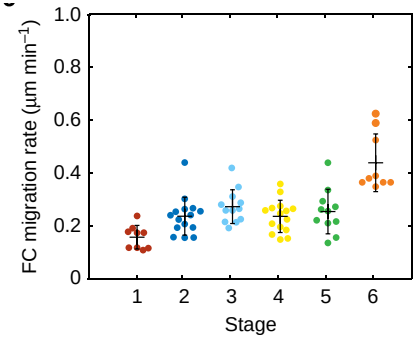
- Cell alignement requires collective cell migration

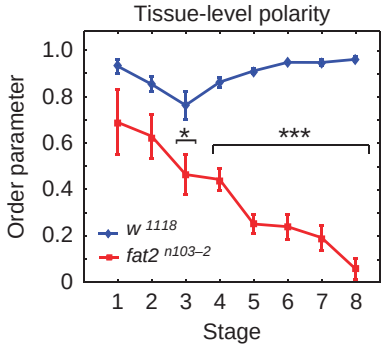
- Nematic order of actin bundles in follicle epithelial cells

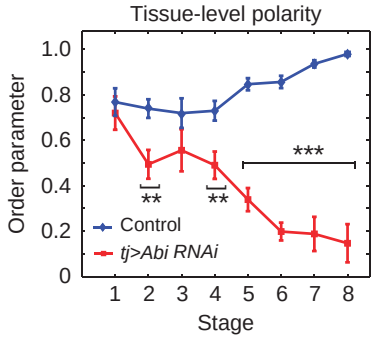


- Nematic order emerges early and persists
- Cell migration (controlled by Abi and the adhesion molecule Fat2) is required for maintenance of cell ordering/alignement.
- Early ordering is independent of tissue rotation









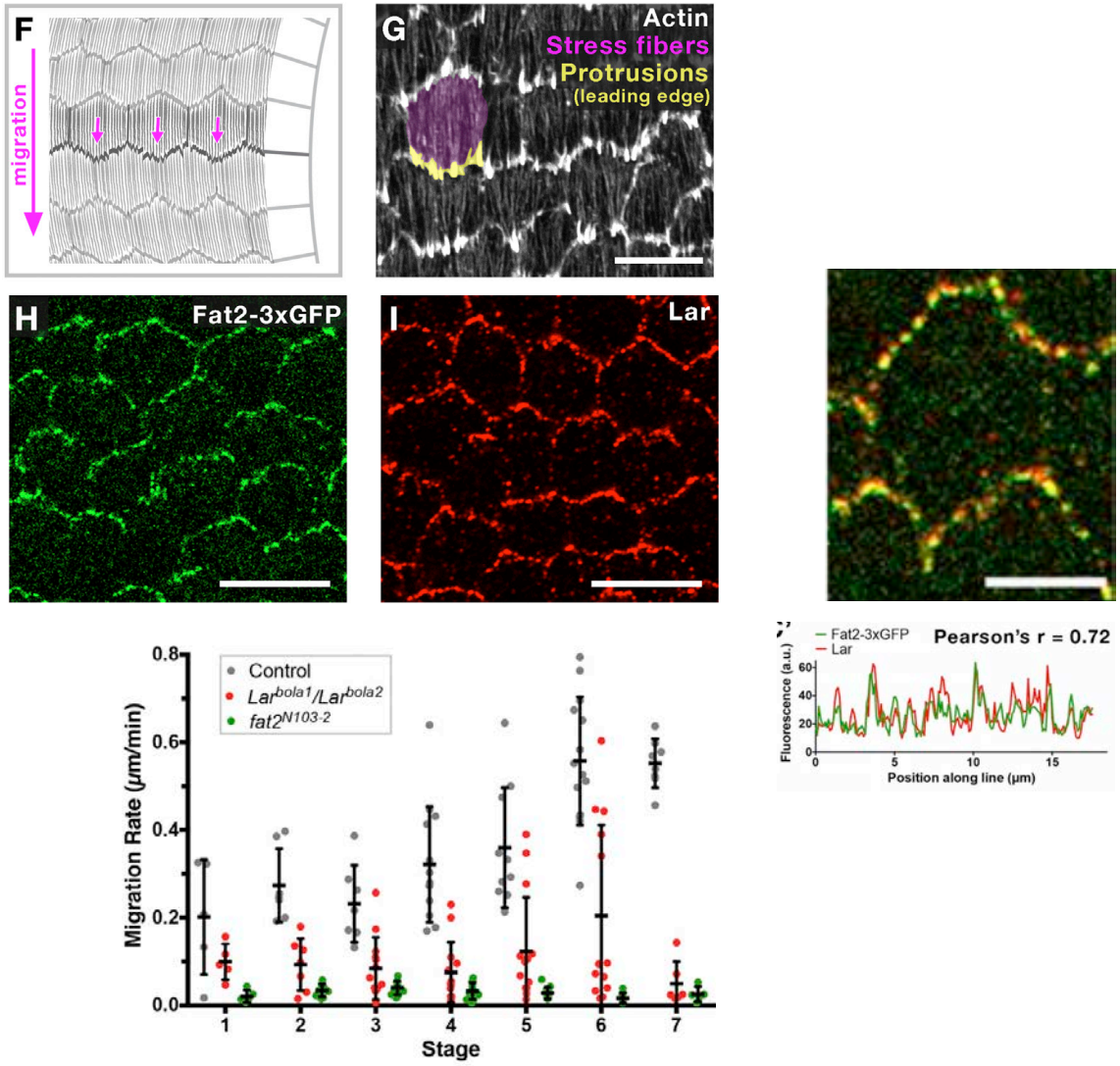
M. Cetera et al. and S. Horne-Badovinac. *Nature Communications.* 5:5511 (2014) (DOI: 10.1038/ncomms6511)

