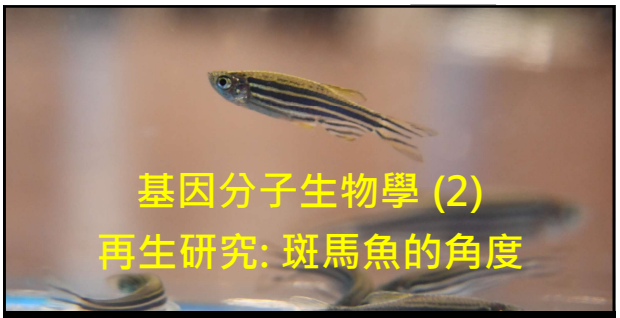


# 基因分子生物學 (2)
# 再生研究: 斑馬魚的角度

Chen-Hui Chen/ 陳振輝
ICOB at Academia Sinica
4 Jan, 2025

## Topics for today

1.為什麼要研究再生?

2.如何利用斑馬魚研究再生?

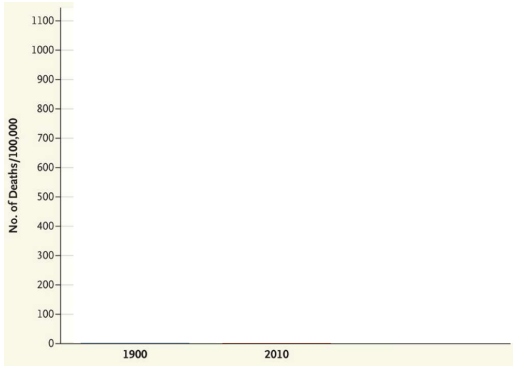
3.人類有一天也可以斷肢再生嗎?

## Some vertebrates are highly-regenerative


## Don‘t try this at home!

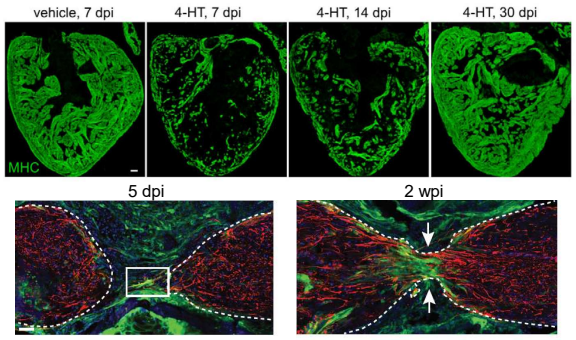
www.inquisitr.com

## What if humans were highly-regenerative?




NEJM, 2012

## Zebrafish are highly-regenerative to repair their internal organs



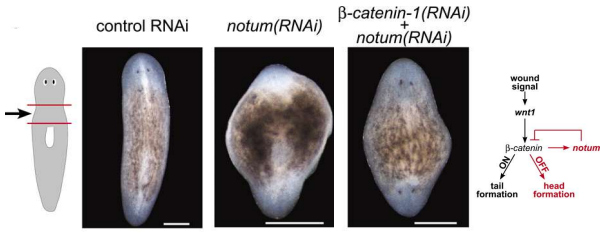

Wang *et al*, 2011; Mokalled et al, 2016

## Challenges in studying regeneration

## Something about planarians


http://pearsonlab.ca/?page_id=6

## Regeneration genes

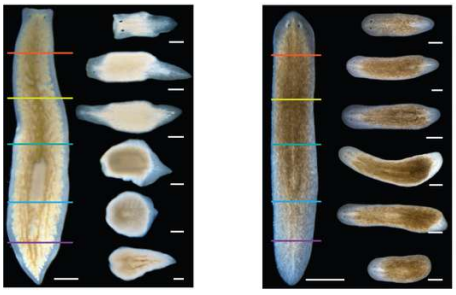



http://scienceintheclassroom.org/research-papers/heads-or-tails/university

## Regeneration and Immortality

http://www.ub.edu/planaria/index.html

## Some planarians can't regenerate



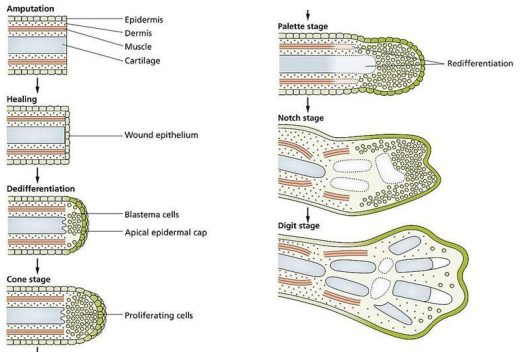
*Dendrocoelum lacteum* *Schmidtea mediterranea*

http://www.nature.com/nature/journal/v500/n7460/full/nature12414.html

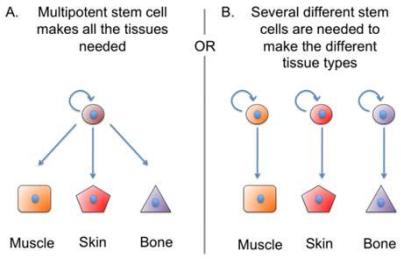
## Models of highly-regenerative vertebrates

mentalfloss.com

## What is the “blastema”?

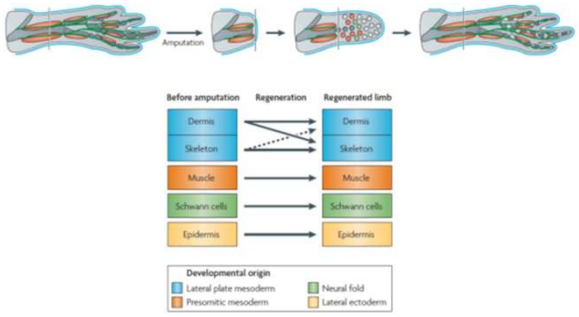



## Stem cells and regeneration




http://www.eurostemcell.org/image/possible-regeneration-models

## Stem cells and regeneration




NRG 2010

Highly regenerative

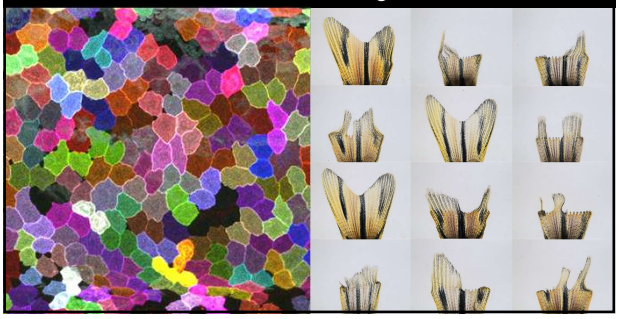
Accessible to many genetic tools

Great for cell imaging studies

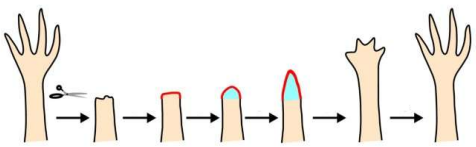
## My research program at ICOB

Direction #1
Collective cell behavior

Direction #2
Regeneration mutants

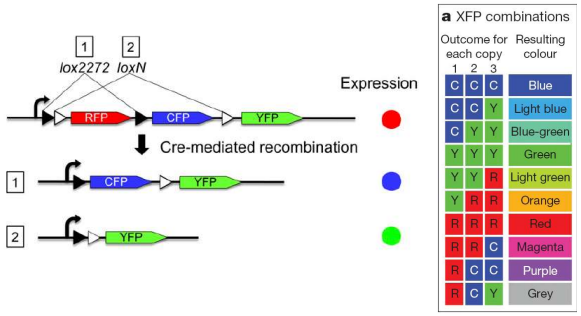


## Construct single-cell behavior atlases



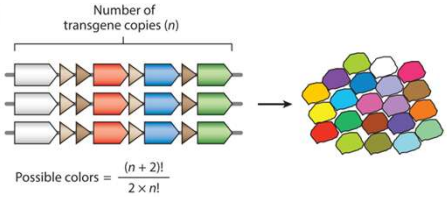
Whited et al, 2009

## *In toto* tracking of every single cell




Livet et al, 2007; Weissman et al, 2015

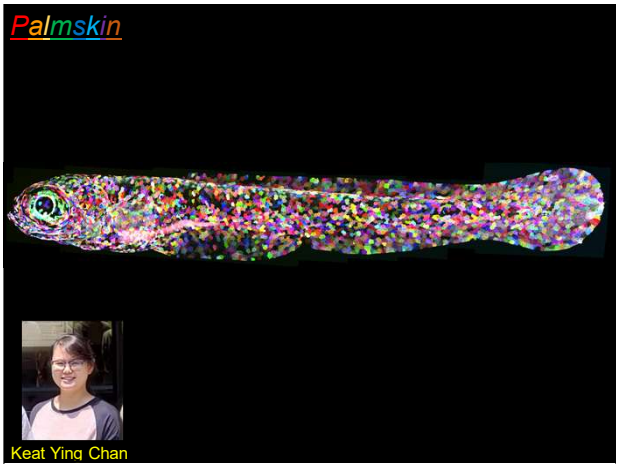
## *In toto* tracking of every single cell

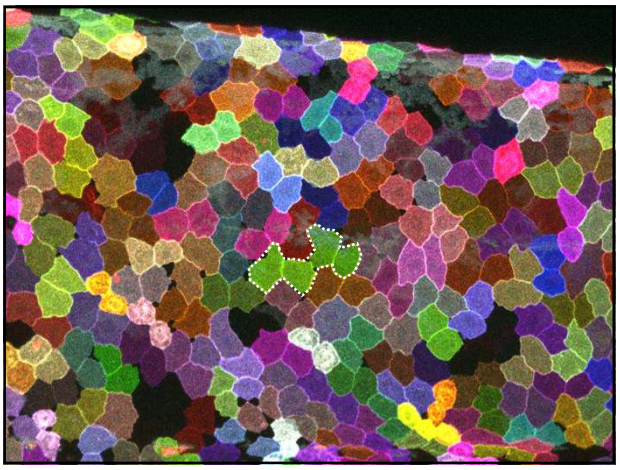


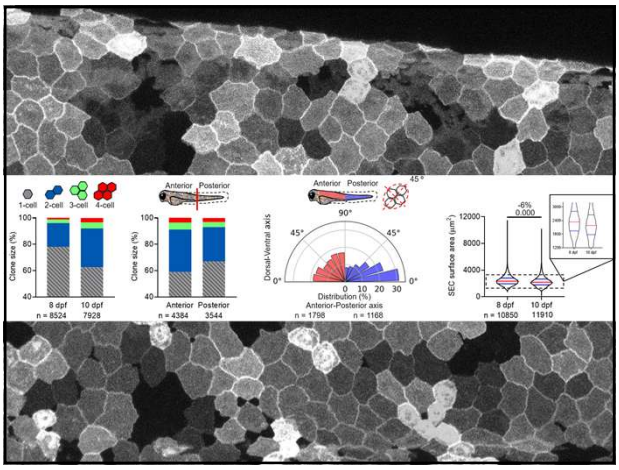

Possible colors = $\frac{(n+2)!}{2 \times n!}$

| Number of copies | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| Possible colors | 3 | 6 | 10 | 15 | 21 | 28 | 36 | 45 | 55 | 66 |

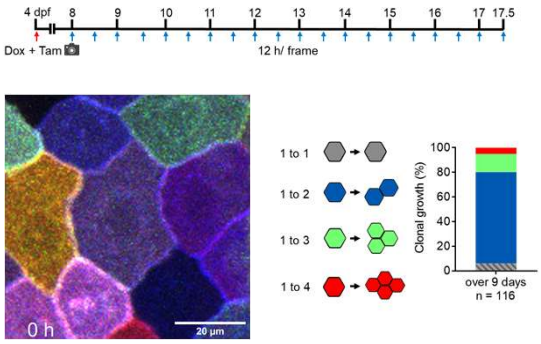
Chen and Poss, 2017



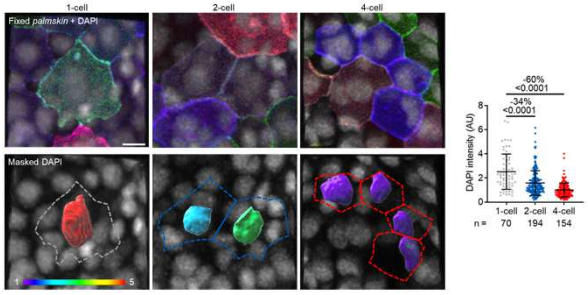





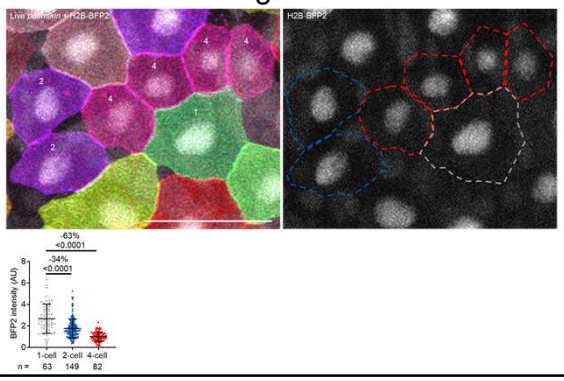
## A single SEC can produce four cells




## SEC division generates somatic cells with a reduced genome size




## SEC division generates somatic cells with a reduced genome size




## How did we come up with the name?

*Asynthetic Fission*

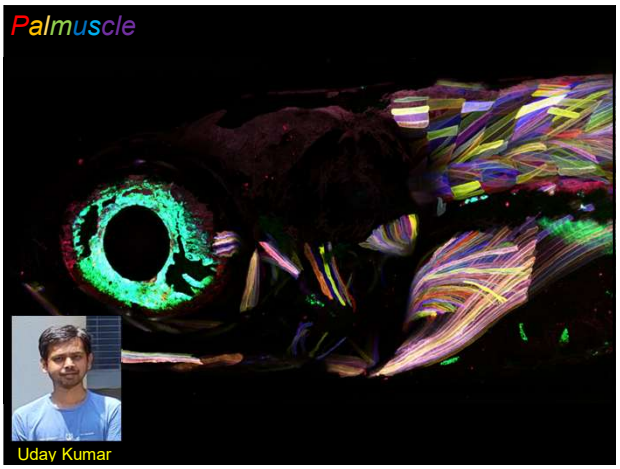
"*a*" as a prefix means "opposite"

"*fission*" means "splitting into two or more"

*Chan et al., Nature* 2022, PMID: 35477758

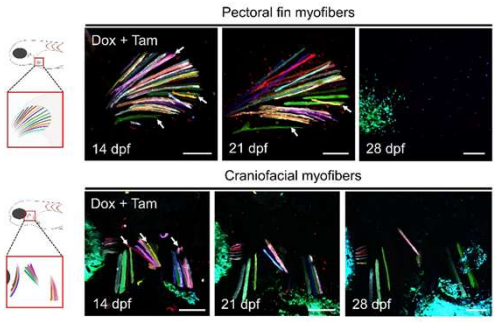
## 基礎研究

1. 正常細胞分裂- 發育 生長 繁殖 再生
2. 不正常細胞分裂- 癌症 疾病 老化
3. 明顯的例外- 基礎細胞分裂機制的研究
4. 斑馬魚是脊椎動物- 其它細胞或物種



*Palmuscle*

*Palmuscle* enables long-term tracking of all myofibers in a growing individual




*In toto* approach identifies a new muscle growth mechanism



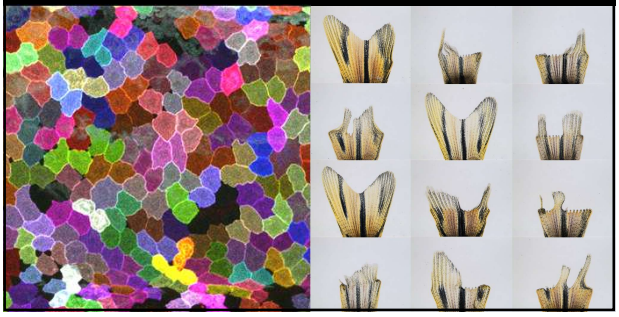
*Kumar et al., EMBO J* 2024, PMID: 38839992

Any questions for the first part?

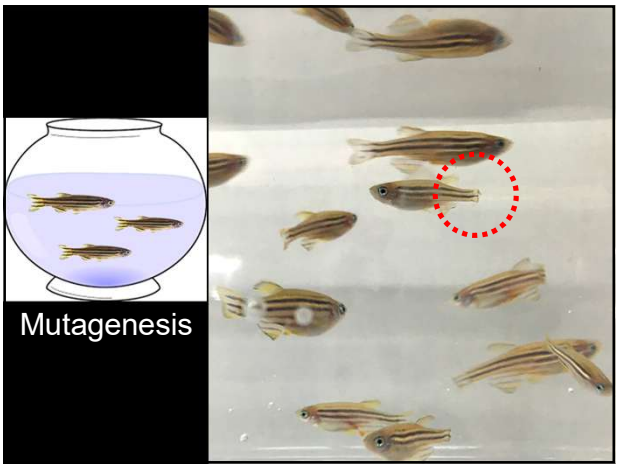
My research program at ICOB

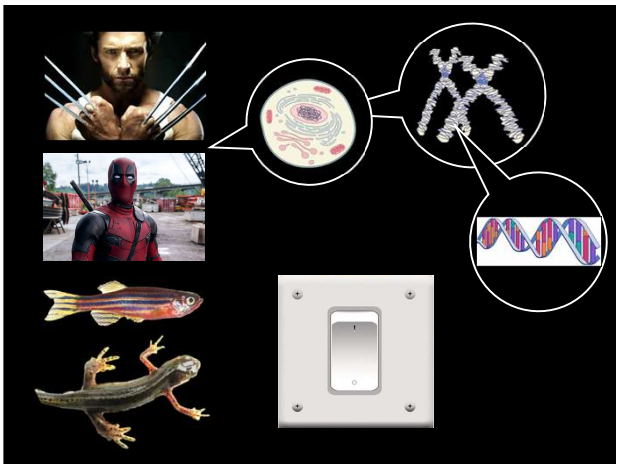
Direction #1
Collective cell behavior

Direction #2
Regeneration mutants

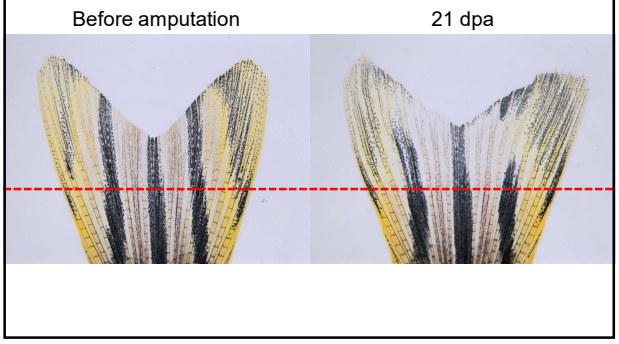


We need to find Wolverines or Deadpools that cannot regenerate!



## Zebrafish tailfin regeneration is robust

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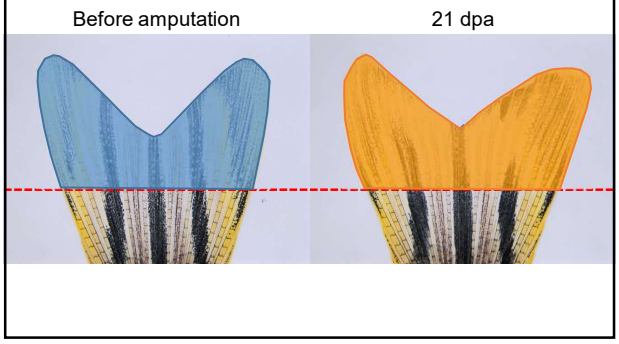
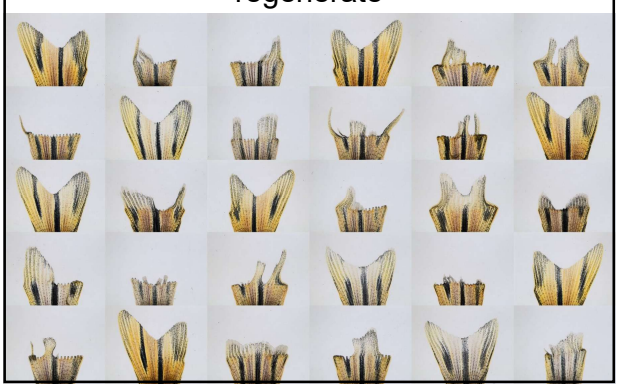
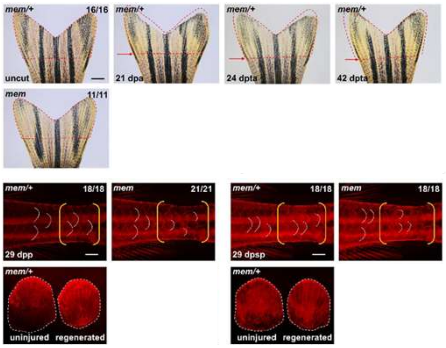


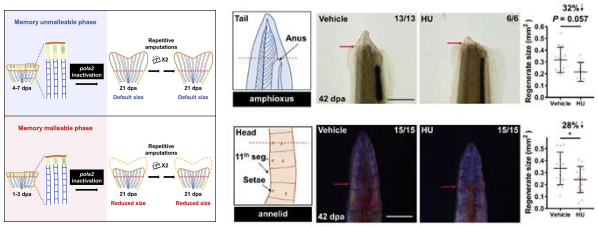

## A fish that cannot remember what to regenerate



## The gene can create new, long-lasting memory in distinct tissues



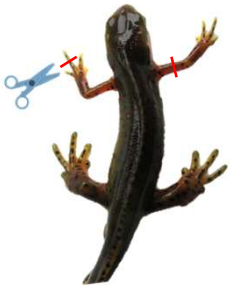
## *Pola2* resets positional memory during regeneration




*Wang et al., Current Biology* 2019, PMID: 31786062

## Regeneration speed vs. injury levels

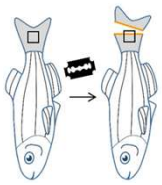
Lazzaro Spallanzani
(1729- 1799)



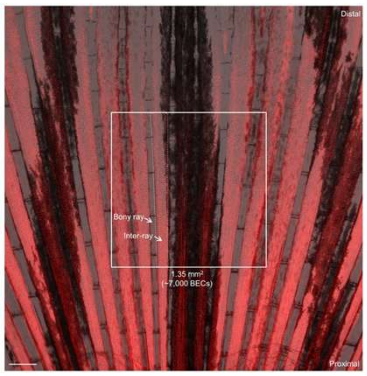
## How do animals sense amputation levels and have different response?


*Lee et al., Dev* (2005)

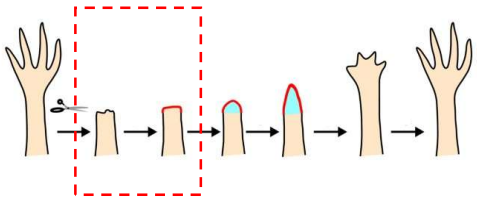
## Rea-time monitoring of 7,000 cells in a live animal



Marco De Leon

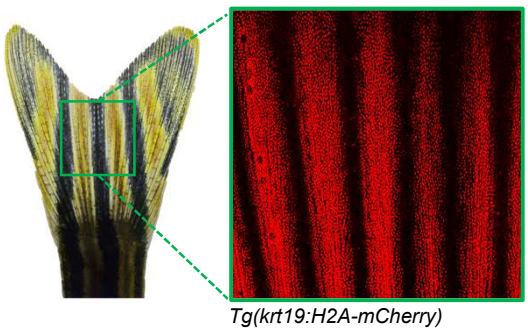



## Wound healing is key to regeneration



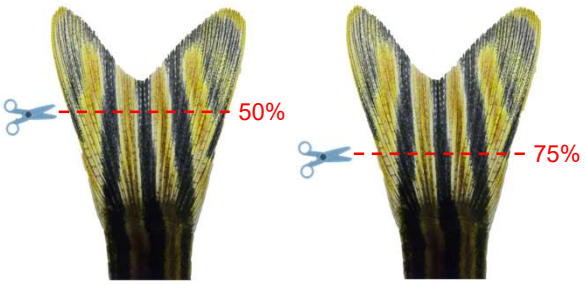
Whited et al, 2009

## Live imaging of wound healing response

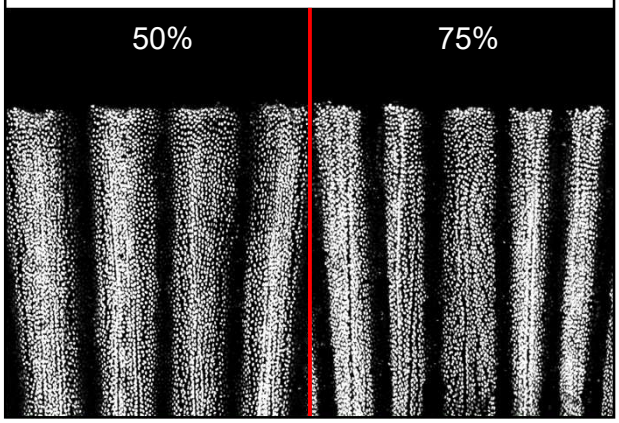


*Tg(krt19:H2A-mCherry)*

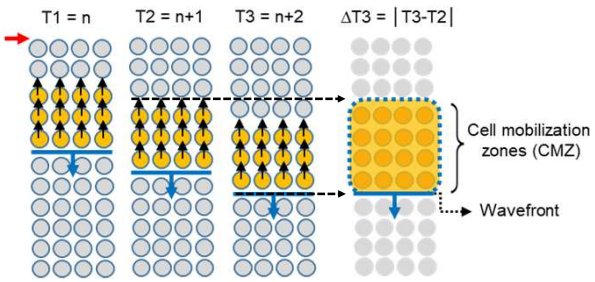
## Distal amputation vs. Proximal amputation




## Amputation levels regulate wound response

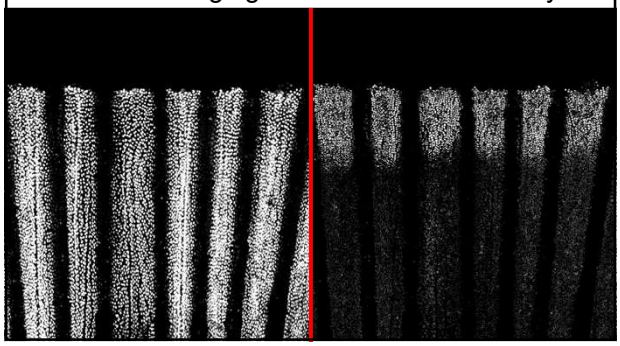



## Amputation triggers “waves” to mobilize cells

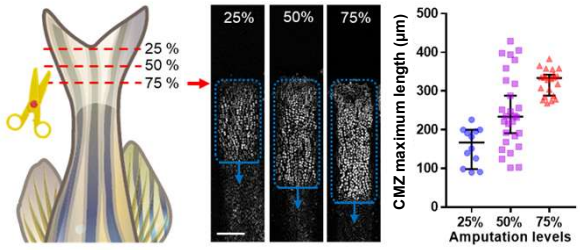



## The wave travels over ~600 μm in an hour

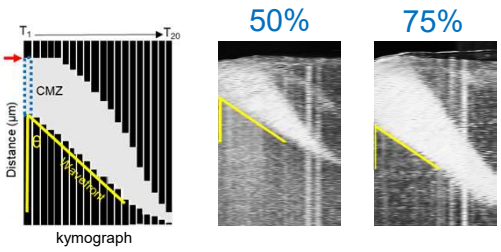
Live cell imaging “White wave” analysis



## Amputation levels regulate wound response




## CMZ travels at a constant speed

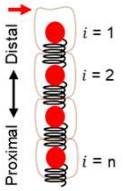


## Time to talk to a physicist!

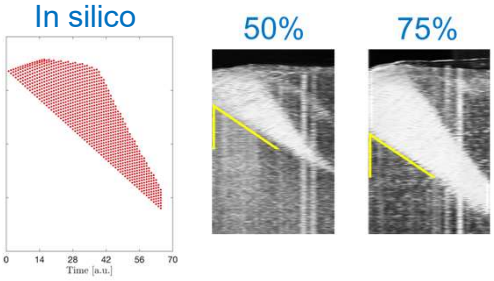
Dr. Lin, Keng-Hui
A soft matter physicist at Academia Sinica

