nature

SWISS NETWORK FOR INTERDISCIPLINARY EDUCATION IN CHEMICAL BIOLOGY

Control of osteoblast regeneration by a train of Erk activity waves

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- Live imaging and computational methods for signaling pathway in **regeneration**

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- Models, Concepts, and Mechanisms of Tissue **Regeneration**
- Heart **Regeneration**

Background

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*"Regeneration is a **complex chain of events** that restores a tissue to its **original size and shape**."*

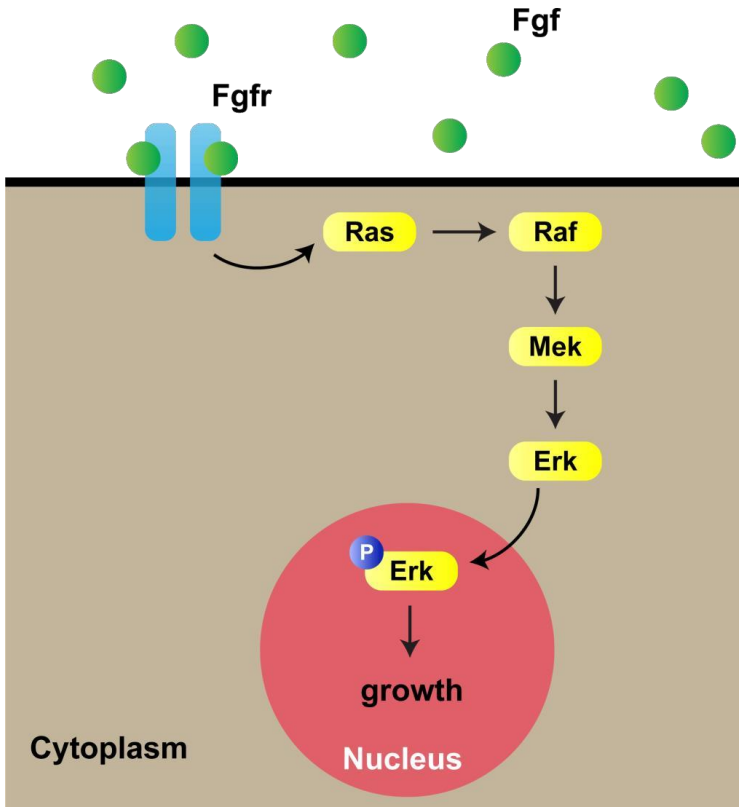

Fig1. Signal pathway of regeneration

Erk signal plays a crucial role for cell growth

Background

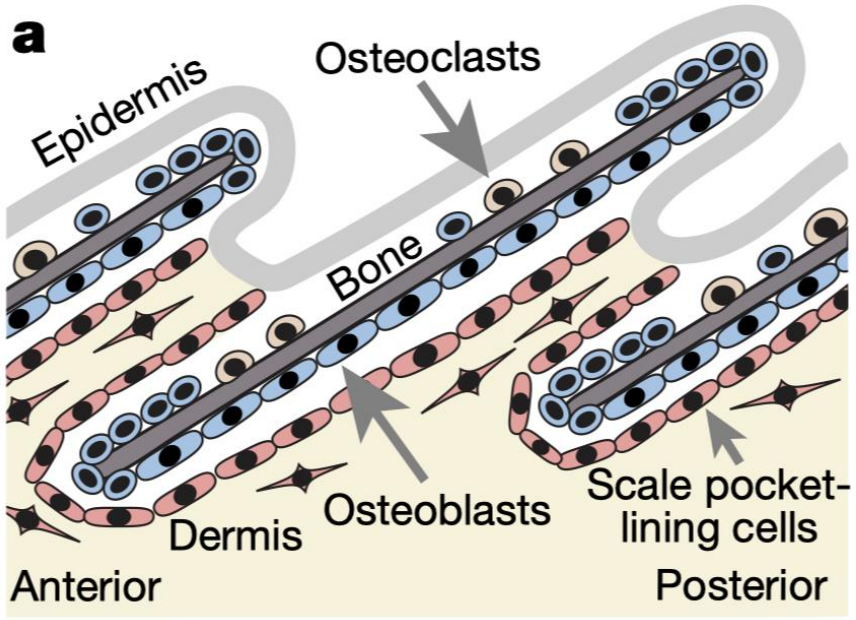

Fig1. Cells in zebrafish scale regeneration

The central Osteoblasts stop proliferation 4 days after plucking and started to grow via **cellular hypertrophy**

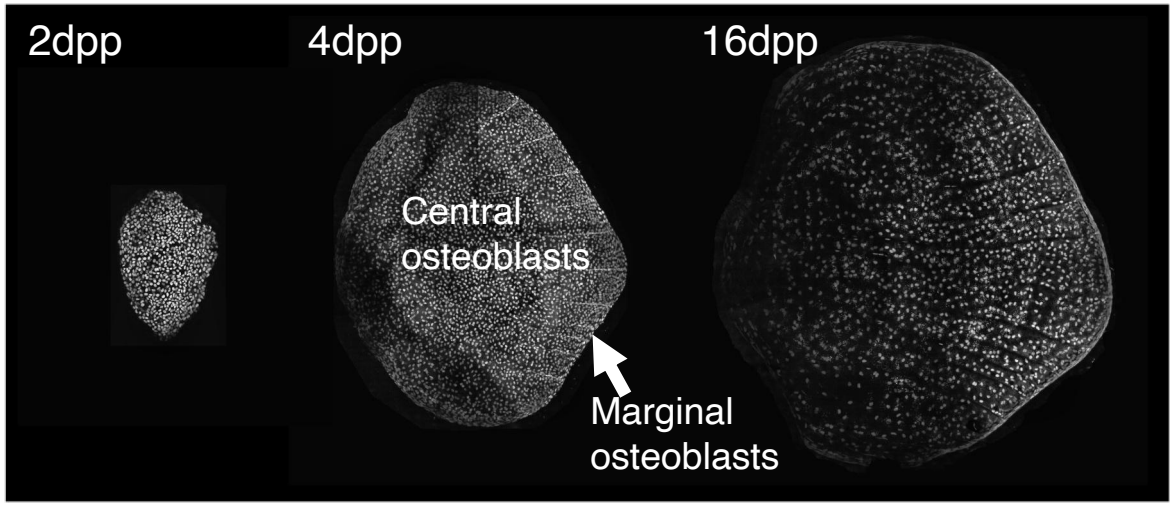

Fig2. Zebrafish scale morphology

- Osteoblasts' key role in **Scale regeneration**
- Similarity to **Mammalian bone formation**

The regeneration after plucking

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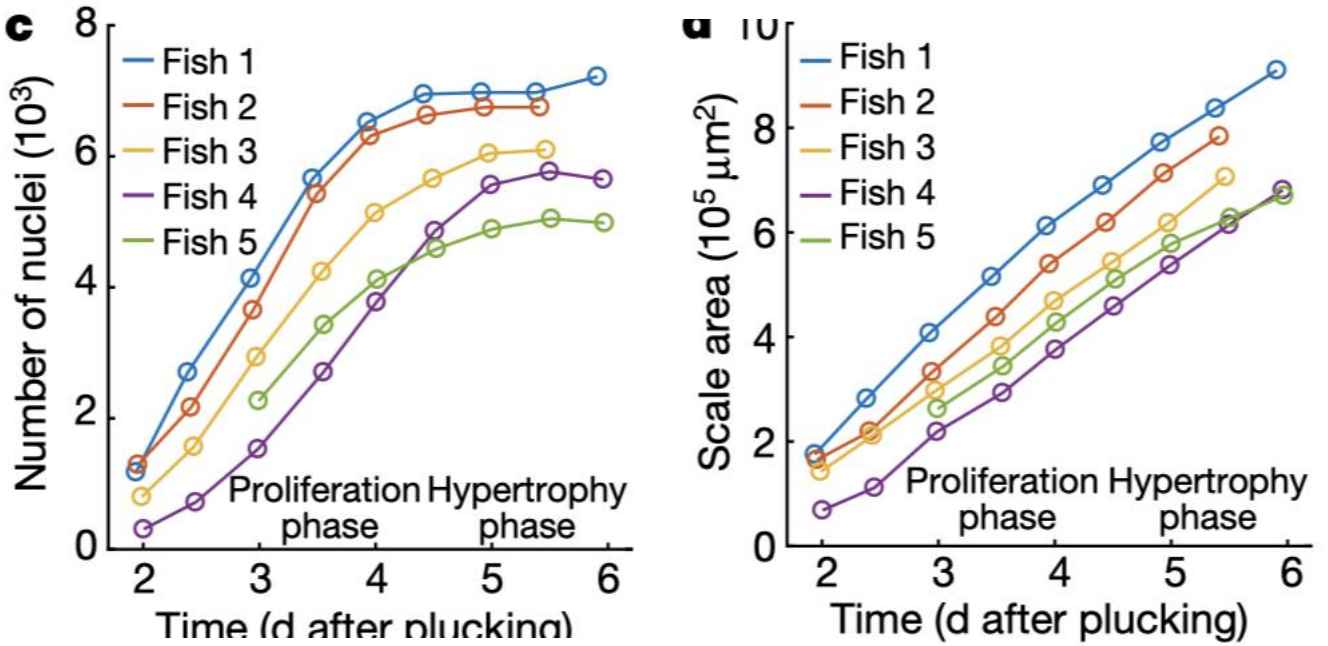