Collective motility and Tissue rotation in vivo

- Coordination of cell polarization at the tissue scale by cell signaling

- The adhesion protein Fat2 and the cytoplasmic protein Lar are localized at cell contacts at the base of follicle epithelial cells

- Fat2 and Lar both required for collective cell motility and tissue rotation

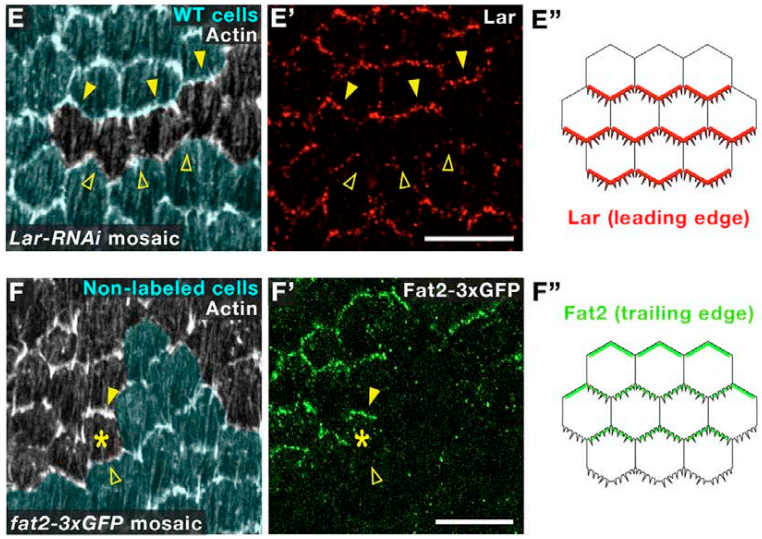


K. Barlan et al., and S. Horne-Badovinac. *Developmental Cell* 40, 467–477 (2017)

Collective motility and Tissue rotation in vivo

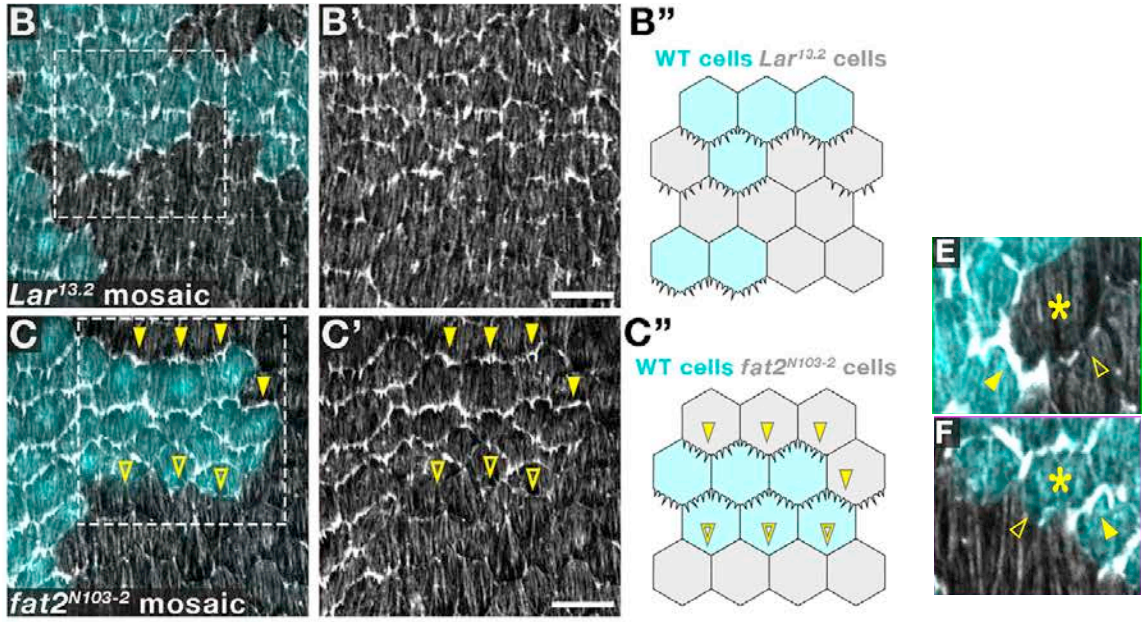
- Coordination of cell polarization at the tissue scale by cell signaling