Dr. Wen, Fu-Lai
A theoretical physicist at NCKU

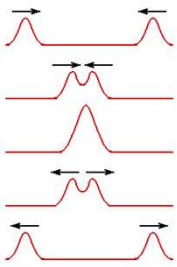
## One-Dimensional Active Spring (ODAS)

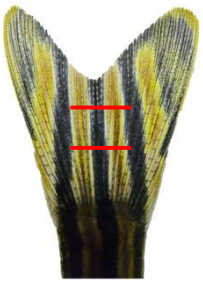



## One-Dimensional Active Spring (ODAS)

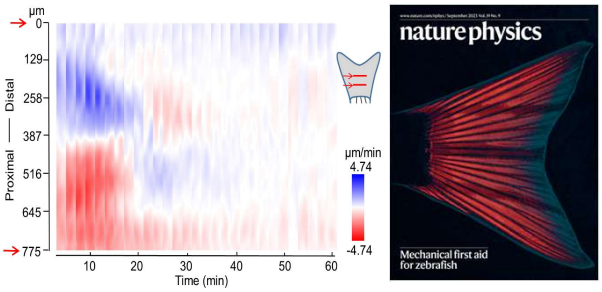



## Mechanical waves vs. Chemical waves





## *Mechanical waves* direct amputation-level dependent tissue responses

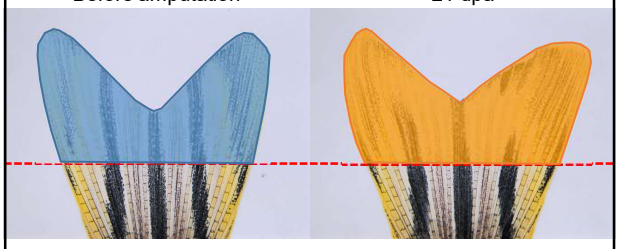



*De Leon et al., Nature Physics* 2023

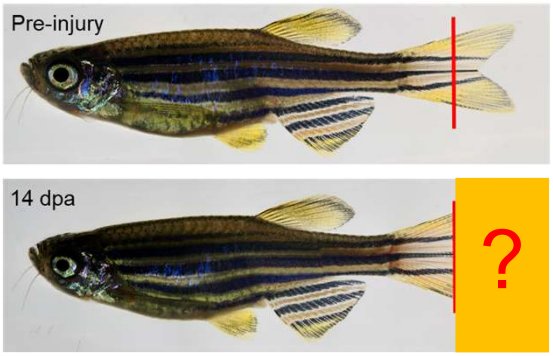
## How does regeneration stop?

Before amputation

21 dpa

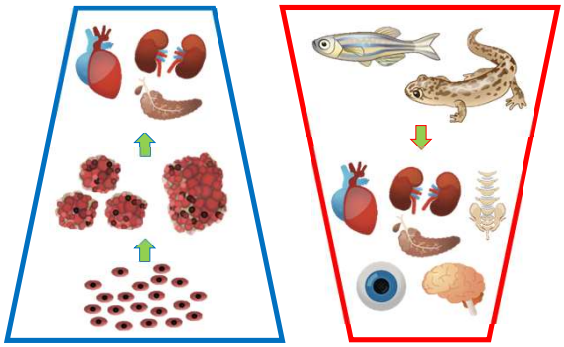


## A fish that cannot stop regeneration




## Can we make non-regenerative animals regenerative?

## *Bottom-up* vs. *top-down* approaches



## Topics for today

1.為什麼要研究再生?

2.如何利用斑馬魚研究再生?

3.人類有一天也可以斷肢再生嗎?

## "你真的想當科學家嗎?"

## Acknowledgements