Fig1. Number of nuclei(Left) and scale area(Right) during regeneration

- The tissue expansion are **not uniform**
- The expansion occurred in a **Ring- and Disc-like pattern**

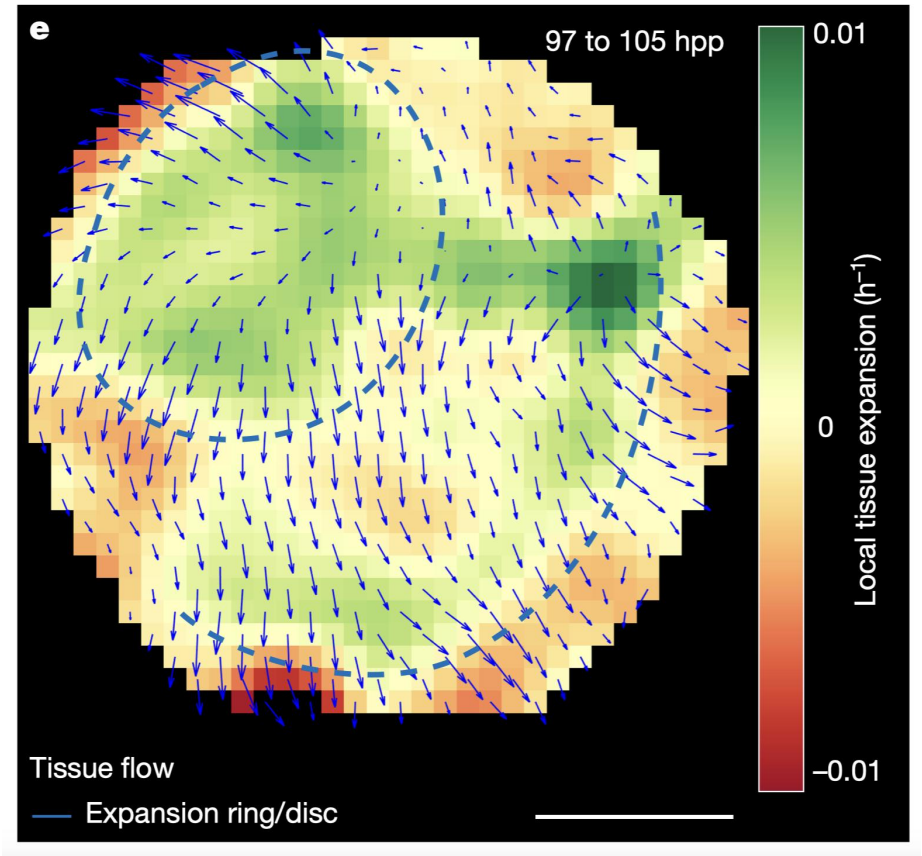

Fig2. Tissue velocity field *v* (tissue flow, blue arrows)

Erk activity highly correlated with the scale regeneration

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"Erk is regulated by many ligand-receptor tyrosine kinase partners, of which fibroblast growth factors (Fgf) and their receptors are candidates in scales."

-------Aman, A

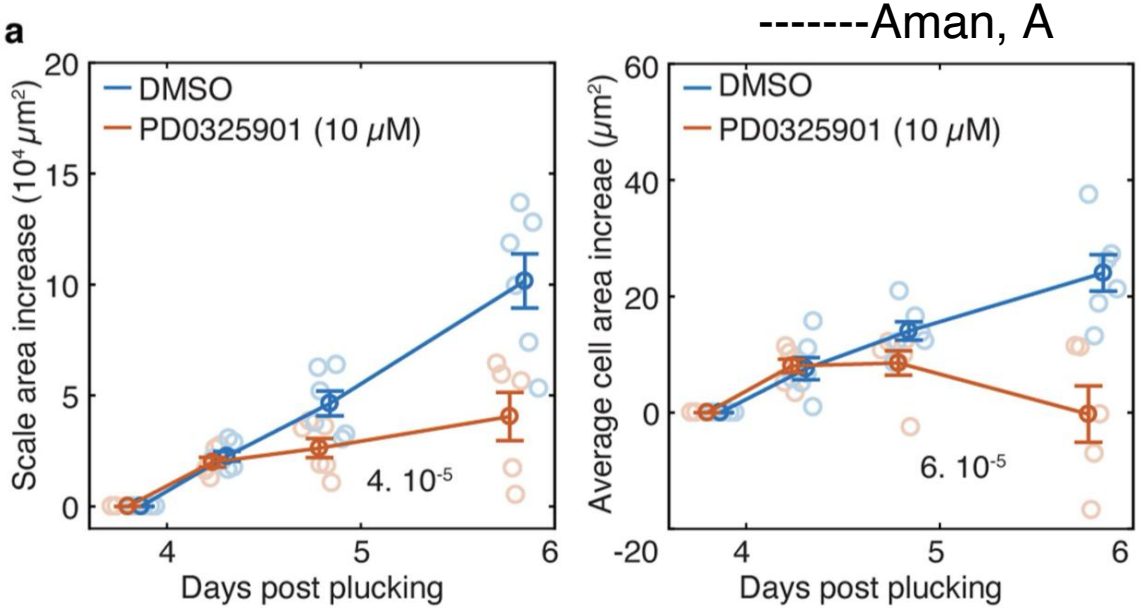

Fig1. Scale area increase (left) and average cell area increase (right) in fish treated with Mek inhibitor

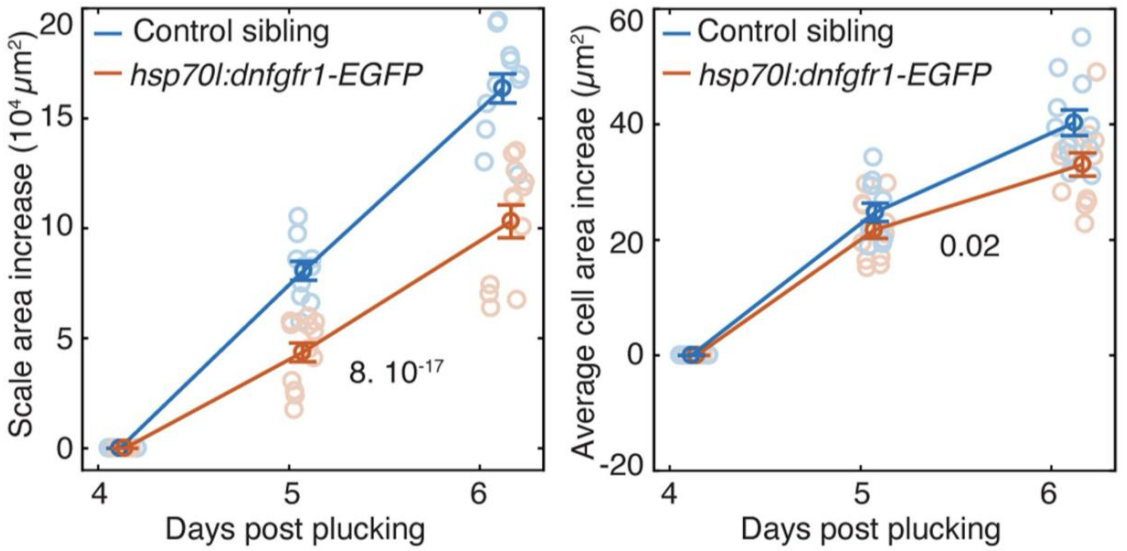

Fig2. Scale area increase (left) and average cell area increase (right) in fish expressing *dnfgfr1-EGFP*

The inhibition of Mek and Fgf could down regulate cell proliferation after plucking, which further prove that the **Erk activity correlated with the regeneration**

The methods to visualize Erk activity in real time

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*"The challenges of visualizing dynamic cell behaviours and signalling pathways **in real time** have limited the ability to investigate mechanisms of regeneration in adult animals."*

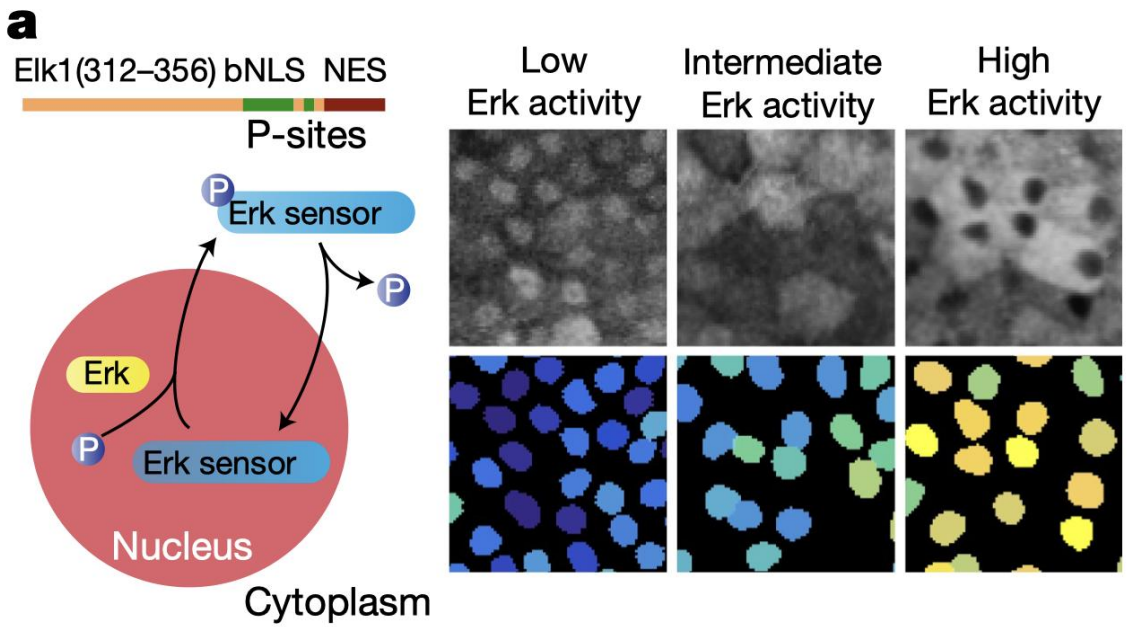

Fig1. Schematic of the Erk sensor

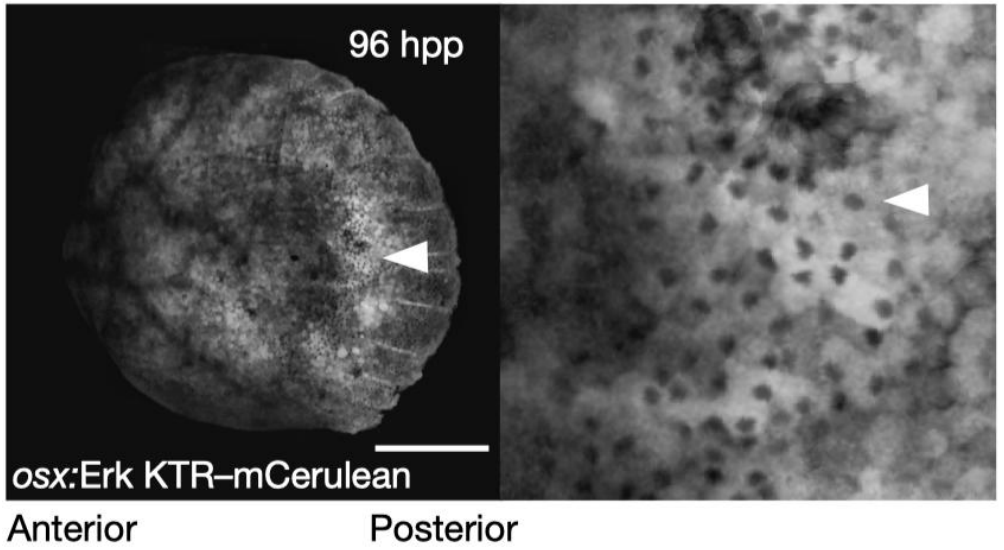

Fig2.Erk sensor in a regenerating scale. Arrowheads, ring of cells in which Erk is active

This methods alow us to **quantify the Erk activity** in the Scale at **any time** point

The Erk Signaling activity was high for 1-3 days after injury

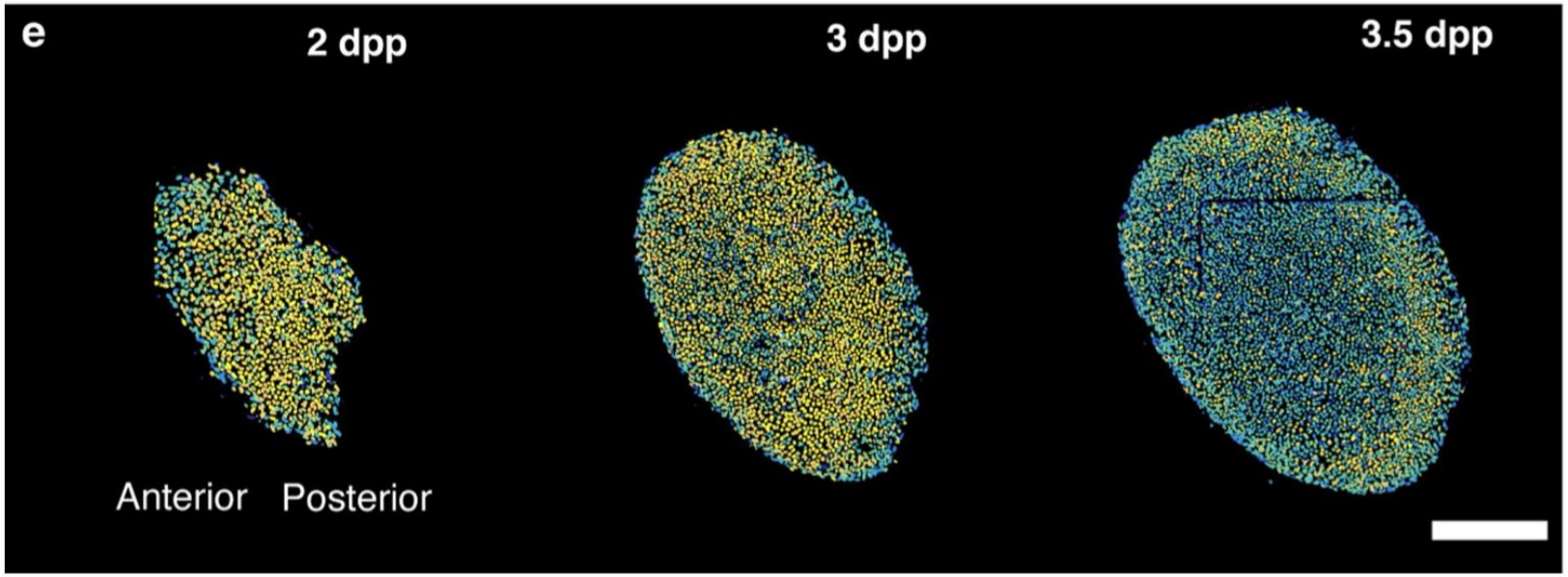

Fig1.Erk sensor in a regenerating scale. Arrowheads, ring of cells in which Erk is active

- The signal started to **diminish** after 3 days of plucking
- The Erk activity was high **for 1-3 days** after injury

The Erk Signaling activates in a similar spatial pattern to that of tissue-expansion

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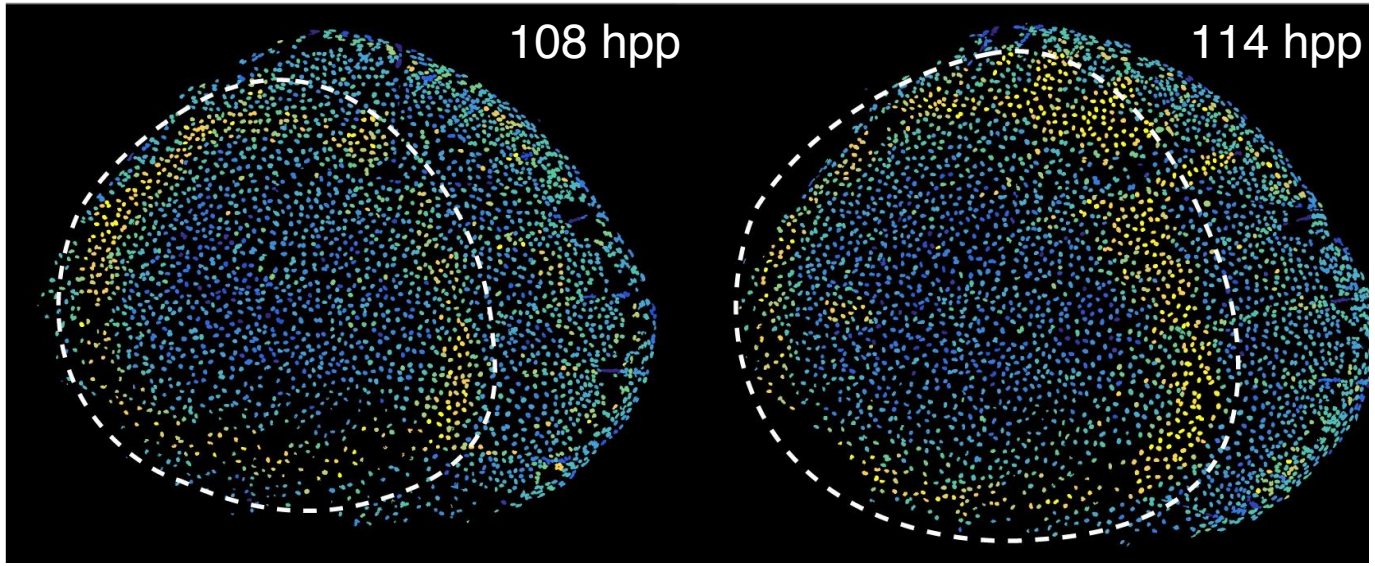

Fig1.Erk sensor in a regenerating scale

- The Erk activity was high **for 1-3 days** after injury
- After that the Erk signal will activate in a **ring-like region**

- The activision of Erk is highly similar to the pattern of **tissue expansion**

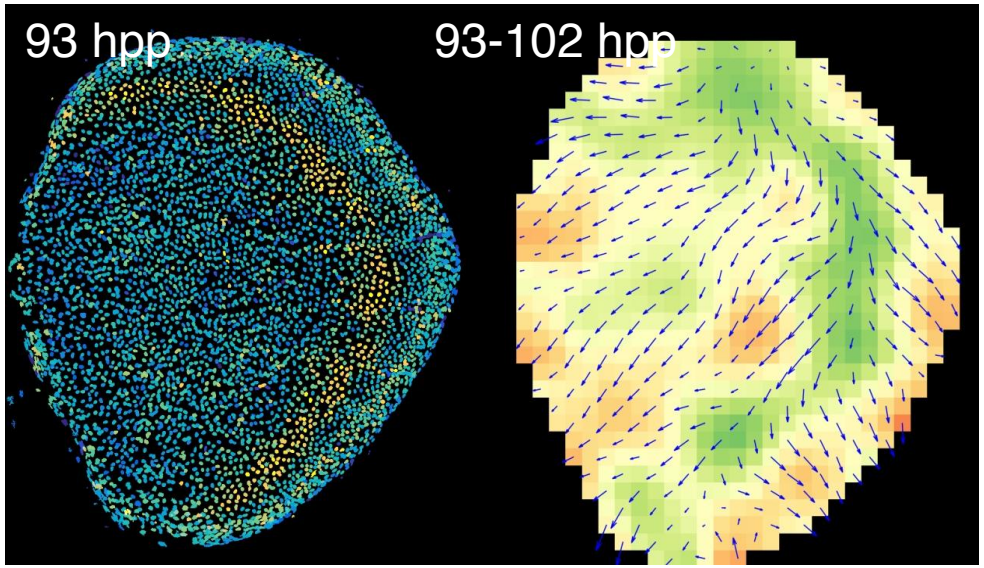

Fig2. Map of Erk activity and tissue velocity

The ring-like Activision of Erk travels across the Scale

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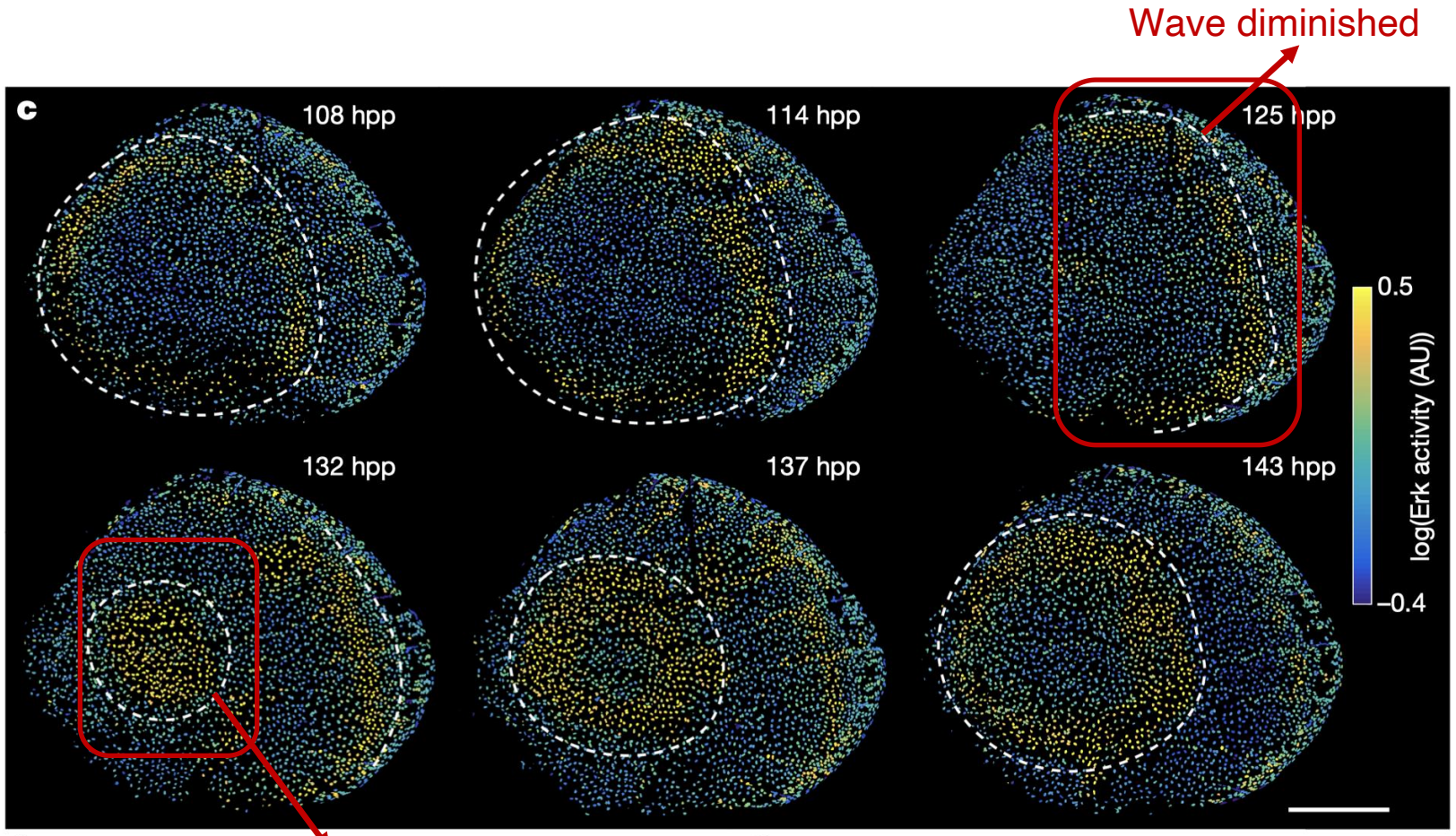

Fig1. Quantification of Erk activity at different time points

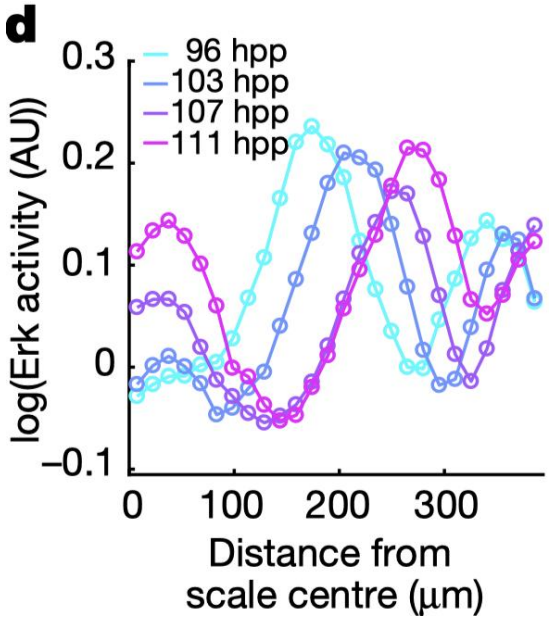

Fig2. Profile of a wave of Erk activity

- Rings of high levels of Erk activity **travel across the scale** moving from one cell to another
- The source of the wave at the **center** and move towards its periphery

Erk signaling is activated in a series repeated concentric waves

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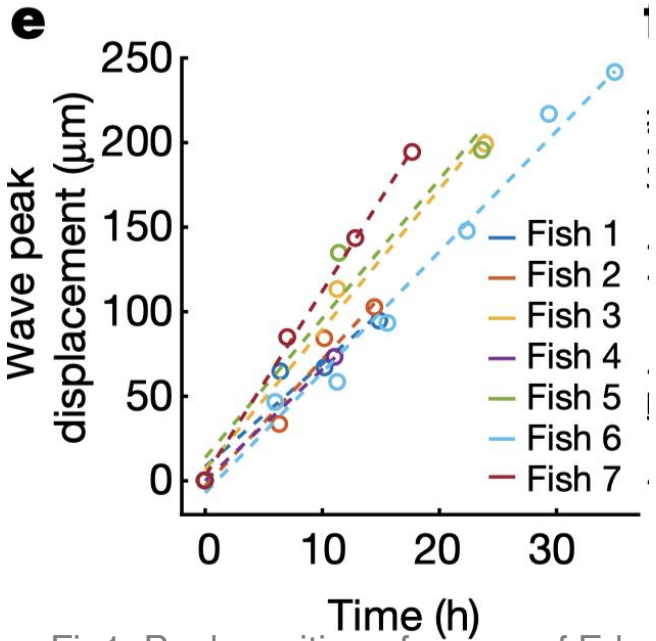

Fig1. Peak position of waves of Erk activity at 4–5 dpp.

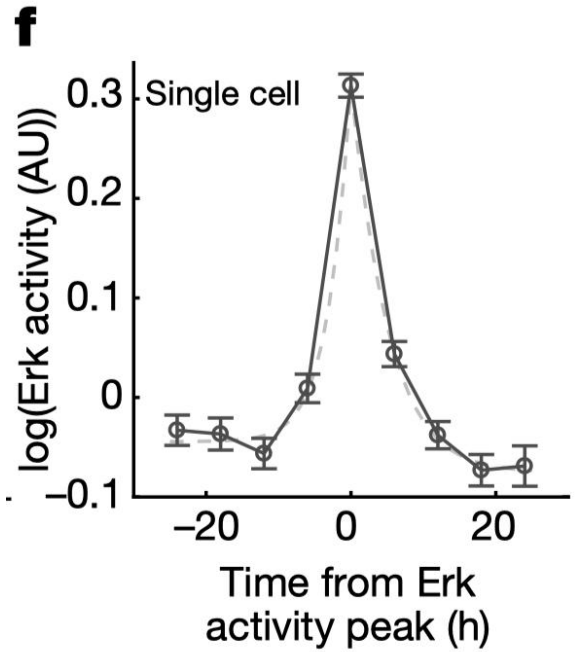

Fig2. Erk activity in tracked individual central osteoblasts

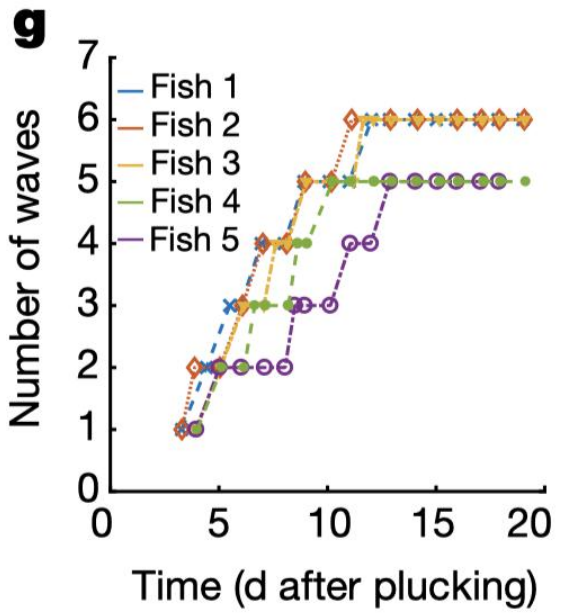

Fig3. Cumulative number of waves during regeneration

- The Erk activity spread outward at **a consistent speed** during regeneration
- Erk signal **impact each cell transiently** and quickly returned to normal
- Erk wave generation stopped at **5 or 6**

How Erk activity organized in Traveling waves?

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*"Diffusible signals can generate excitable '**trigger waves**' in reaction–diffusion systems that include positive and negative feedback"*

-----Murray, J. D

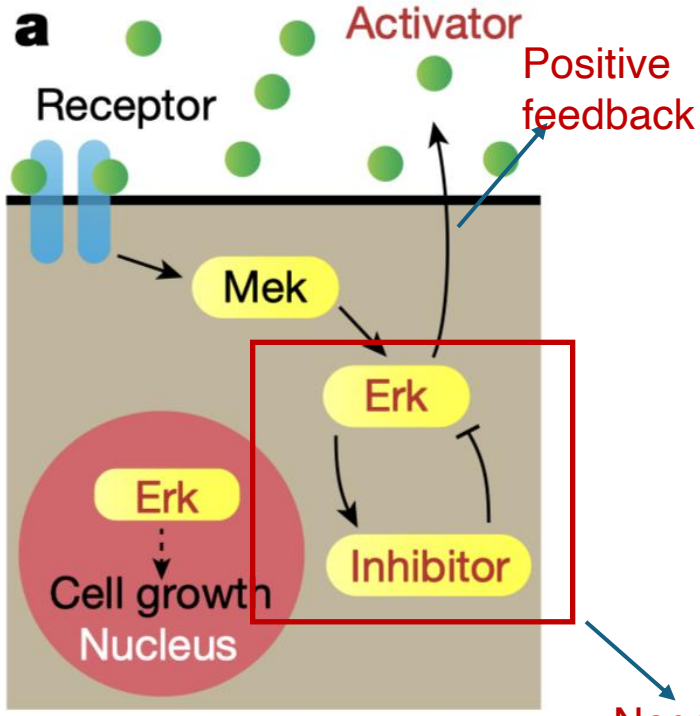

Fig1. Schematic of reaction-diffusion system

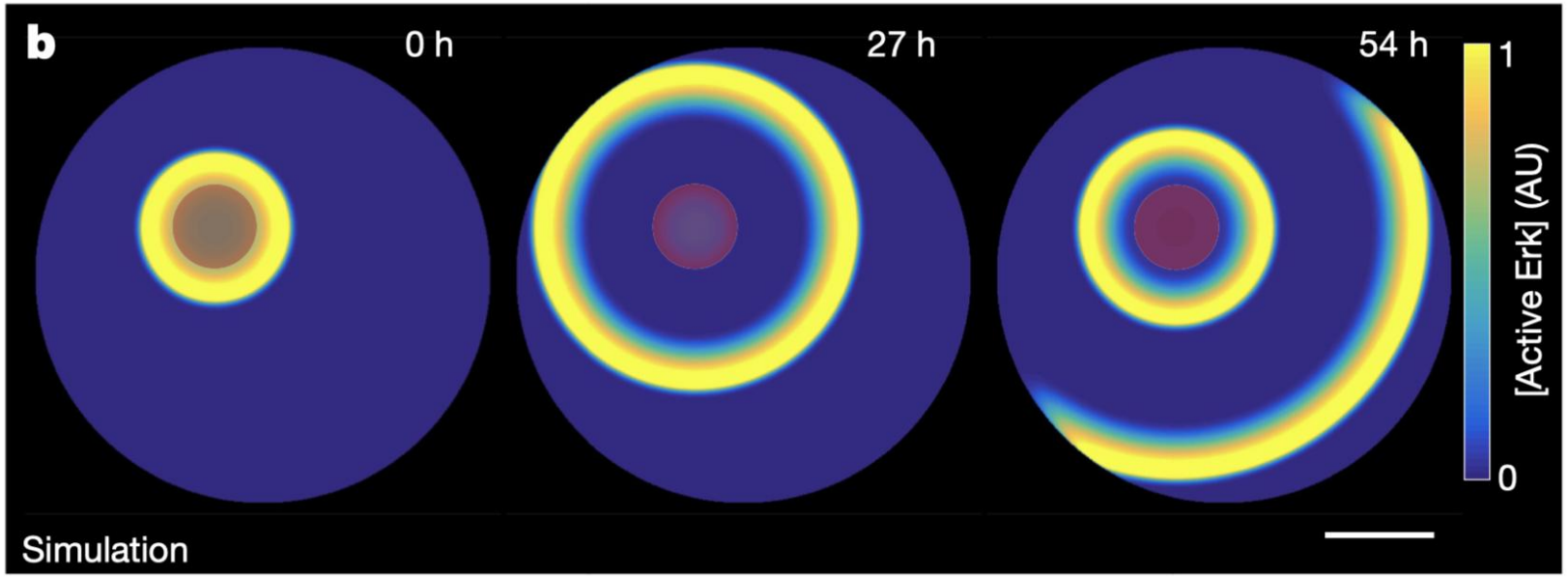

Fig2. Develop a math model to test whether these features are sufficient to generate waves

- The process of Erk activation including **positive and negative feedback**
- Simulations demonstrate the wave of Erk activity spread outward from a central source

The model predict the Erk signal wave travel as excitable trigger waves

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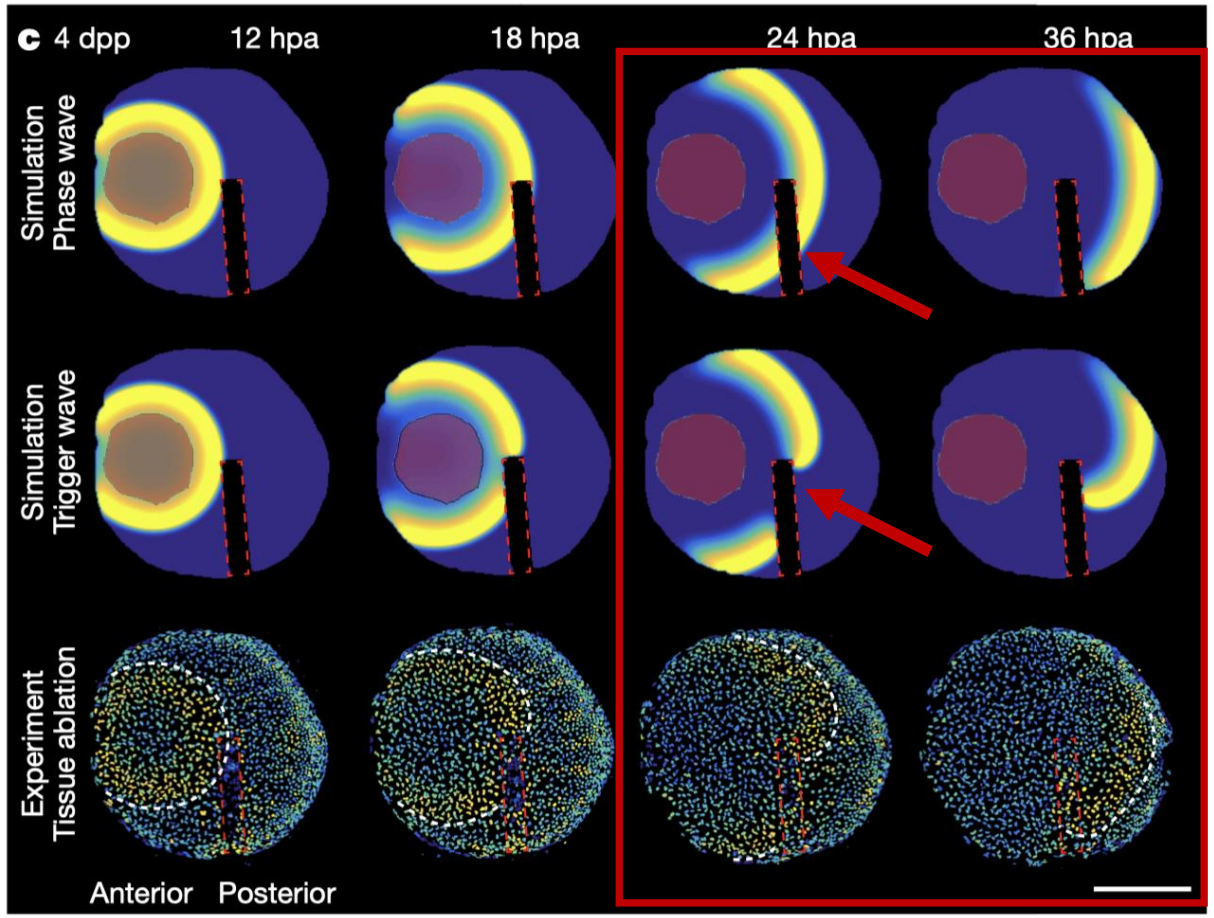

Fig1. Simulation and the experiment result with a gap on the scale

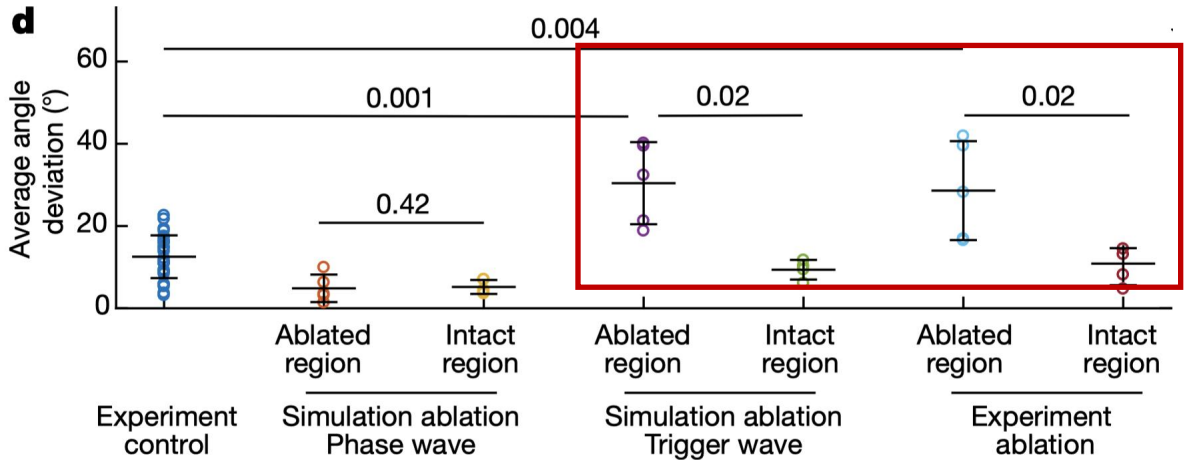

Fig2. Wave-front angle with respect to a circular front

- The Erk wave and the trigger wave simulation both bend and **turn around gap**(disrupted tissue)
- Quantification of the Wave front angle prove the Erk wave is more **similar to the pattern of trigger wave**

The Erk cascade and geometry of waves affect the Speed of Erk waves

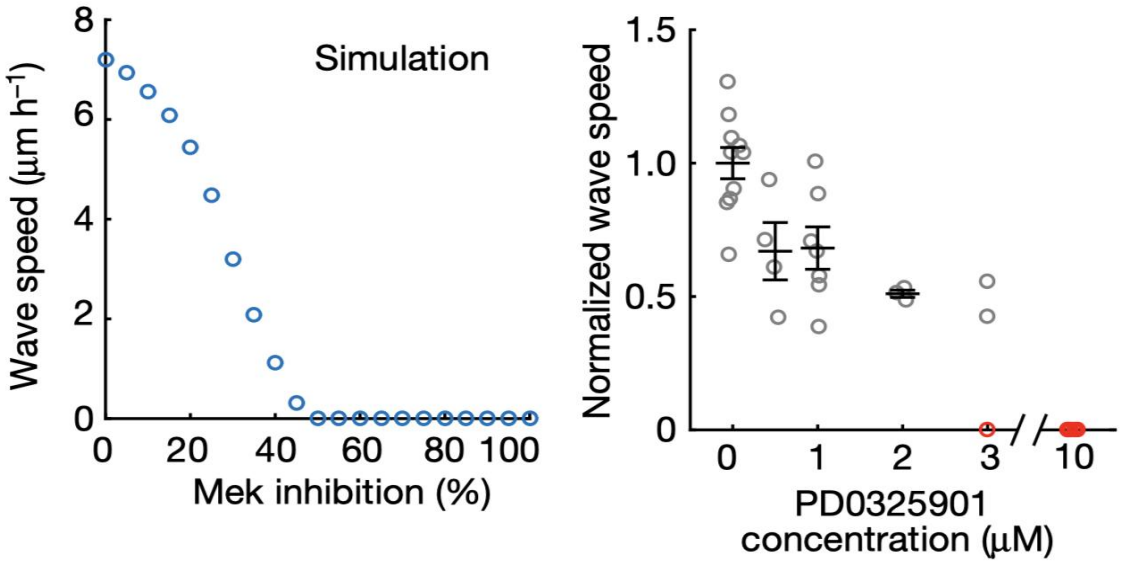

Fig1. Model prediction(Left) and experiment result(Right) of the speed of the Erk wave upon inhibition of Erk

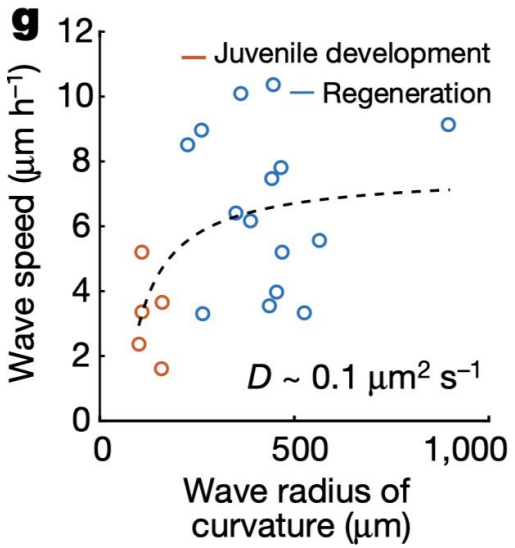

Fig2. The speed of waves in different wave radius

- The slowing of Erk cascade will **decrease** wave speed
- Smaller wave **slower than** larger wave

Whether waves can instruct the growth of tissue?

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*Compared **tissue expansion map** with **Erk signaling map**….*

They are correlated closely

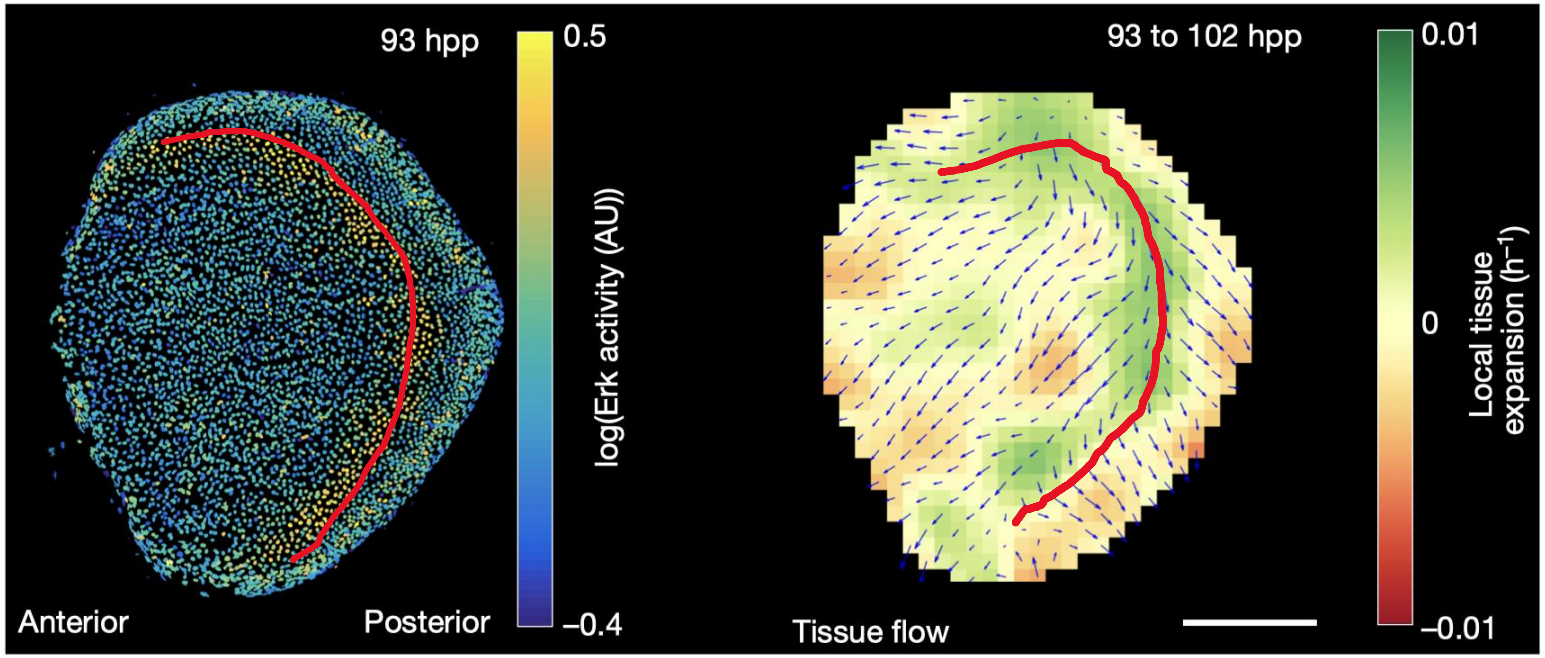

Fig1. Comparison between tissue expansion map and Erk signaling map

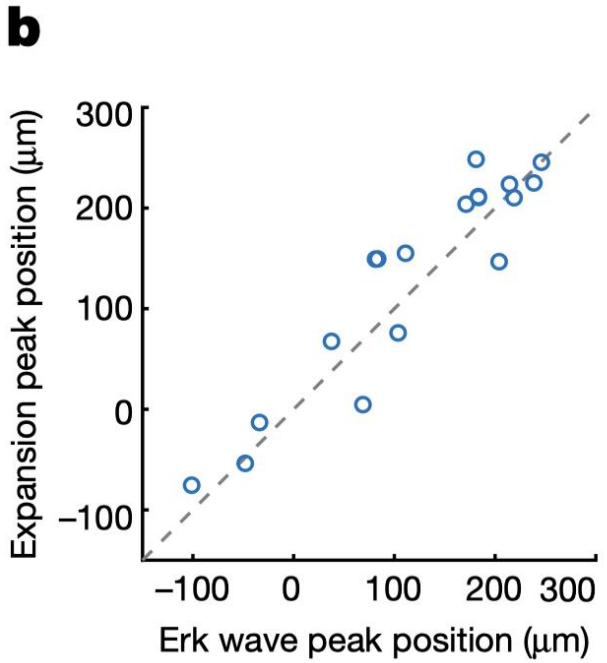

Fig2. Correlation between Expansion peak and Erk peaks

The Erk waves direct osteoblasts' growth in both time and space

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*"Moreover, tissue flows are **strongly perturbed** and tissue expansion rings are **significantly reduced** upon blockade of Erk activity with PD0325901"*

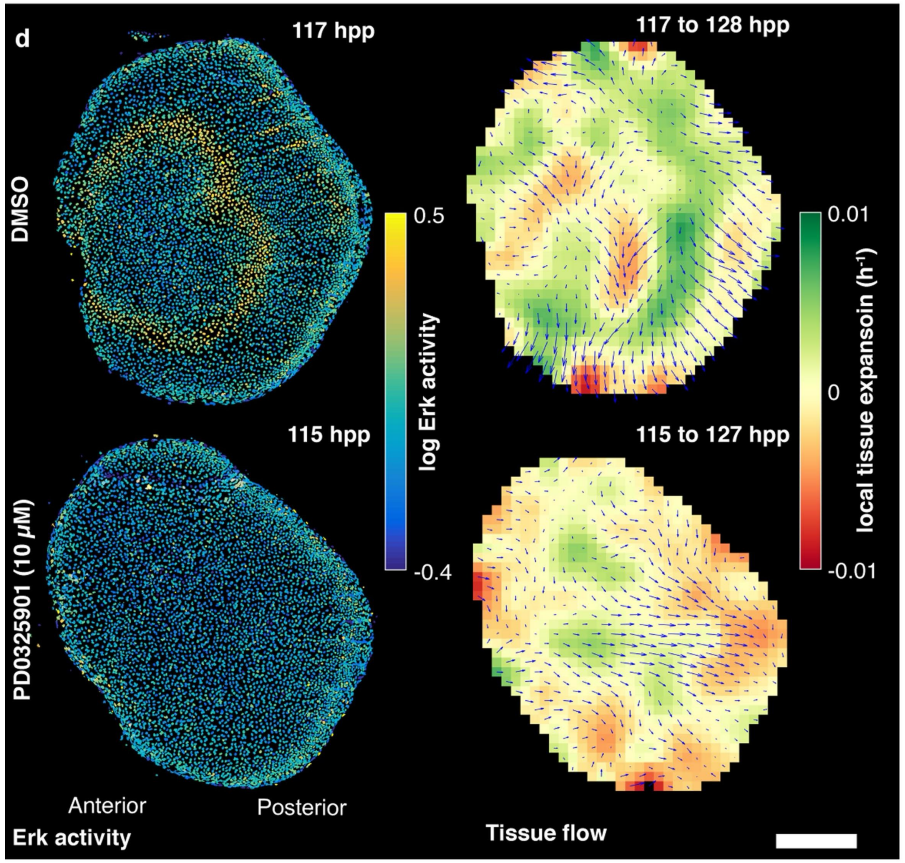

Fig1. Erk activity, tissue in scales of fish treated with the Mek inhibitor PD0325901 and DMSO control

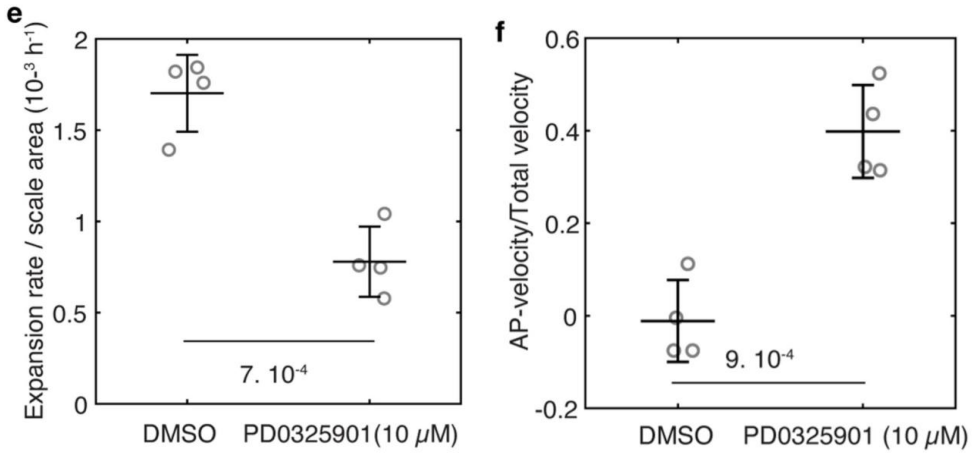

Fig2. Total expansion rate of expanding and anterior–posterior (AP)- velocity component (f) in fish treated with PD0325901

- Erk inhibitor obviously decrease the **expansion rate** of scale
- The scale regeneration become **slow**

Whether regulation of Erk traveling wave is key for regeneration?

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- *Hypothesis: **The regulation of Erk signaling in the form of traveling wave** plays a key role in Regeneration*

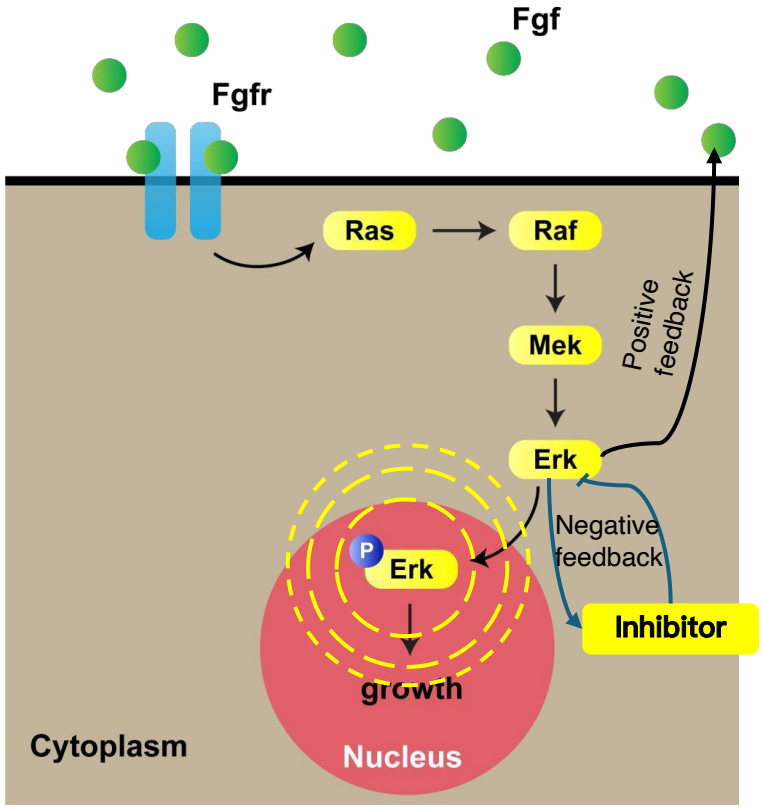

Fig1. Signal pathway of regeneration

The author utilize the **Fgf20 and Fgf3 to activate the Erk** signal to see whether the ectopic activation of Erk could promote the regeneration of scale.

- If yes, the feedback regulation of Erk is not important in the regeneration process
- If no, the feedback regulation plays a key role in regeneration, which means the Erk activity traveling in the wave form can be favourable to regeneration

Traveling waves of Erk is favourable to Erk activation for scale growth

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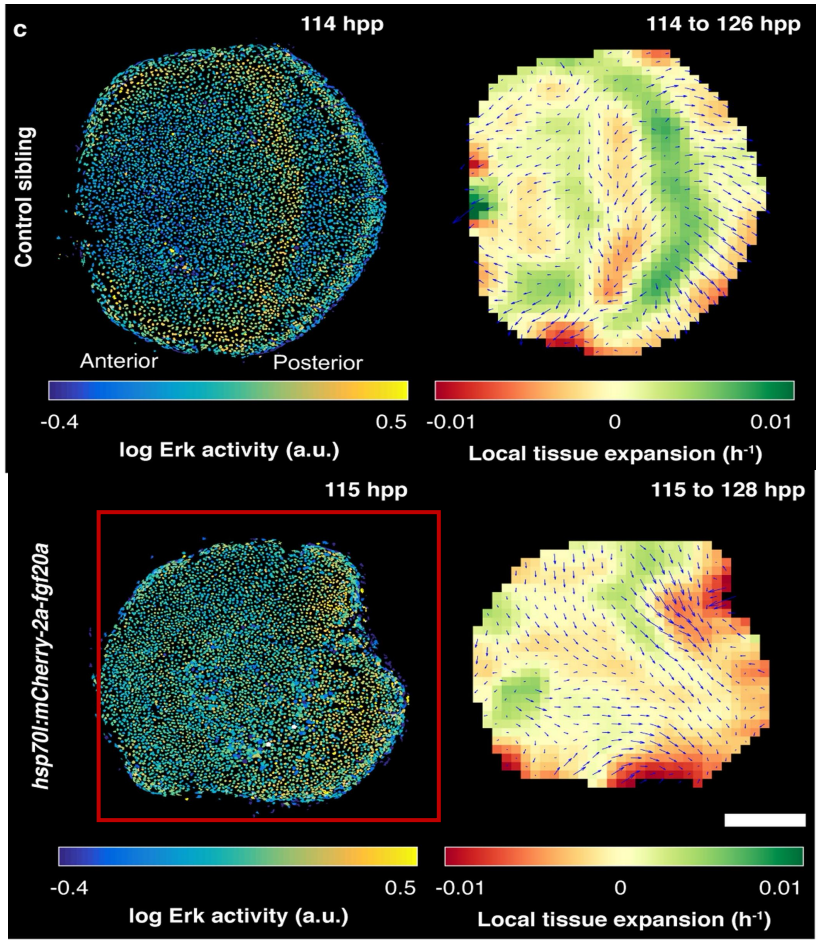

Fig1. Erk activity, tissue velocity field v after Fgf20a Treated(Down) and control(up)

- The activation of Erk signal **did not** lead to an increase of Scale regeneration

- The **negative feedback** inhibit the activation of Erk signal, which result in the stop of regeneration

- Such **feedback mechanism** is important for Erk signal. The **traveling wave** can be favourable to scale growth

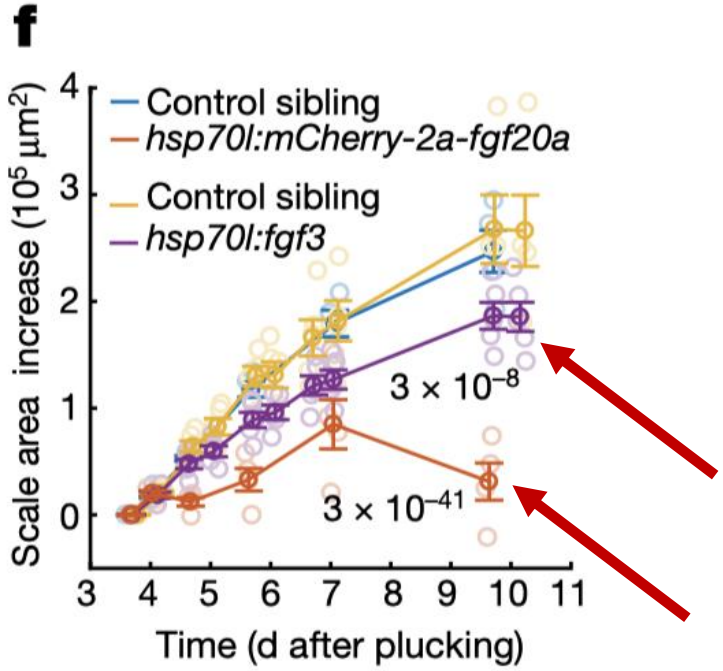

Fig2. Scale area increase in transgenic fish and respective control

Conclusion and Limitation

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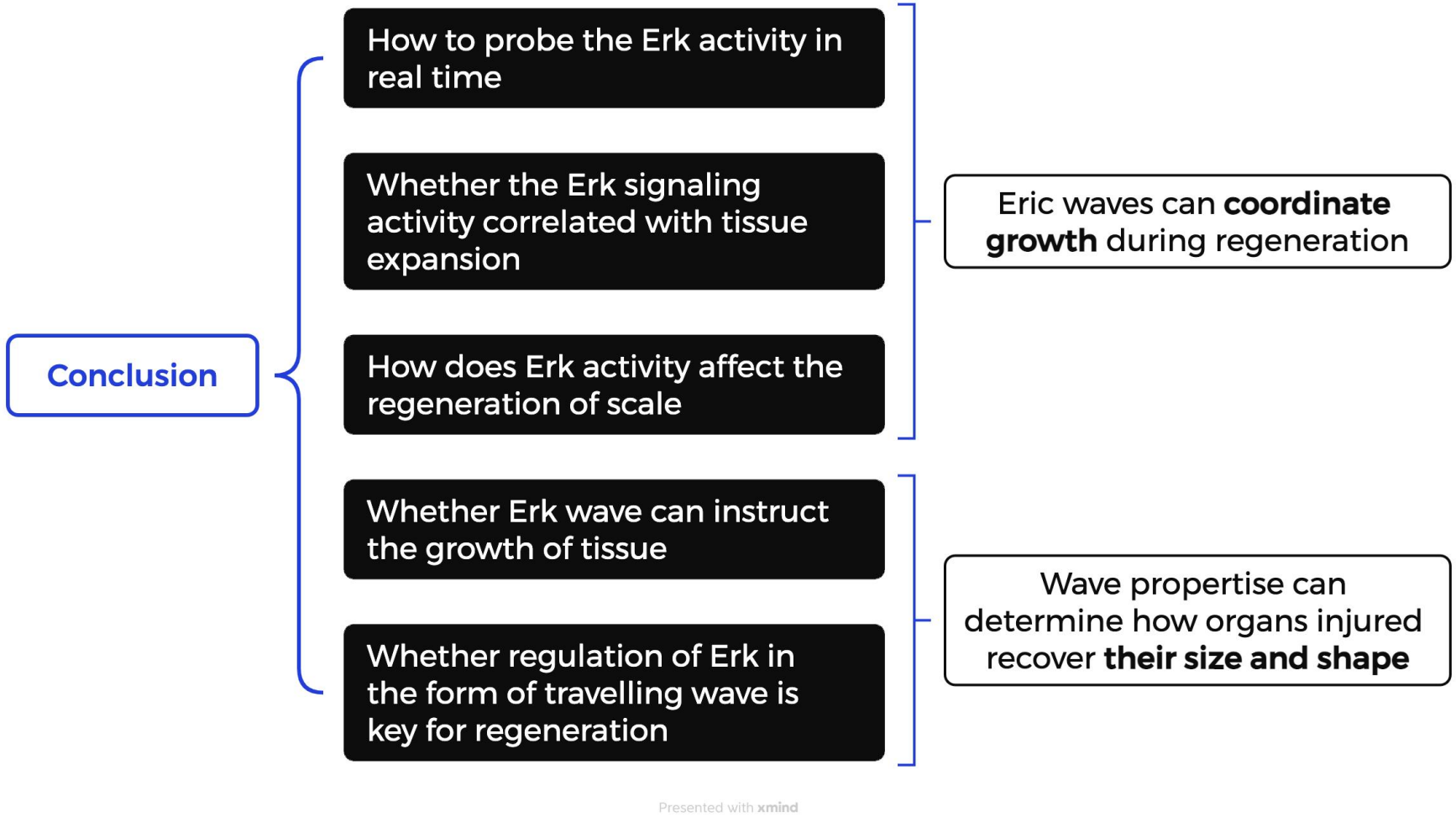

Limitation

This research mentioned the wave could restrict the mechanical stress but do not further prove that

The mechanism of the formation at the early stage is not described

Only focus on one signaling pathway of regeneration, this process could be influenced by other signals

Questions

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1. Why this article could be published on *Nature?*

- New phenomenon
- New solution

2.Why the pattern of Erk activity is an approximate wave form instead of a regular wave form?