- Mosaic experiments reveal that Lar localizes at the leading edge and Fat2 at the trailing edge of follicle epithelial cells



Wildtype cells are marked in blue
Mutant cells are black

- Lar is required for cell protrusions at the leading edge cell autonomously
- Fat2 is required non-cell autonomously: it promotes protrusions in cell *behind* from the contacting, trailing edge.

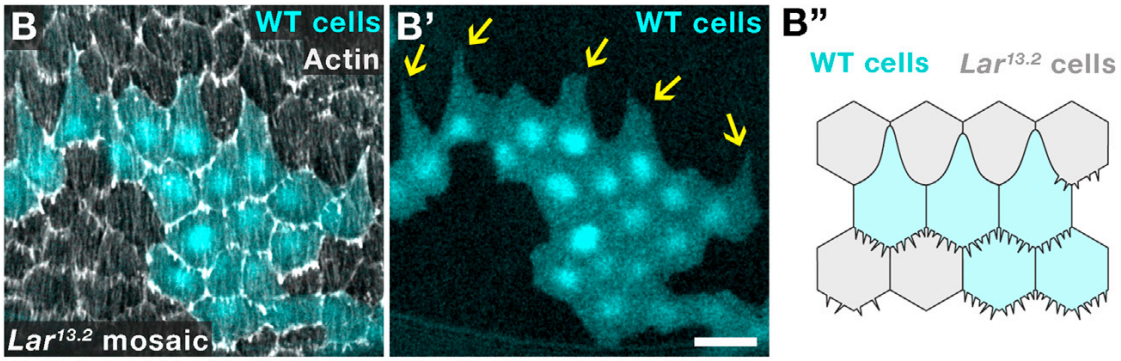


K. Barlan et al., and S. Horne-Badovinac. *Developmental Cell* 40, 467–477 (2017)

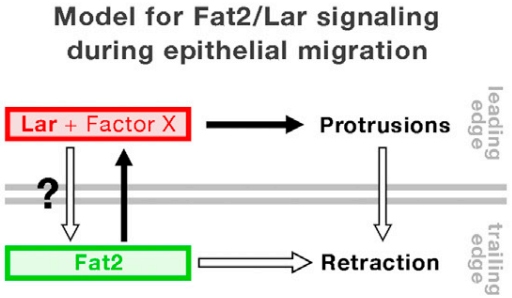
Collective motility and Tissue rotation in vivo

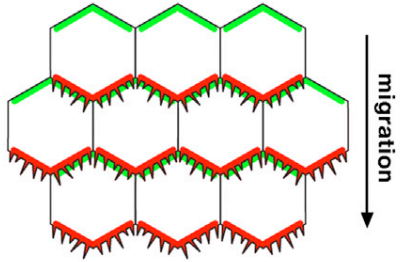
- Coordination of cell polarization at the tissue scale by cell signaling

- Lar promotes non cell autonomously cell retraction at trailing edge of anterior cell



- Fat2 is required for proper polarization of Lar. But Lar is only weakly required for Fat2 polarization.
- Parallel Semaphorin-5c Plexin A signaling has the same function.



