Erk signaling activity is enhanced during collective migration on corrugated substrates

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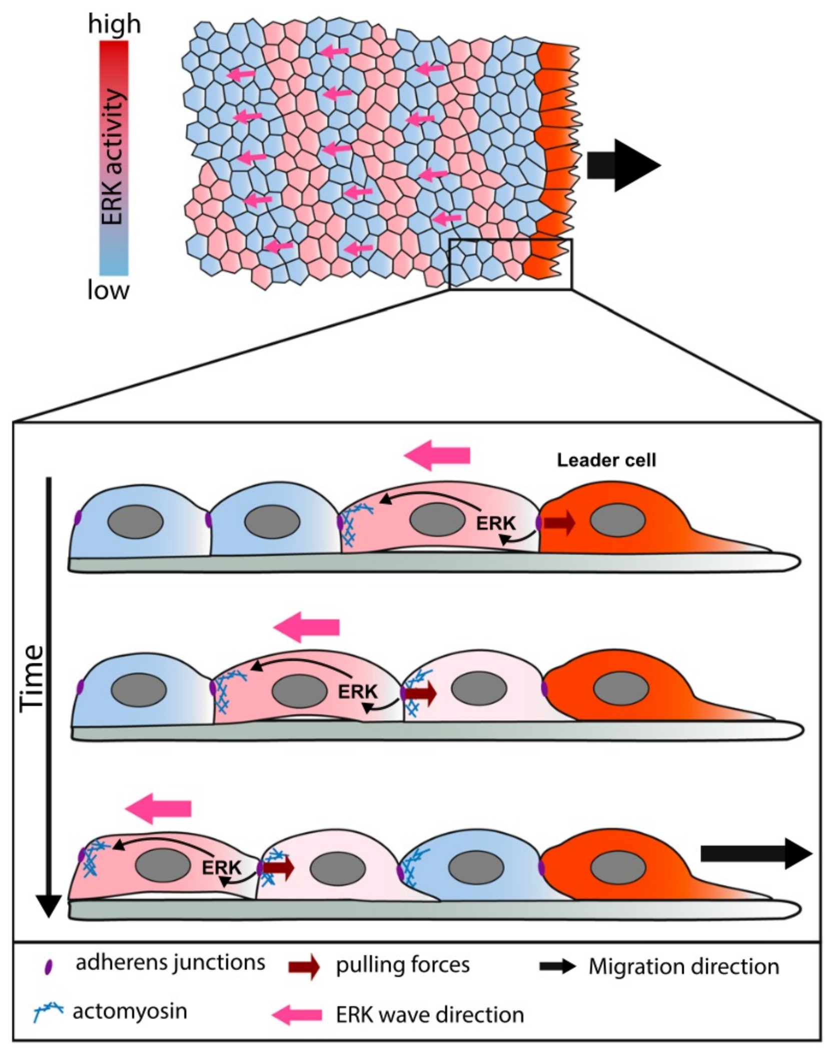
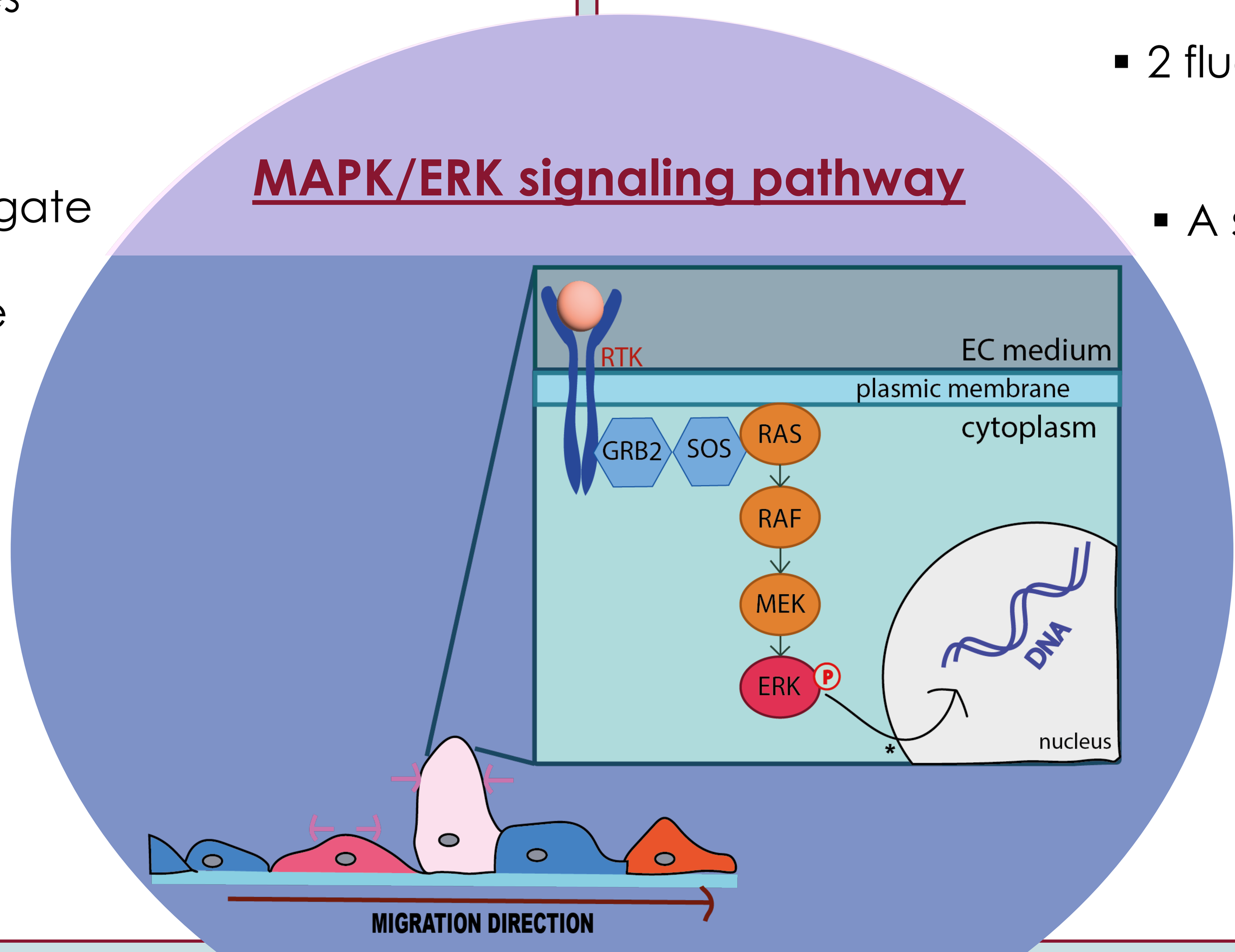
Collective migration plays a pivotal role in numerous epithelial tissues, under both physiological and pathological conditions. Recent evidence suggests a correlation between the activation waves of extracellular signal-regulated kinase (ERK) and cell deformation, which together orchestrate collective cell migration. Additionally, emerging evidence indicates that localized changes in matrix curvature can influence the migration of individual epithelial cells (known as curvotaxis). However, the precise mechanism by which local changes in curvature modulate ERK propagation and contribute to coordinating collective movement remains unclear. Here we utilize a photopolymerization technique to create well-defined corrugation patterns of varying wavelengths in soft hydrogels, thereby mimicking the multiscale curvature found in human tissues. To elucidate the role of ERK waves in directing cell migration, we employ Förster resonance energy transfer (FRET)-based biosensor in MDCK cells, conducting time-lapse experiments lasting 24 hours on culture substrates featuring both flat and corrugated regions. Our findings reveal distinct flow directions within the same epithelial tissue, transitioning from flat to corrugated hydrogels. Furthermore, we demonstrate that ERK activity is significantly heightened in corrugated regions, suggesting a mechanism that facilitates collective cell migration on curved substrates.

ERK activity couples to polarization to direct collective cell migration



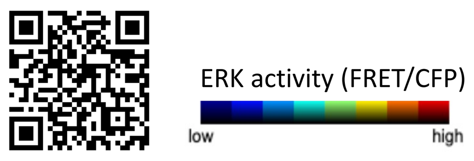
- Cell stretching promotes ERK activity via mechanical forces through adherens junctions
- ERK waves propagate towards the back side in a opposite direction of migration
- High-persistent ERK activity is present at the leader edge

Crozet F. *et al.*, *Cellular and Molecular Life Sciences*, 2023



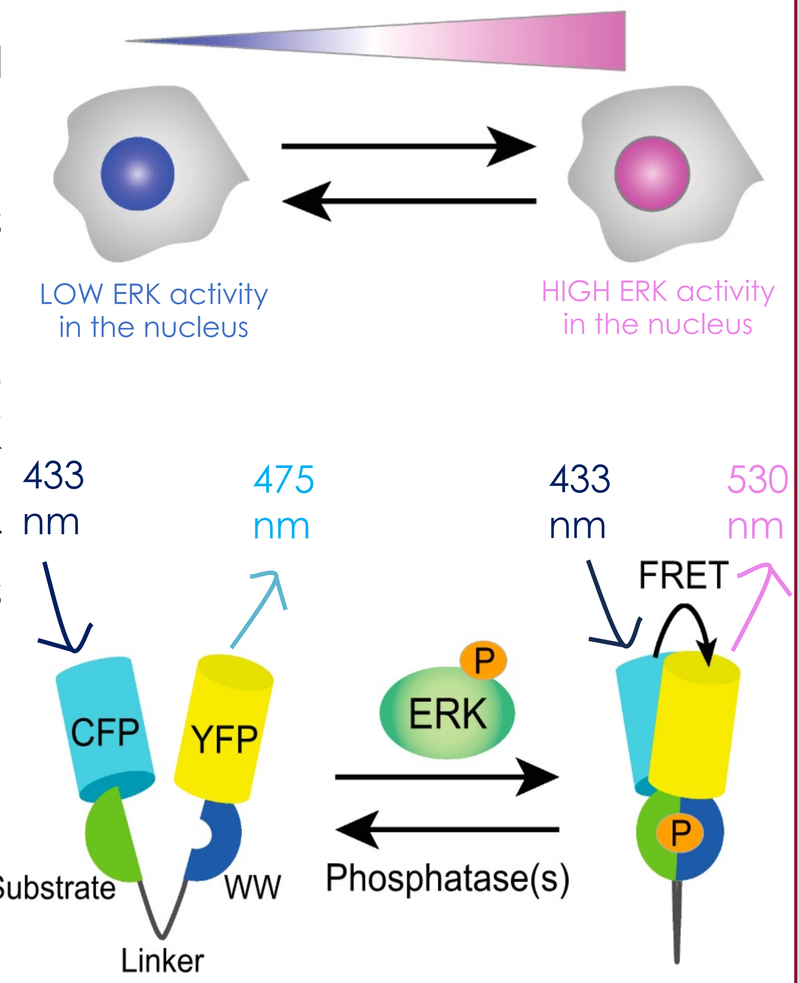
*Modulation of DNA gene transcription in the nucleus

ERK activity is quantified by FRET biosensor



EKAREV (Erk signal activity reporter) :

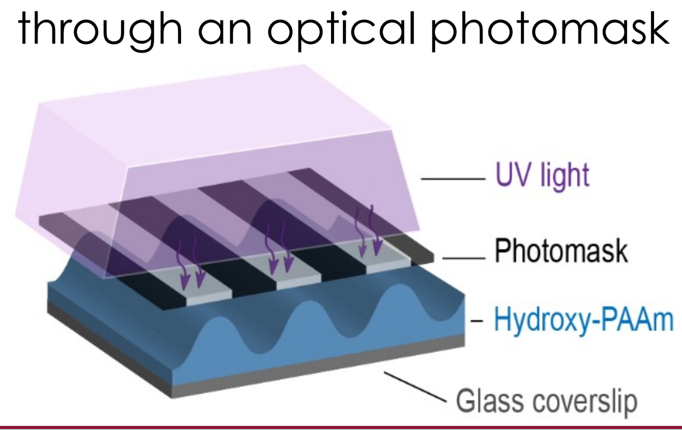
- 2 fluorescent proteins (CFP & YFP)
- A specific substrate for ERK
- A domain that binds to this substrate when phosphorylated



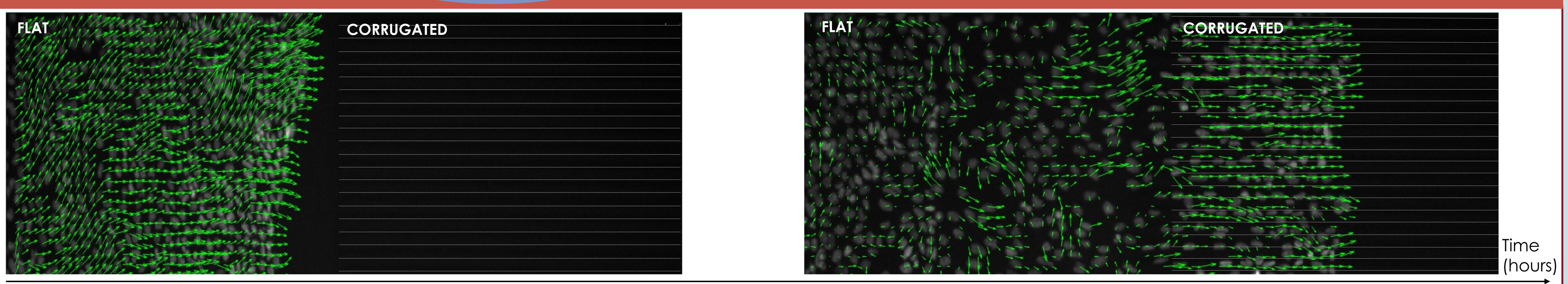
Hirashima T. *et al.*, *Biochemical Journal*, 2022

Substrate corrugation patterns control the direction of the collective cell flow

UV photo-polymerization of hydroxy-PAAm hydrogels through an optical photomask

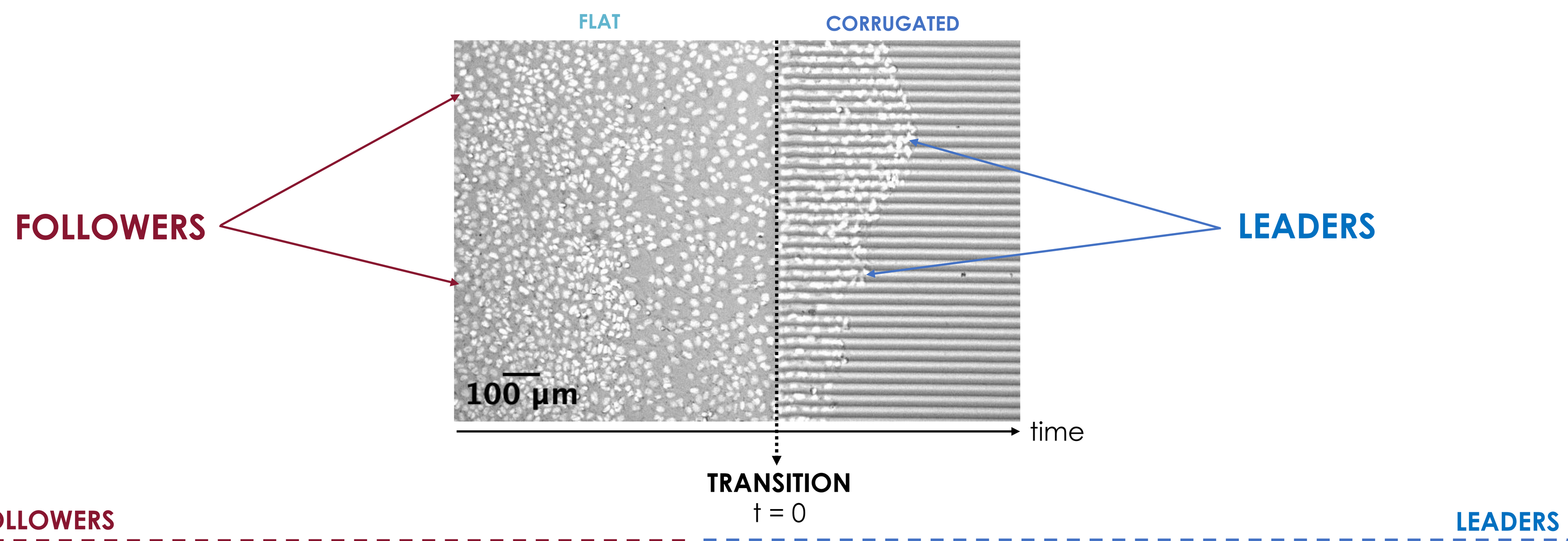


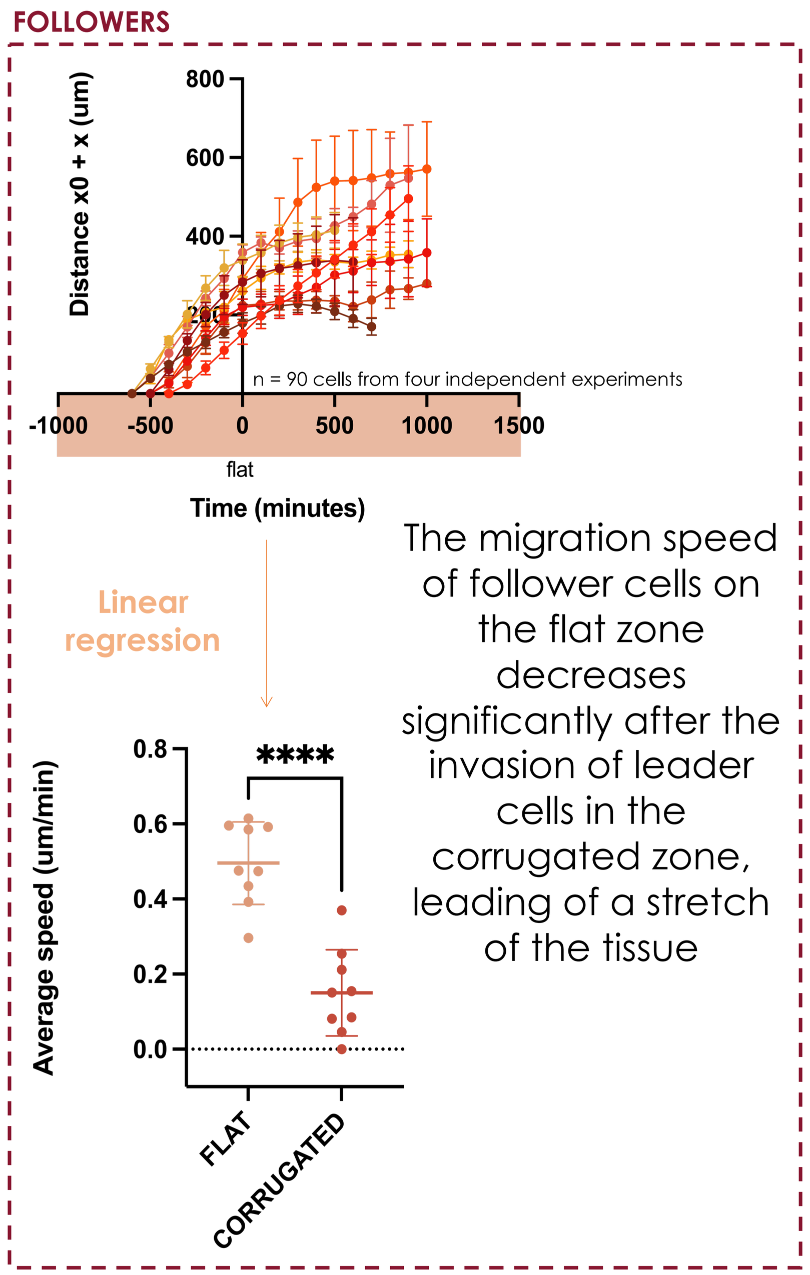
PIV



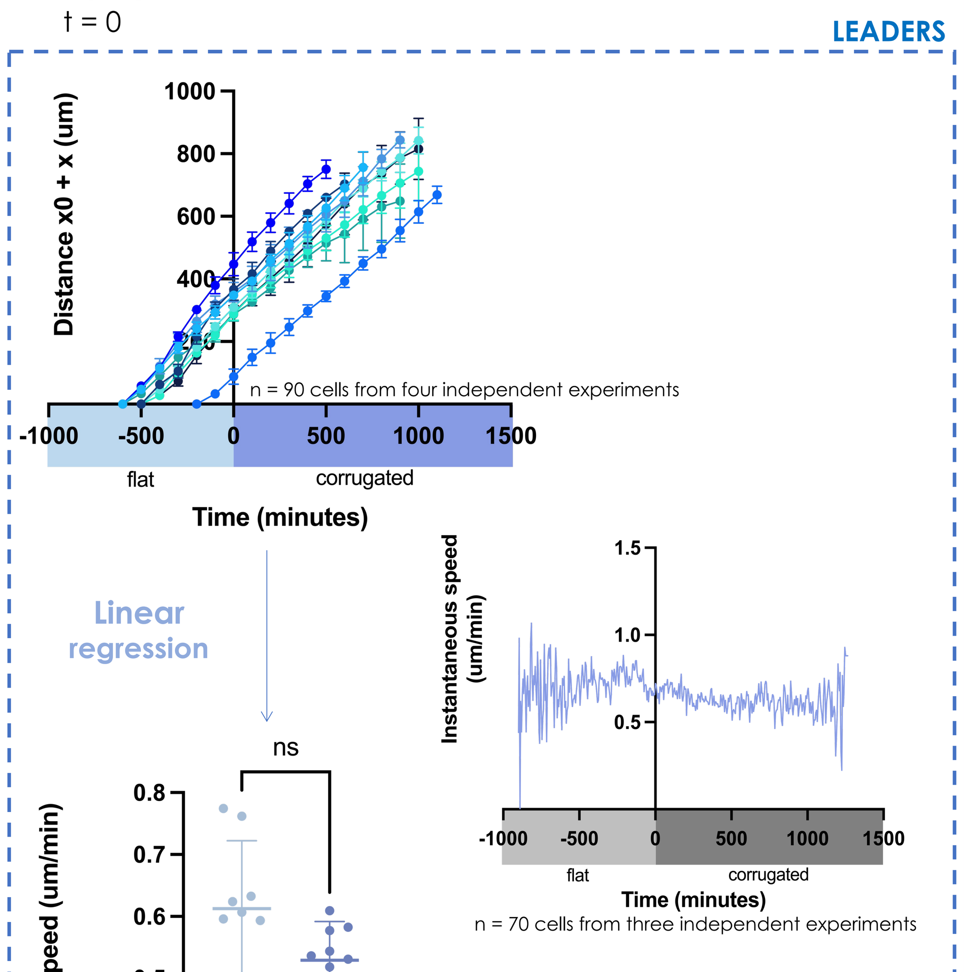
The epithelial flow is oriented parralel to the corrugations, while the tissue on flat zone shows isotropic flows and vortices

Followers slow down after leaders invade corrugations



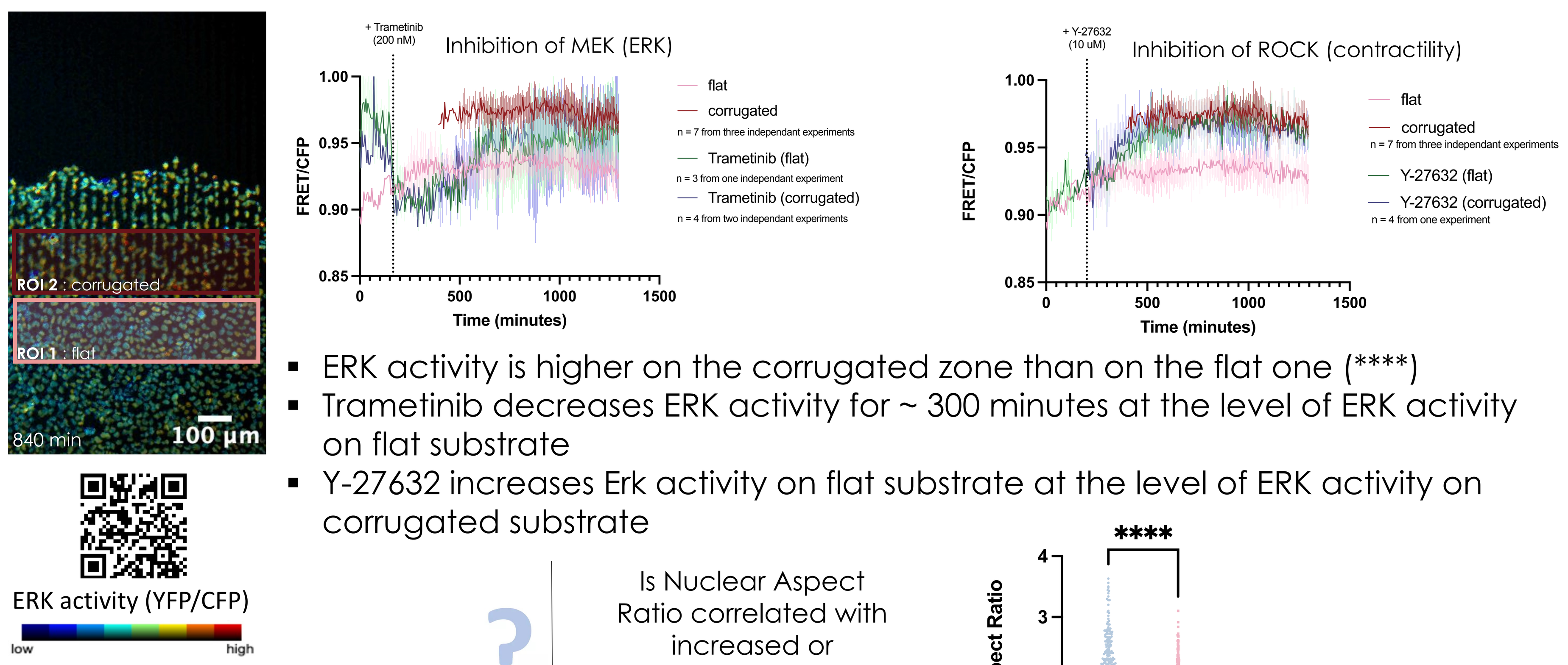


The migration speed of follower cells on the flat zone decreases significantly after the invasion of leader cells in the corrugated zone, leading of a stretch of the tissue

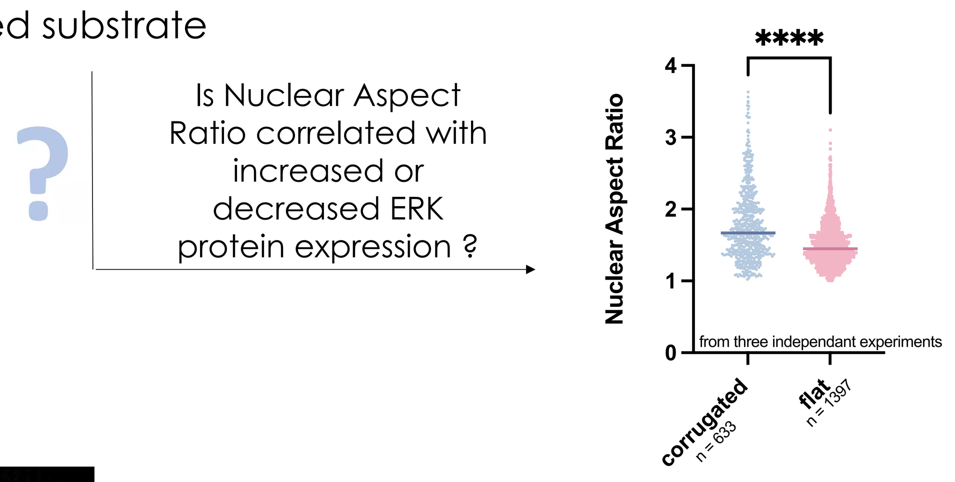


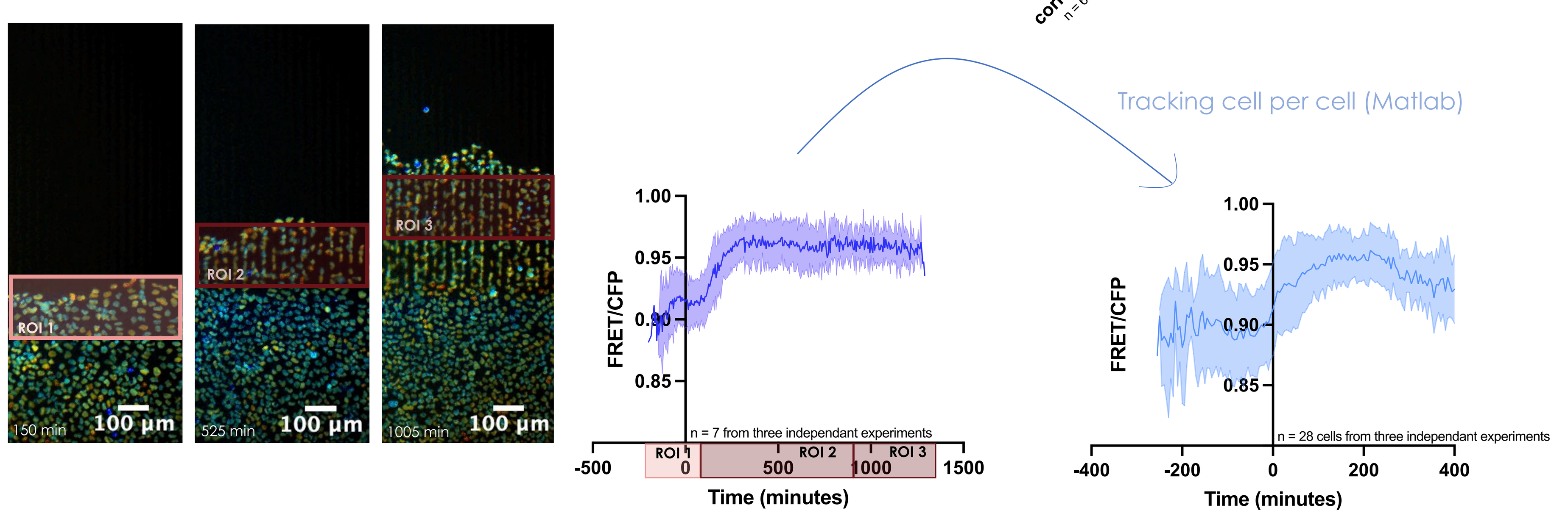
The transition from a flat to a corrugated zone doesn't affect the migration velocity of leader cells

Erk activity: transition from a flat to a corrugated zone



- ERK activity is higher on the corrugated zone than on the flat one (****)
- Trametinib decreases ERK activity for ~ 300 minutes at the level of ERK activity on flat substrate
- Y-27632 increases Erk activity on flat substrate at the level of ERK activity on corrugated substrate





- ERK activity increases when cells enter the corrugated zone
- ERK activity remains higher than the basal level over time on the corrugated zone
- ERK pre-activation time ~ 100 minutes

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