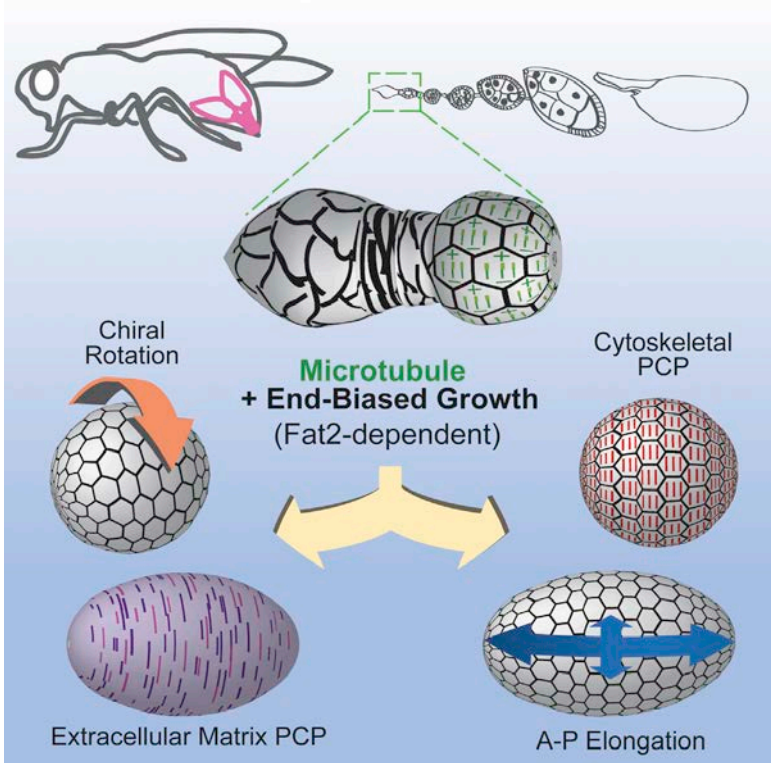


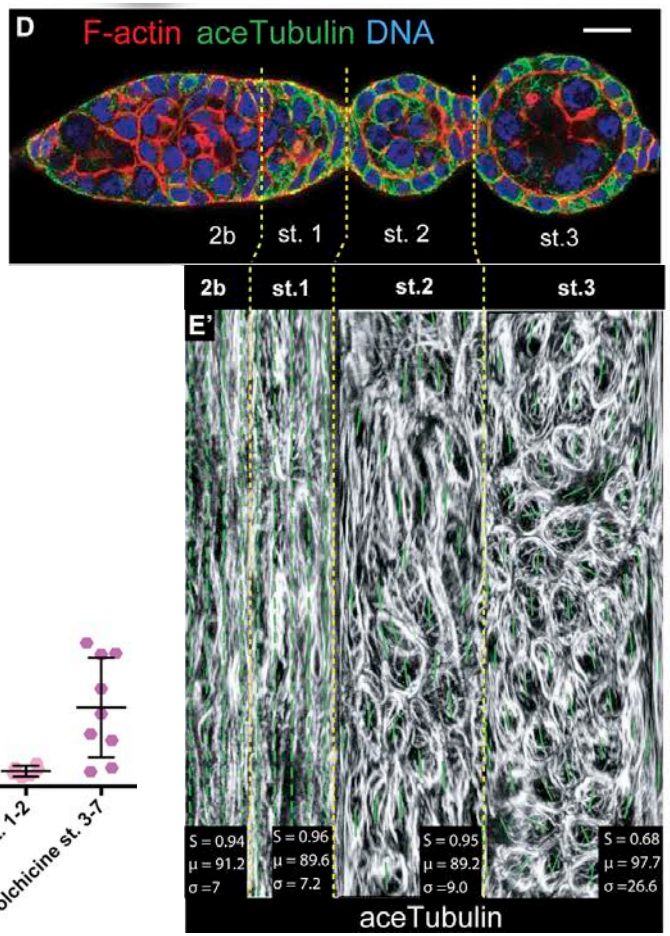
Fat2-Lar: K. Barlan et al., and S. Horne-Badovinac. *Developmental Cell* 40, 467–477 (2017)

Sema5c-PlexA: C. Steven et al and S. Horne-Badovinac. *Current Biology* 29, 908–920 (2019)

Collective motility and Tissue rotation in vivo

- Symmetry breaking in the egg chamber involves microtubule biased growth
- Fat2 is required for microtubule biased growth





DY. Chen et al., and D. Bilder. *Cell Reports* 15, 1125–1133 (2016)

Collective motility and Tissue rotation in vivo

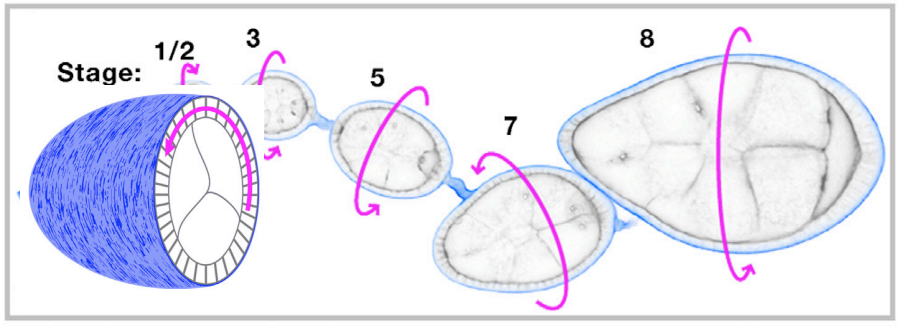
- **Conclusions:**

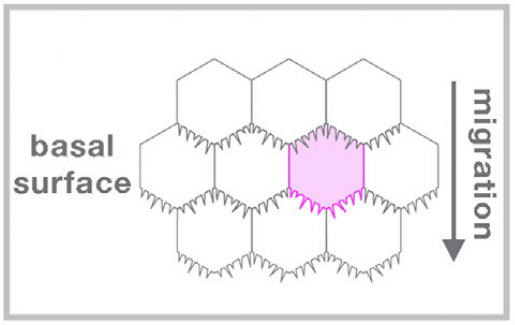
— Developmental context:

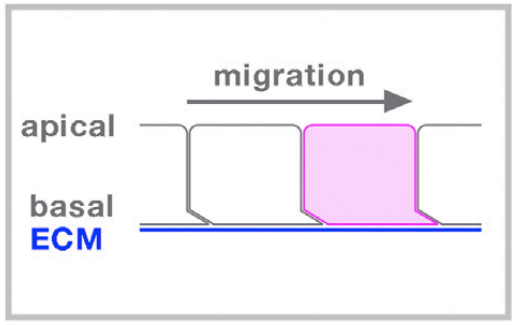
- Collective motility of epithelial sheet drives tissue rotation (periodic boundary condition)
- Tissue rotation patterns the assembly of a molecular corset in the surrounding ECM layer consisting of Collagen IV.
- This molecular corset is required for elongation of the growing egg chamber.

— Mechanisms:

- Cells are intrinsically polarized with a leading edge and a trailing edge.
- Cells are also collectively organized to yield a nematic order within the tissue.
- Global polarization involves first microtubule alignment via biased +end growth mediated by the adhesion protein Fat2.
- This is followed by local cell coordination via two planar polarity systems: Fat2-Lar and Sema5c-PlexA.



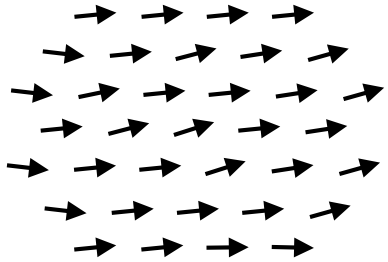




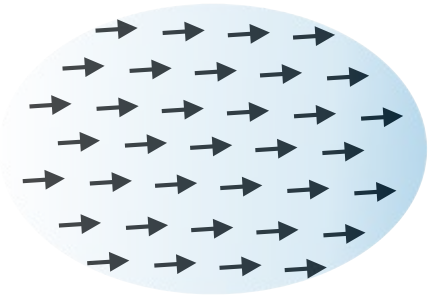
Collective motility without leaders

• Conclusions

- Intrinsic capacity to break symmetry at cellular scale
- Cell interactions reorganize local polarities and lead to local ordering
- This involves coupling between curvature, velocity and polarity (the mechanisms are not understood, phenomenological model)
- Role of local polarity coupling mechanisms using PCP signaling systems
- There is no need for long range ordering (by mechanochemical gradients, eg, chemotactic. Cues or durotactic signals).
- Yet such long range cues could potentially increase robustness or velocity alignments (ie. Increase the velocity and polarity correlation lengths).



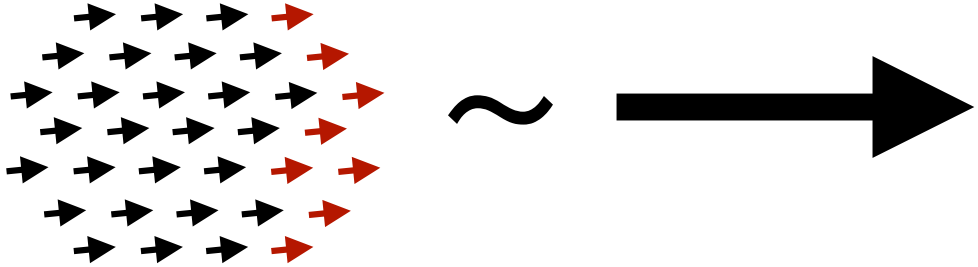
Purely self-organized



Biased & self-organized

Conclusions

- Collective migration with leaders:



- Collective migration without leaders: