



圖書館Master講堂「學者領航・智慧開講」



# Beyond the Books— 探索研究、挑戰、突破

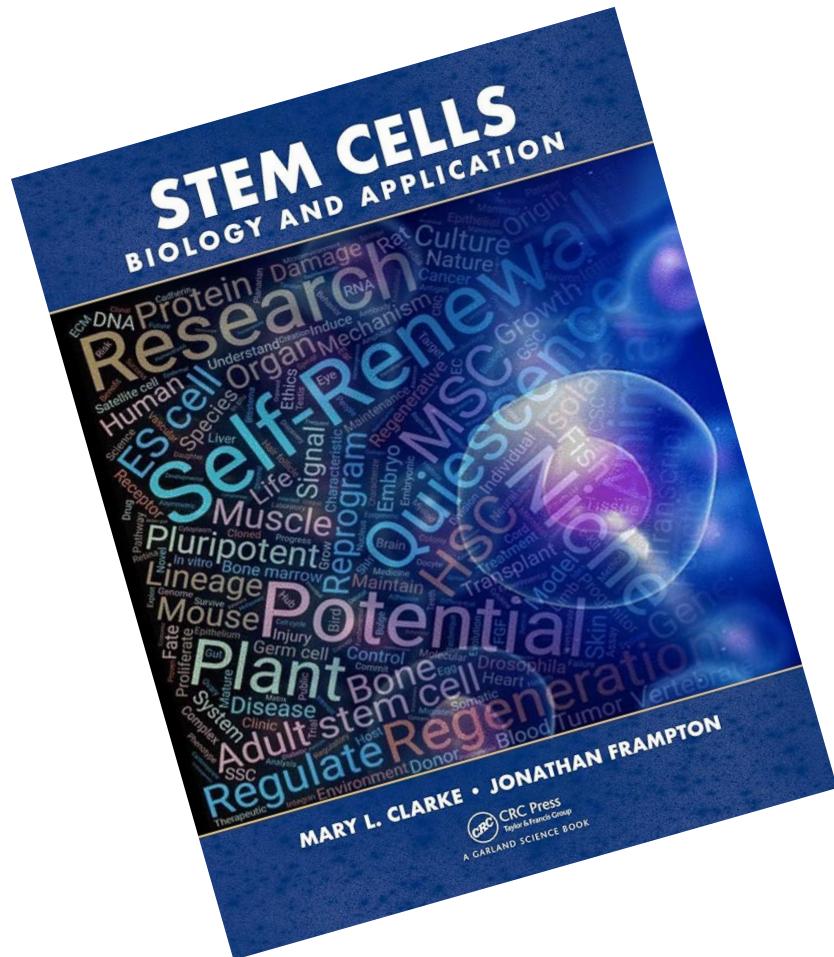
蔡素宜

生命科學系  
國立台灣大學

2024/04/30

# 探索研究

# —解決未知的事情

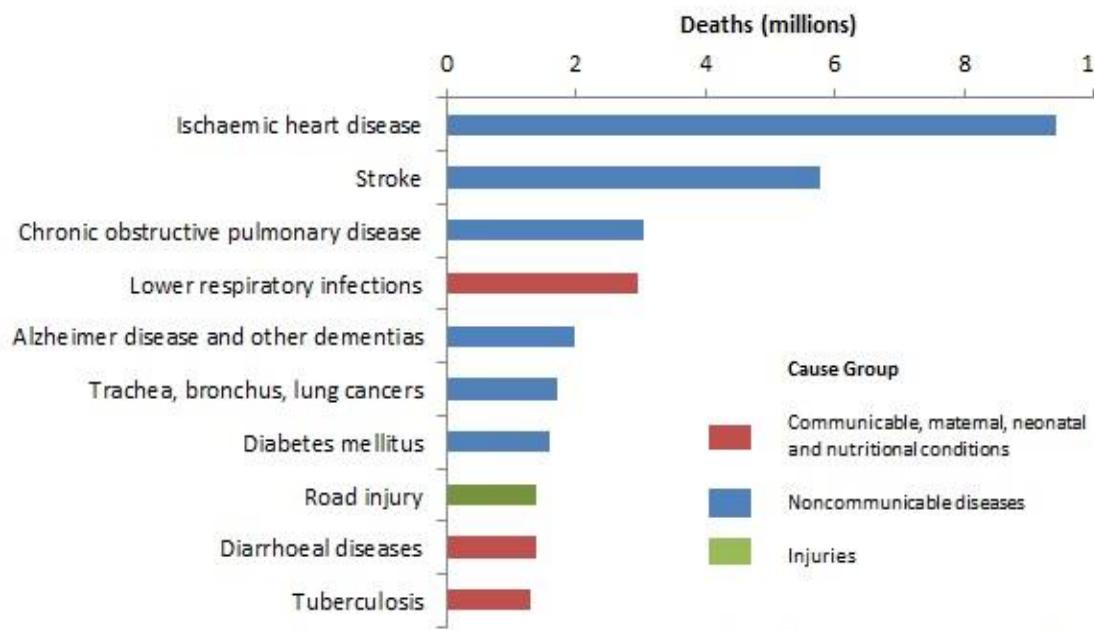


## 書本告訴我們的事 --已知的

# Cardiovascular disease

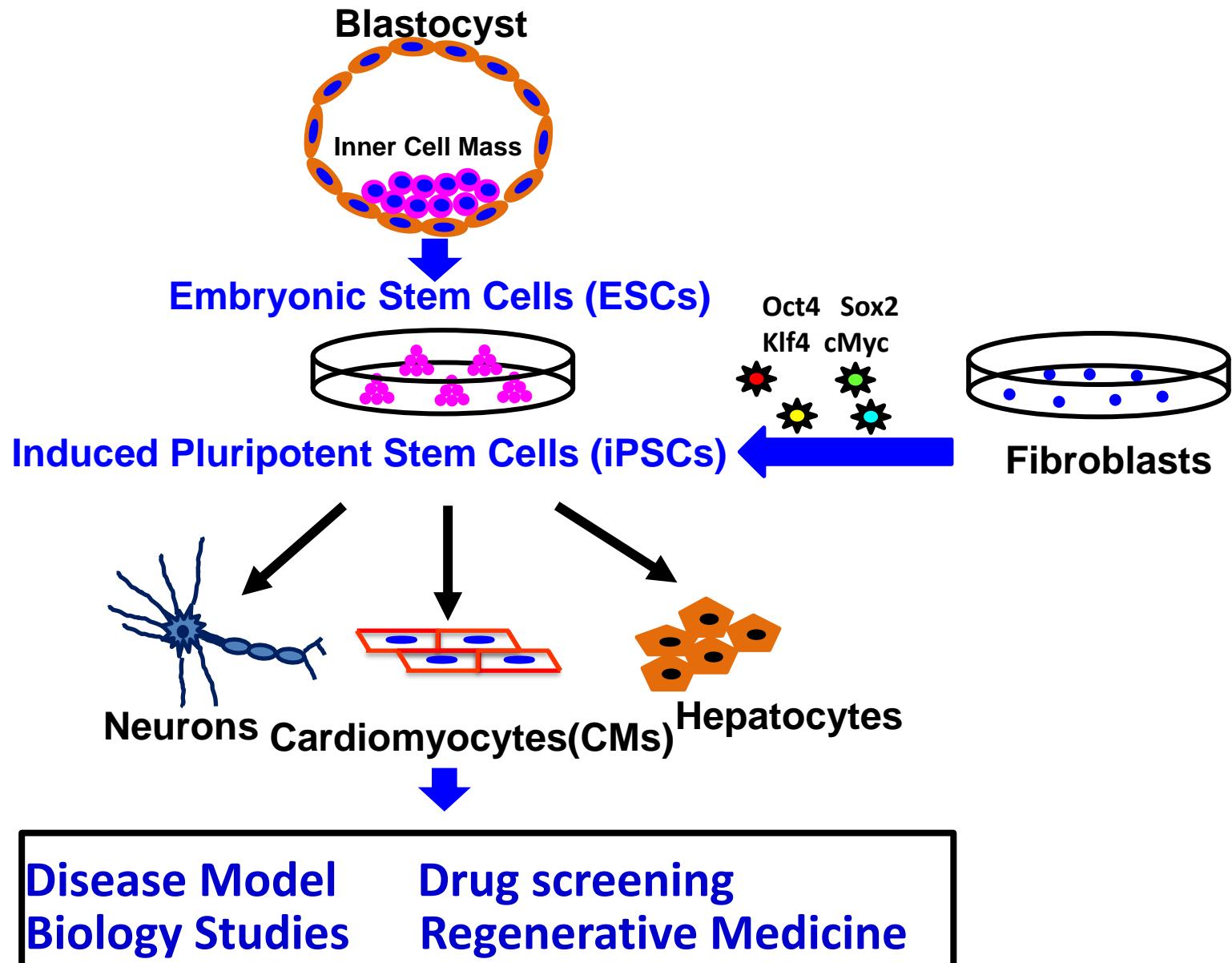
- **Cardiovascular disease is the leading cause of death and disability in the world (Murphy et al., 2012, National Vital Statistics reports).**
- **Cardiac arrhythmias** account for almost half of all cardiovascular deaths
- **Source of human materials is always a bottleneck for studying the function of cardiac genes and heart diseases.**

Top 10 global causes of deaths, 2016



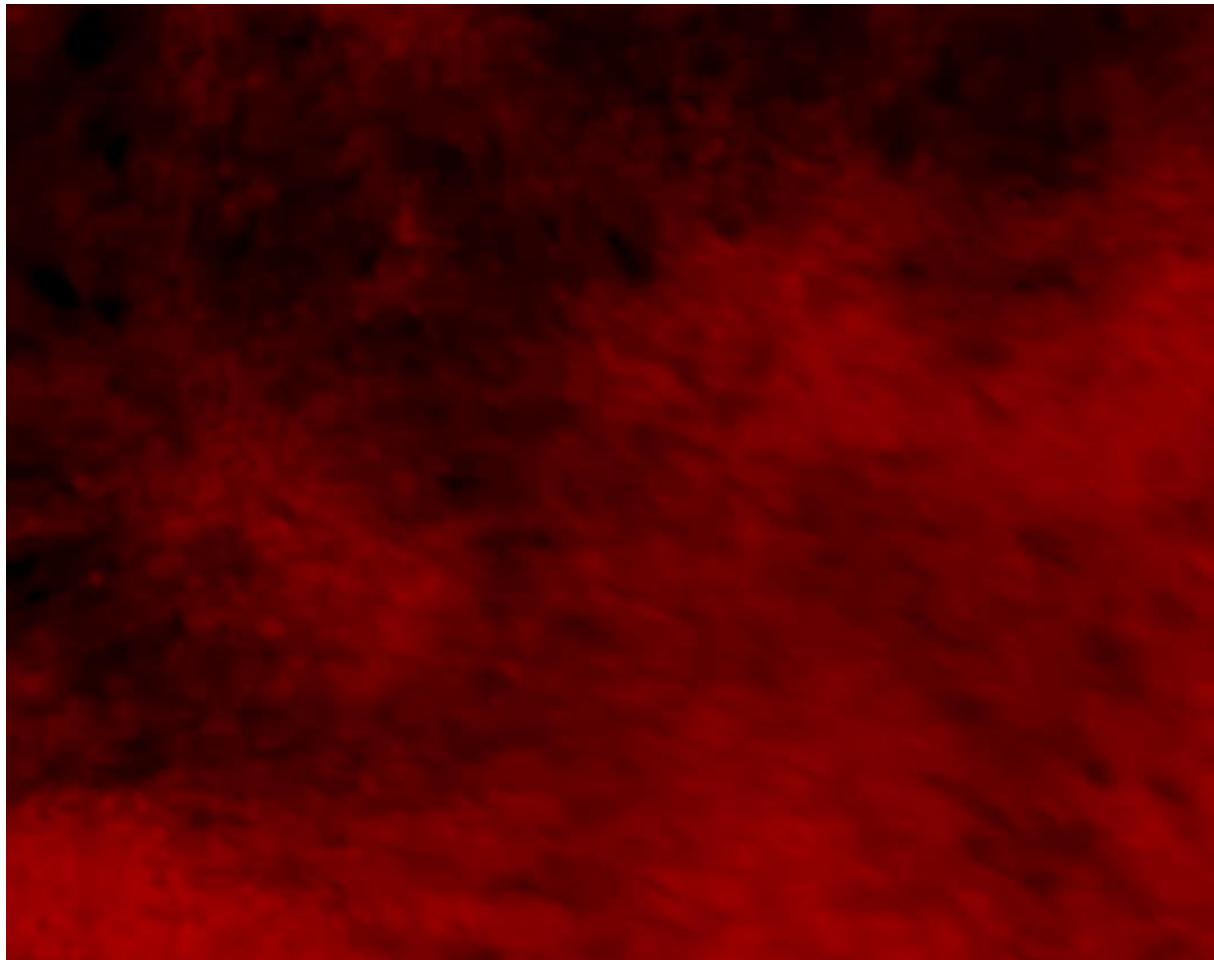
Source: Global Health Estimates 2016: Deaths by Cause, Age, Sex, by Country and by Region, 2000-2016. Geneva, World Health Organization; 2018.

# The promise of human pluripotent stem cells



# **Generation of a knock-in MYH6:mCherry hESC cardiac reporter line using the CRISPR/Cas9-based gene targeting**

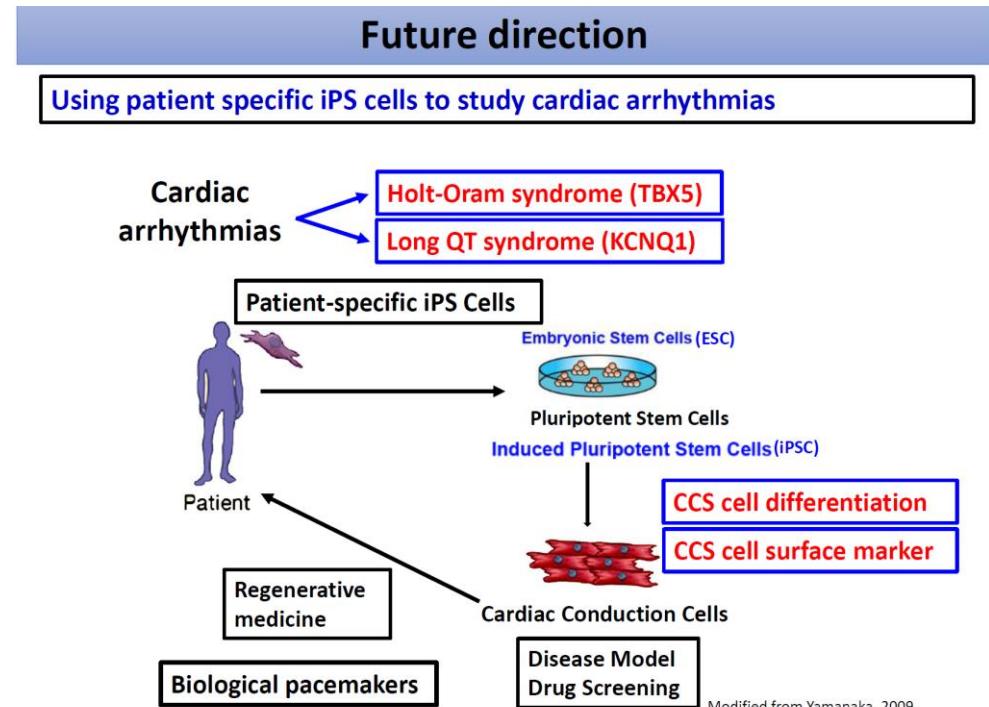
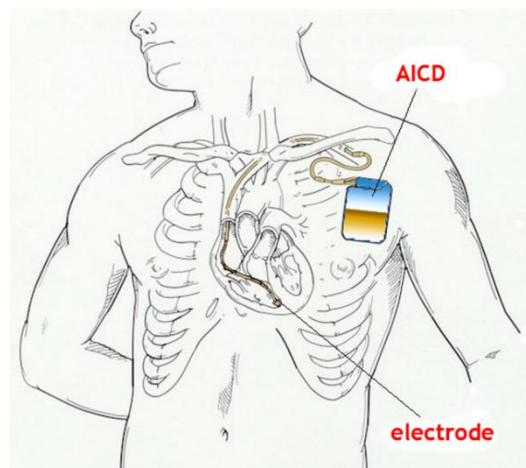
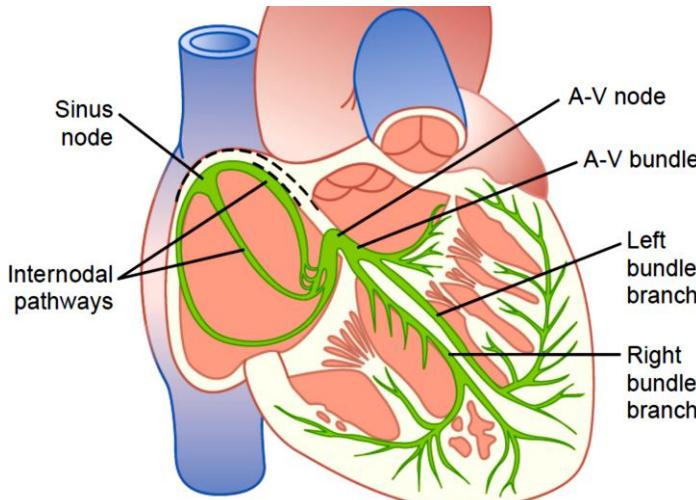
**MYH6:mCherry hESC CMs**



# 探索研究

## --心臟傳導細胞的分化

## --心律不整的病理機制與治療方法



# 探索研究、挑戰

--現實是殘酷的

昂貴的細胞模型

國科會計畫

幹細胞培養液一罐：~10,000元/500ml

平均：~1,000,000元

平均：100罐/年!!

# 探索研究、挑戰

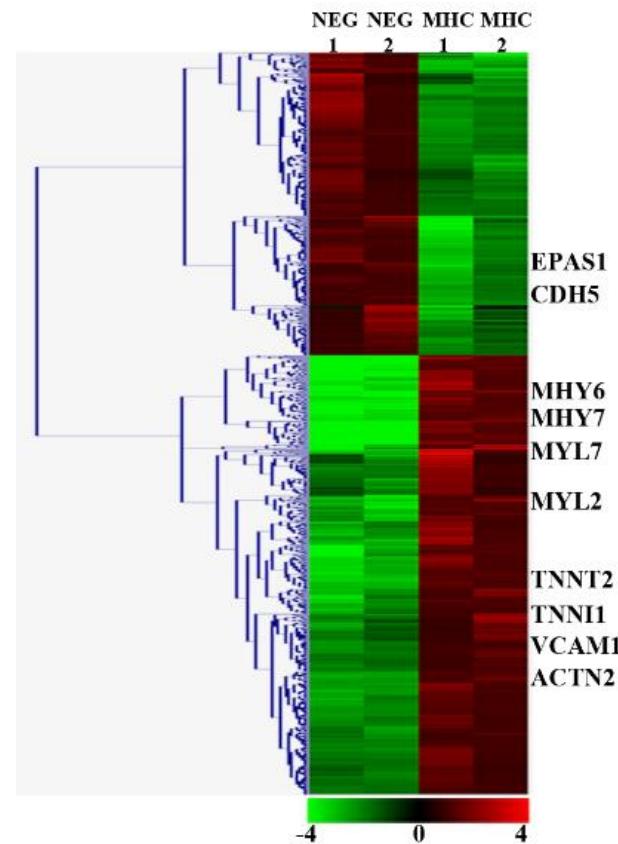
--現實是殘酷的

--小實驗室如何對抗大鯨魚

--面對現實與挑戰

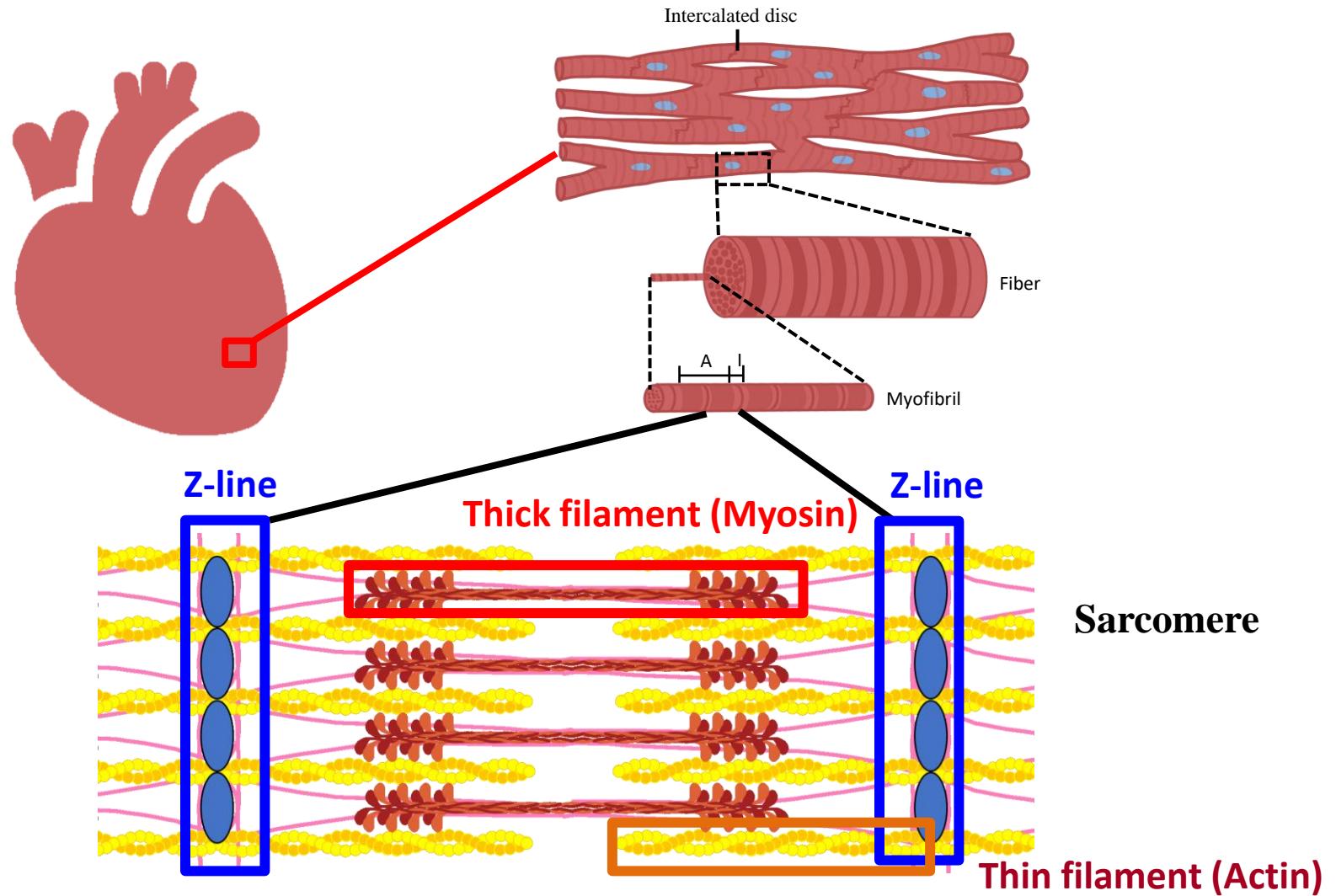
--不怨天尤人，努力創造CP值

--找出自己的優勢（優點與特色）



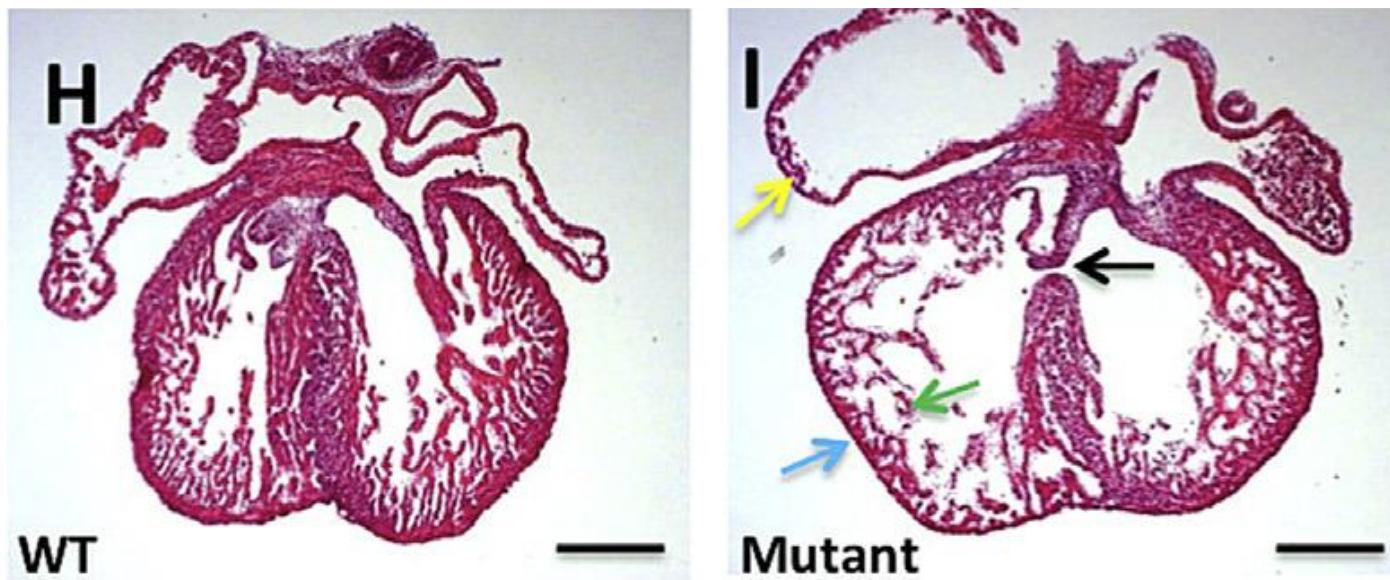
# Sarcomere structure

- Its assembly requires a proper temporospatially transcriptional regulation of genes.



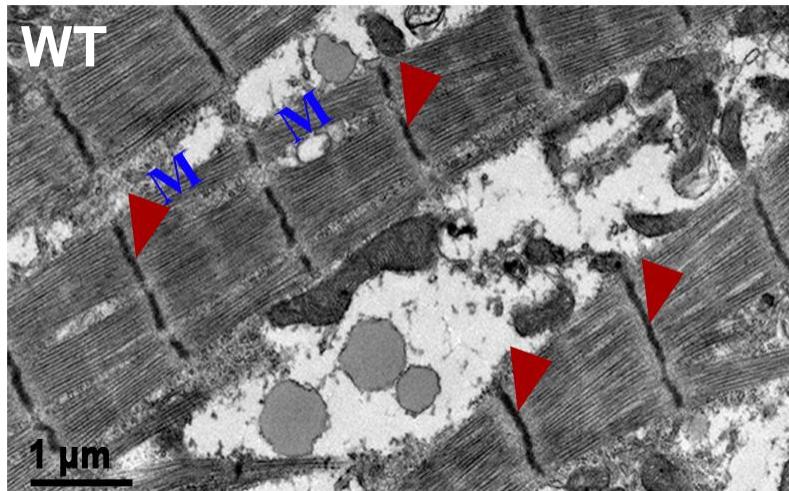
# Ablation of *Rbm24* is embryonic lethality and cause multiple cardiac malformations in mice.

- Mutant died between E12.5 to E14.5
- Ventricular septum defects, reduced trabeculation and dilated right atrium

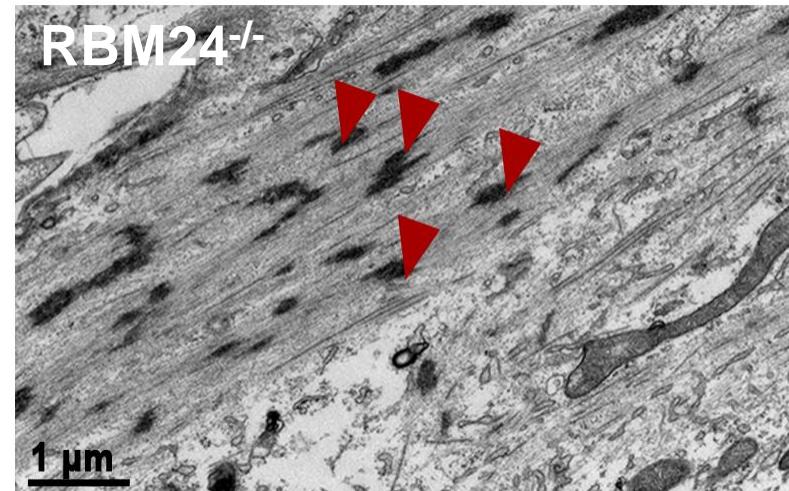


# RBM24<sup>-/-</sup> CMs exhibited severely disturbed sarcomeric structure\_punctate Z-line

D30



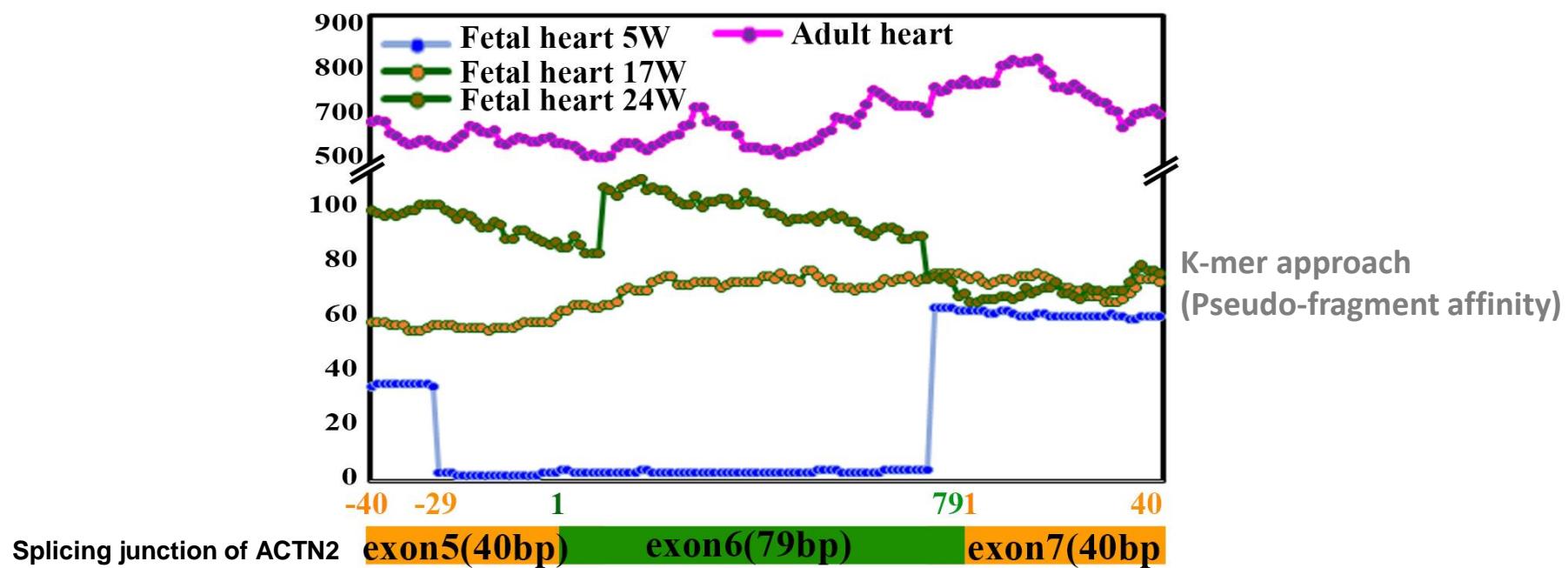
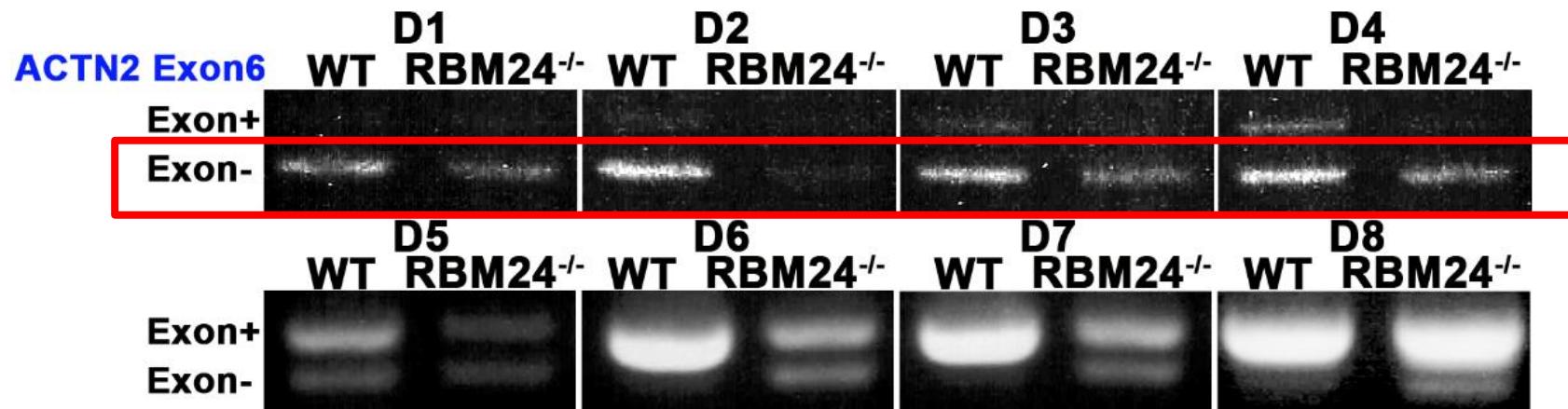
Scale Bar: 1 μm



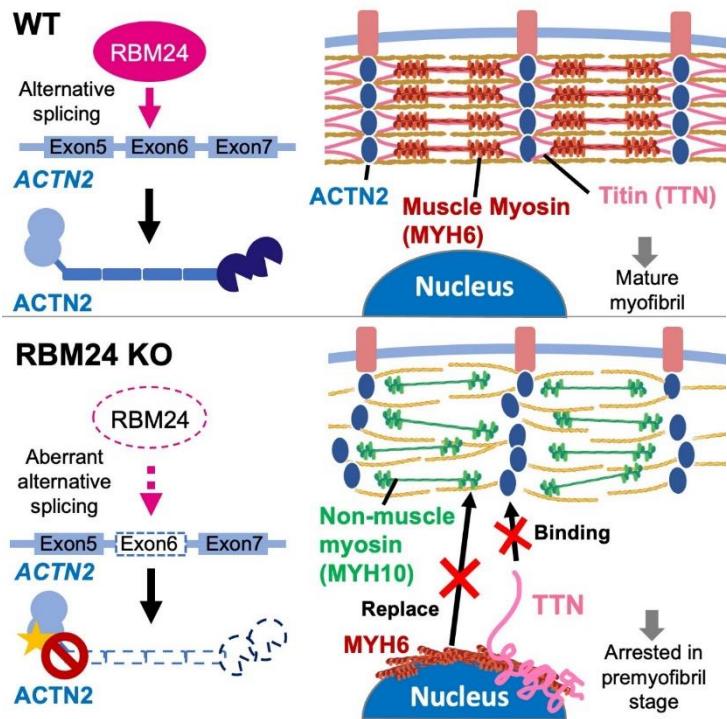
Transmission Electron Microscopy (TEM)

**RBM24 plays essential roles in sarcomere assembly**

# Exon6 exclusion of ACTN2 is presented during early cardiac development



# 探索研究、挑戰、突破



Circulation Research

## ORIGINAL RESEARCH

Alternative Splicing Mediated by RNA-Binding Protein RBM24 Facilitates Cardiac Myofibrillogenesis in a Differentiation Stage-Specific Manner

Serena Huei-An Lu<sup>ID</sup>, Kang-Zheng Lee<sup>ID\*</sup>, Paul Wei-Che Hsu\*, Liang-Yu Su\*, Yu-Chen Yeh, Chien-Yuan Pan, Su-Yi Tsai<sup>ID</sup>

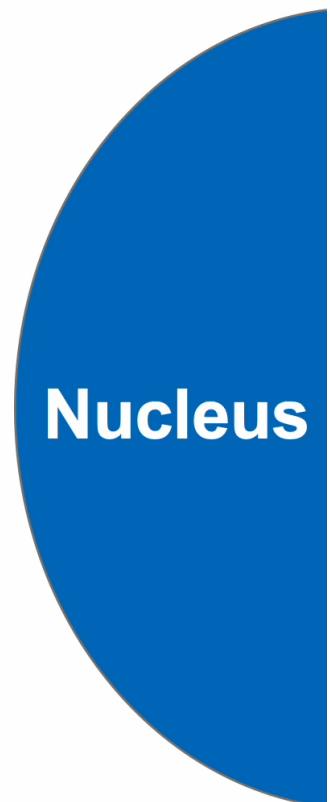
心血管期刊排名第4名!!

# Deciphering the stepwise processes of cardiac myofibrillogenesis in hESC-derived CMs

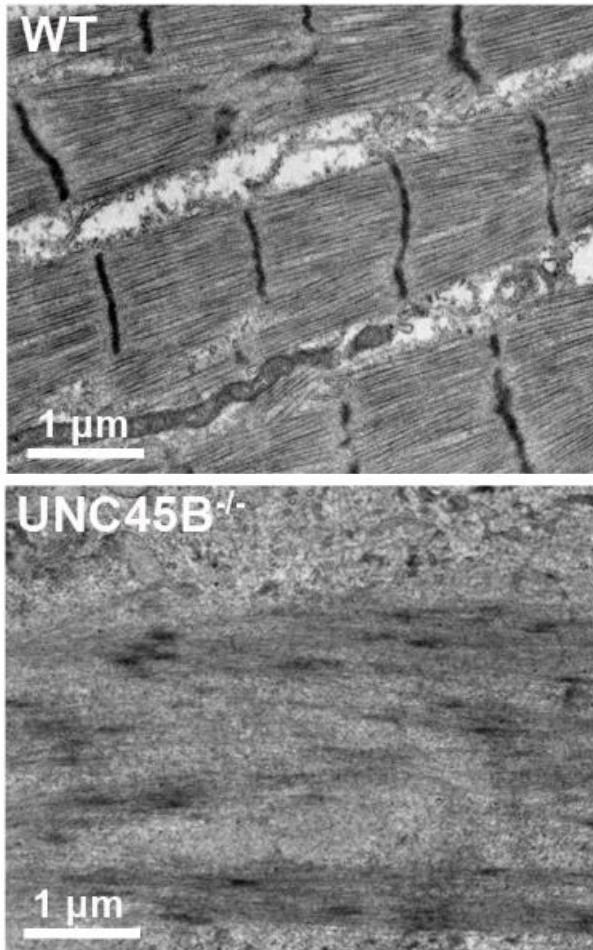
D4

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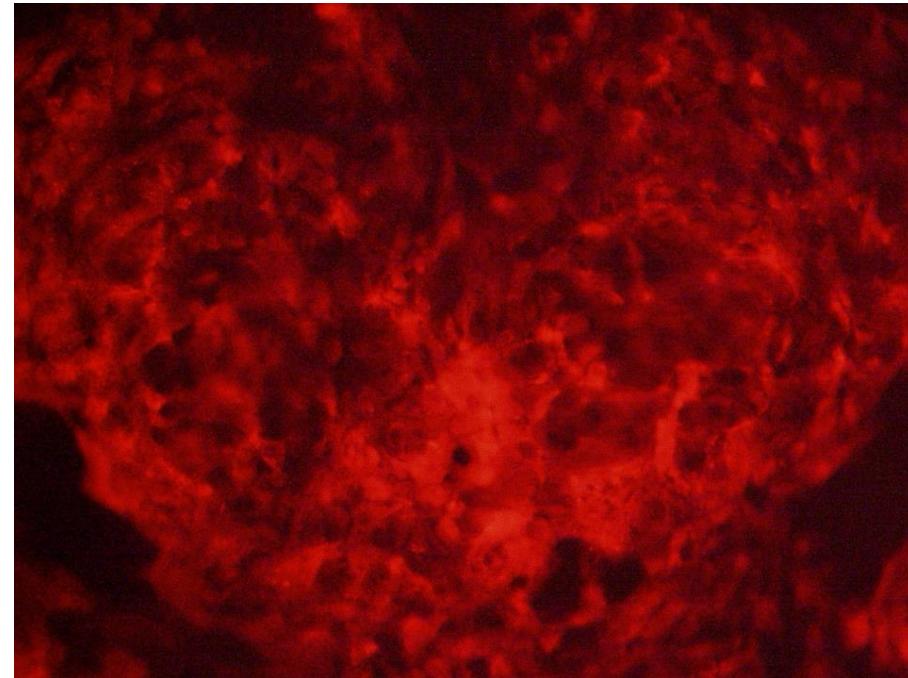
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# 探索研究、挑戰



**hESC-UNC45B<sup>-/-</sup> CMs do not beat and exhibit severely disrupted sarcomeric structures**



# A working model of the role of UNC45B in sarcomere assembly

## Nascent myofibrill



UNC45B<sup>-/-</sup>

Stem Cell Reports

Article

ISSCR

OPEN ACCESS

Cardiac myofibrillogenesis is spatiotemporally modulated by the molecular chaperone UNC45B

Serena Huei-An Lu,<sup>1,5</sup> Yi-Hsuan Wu,<sup>1,5</sup> Liang-Yu Su,<sup>1,5</sup> Zi-Ting Hsu,<sup>1,5</sup> Tzu-Han Weng,<sup>1</sup> Hsin-Yu Wang,<sup>1</sup> Chiao Yu,<sup>1</sup> Paul Wei-Che Hsu,<sup>4</sup> and Su-Yi Tsai<sup>1,2,3,\*</sup>

<sup>1</sup>Department of Life Science, National Taiwan University, Taipei 10617, Taiwan

<sup>2</sup>Research Center for Developmental Biology and Regenerative Medicine, National Taiwan University, Taipei 10617, Taiwan

<sup>3</sup>Genome and Systems Biology Degree Program, National Taiwan University, Taipei 10617, Taiwan

<sup>4</sup>Institute of Molecular and Genomic Medicine, National Health Research Institutes, Miaoli County 350, Taiwan

<sup>5</sup>These authors contributed equally

\*Correspondence: suyitsai@ntu.edu.tw

<https://doi.org/10.1016/j.stemcr.2023.05.006>



KIND2



UNC45B



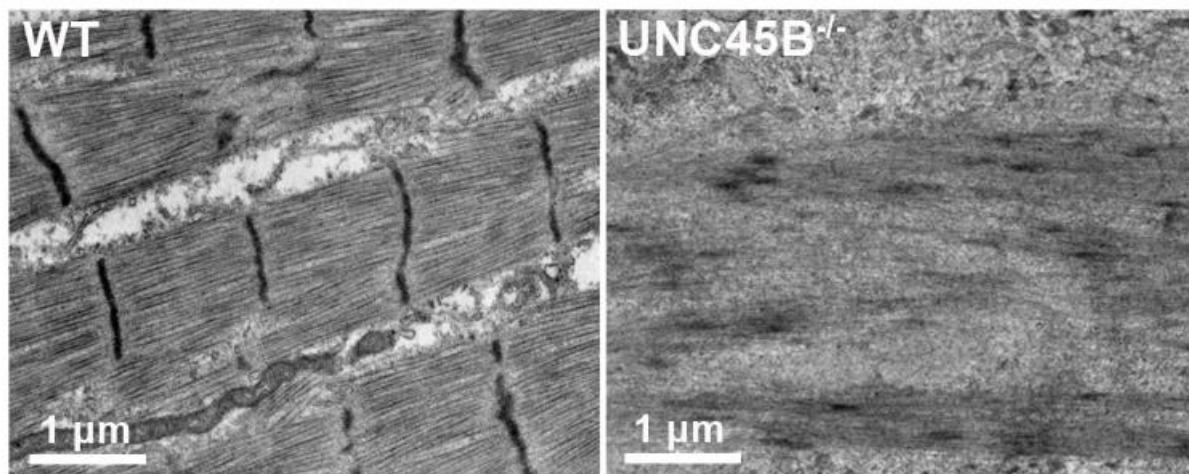
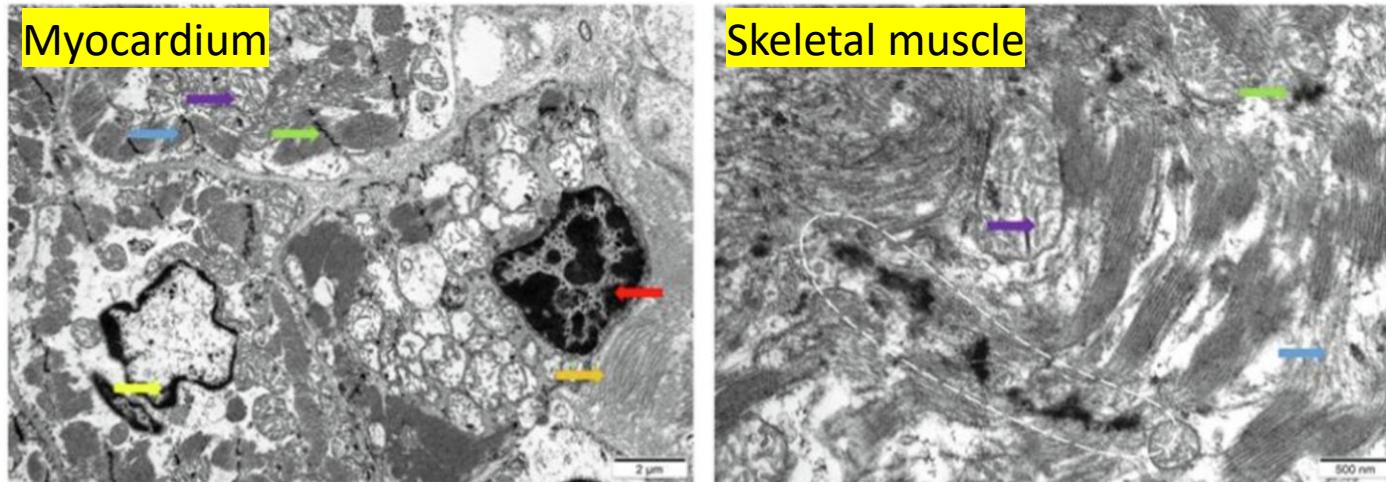
TTN



MYH10

# Neonatal myofibrillar myopathy type II associated with biallelic *UNC-45B* gene novel mutation and perinatal myasthenia as the core phenotype

a compound heterozygous mutation in *UNC-45B* (新生兒肌原纖維肌病II型)



(Shi et al., 2022)

# 探索研究、永遠的挑戰

## --文章背後沒有說的事…

Stem Cell Reports

Article



OPEN ACCESS

## Cardiac myofibrillogenesis is spatiotemporally modulated by the molecular chaperone UNC45B

Serena Huei-An Lu,<sup>1,5</sup> Yi-Hsuan Wu,<sup>1,5</sup> Liang-Yu Su,<sup>1,5</sup> Zi-Ting Hsu,<sup>1,5</sup> Tzu-Han Weng,<sup>1</sup> Hsin-Yu Wang,<sup>1</sup> Chiao Yu,<sup>1</sup> Paul Wei-Che Hsu,<sup>4</sup> and Su-Yi Tsai<sup>1,2,3,\*</sup>

<sup>1</sup>Department of Life Science, National Taiwan University, Taipei 10617, Taiwan

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<sup>3</sup>Genome and Systems Biology Degree Program, National Taiwan University, Taipei 10617, Taiwan

<sup>4</sup>Institute of Molecular and Genomic Medicine, National Health Research Institutes, Miaoli County 350, Taiwan

<sup>5</sup>These authors contributed equally

\*Correspondence: suyitsai@ntu.edu.tw

<https://doi.org/10.1016/j.stemcr.2023.05.006>

# 努力就會成功？

112	專題研究計畫	20230801~ 20240731	未獲通過	計畫主持人
112	專題研究計畫 (國際年輕傑出學者研究計畫)	20230801~ 20240731	未獲通過	計畫主持人
111	專題研究計畫 (一般研究計畫)	20220801~ 20230731	未獲通過	共同主持人
110	專題研究計畫 (新進人員研究計畫)	20210801~ 20220731	未獲通過	計畫主持人
110	專題研究計畫 (新秀學者研究計畫)	20210801~ 20220731	未獲通過	計畫主持人
109	專題研究計畫	20200801~ 20210731	未獲通過	計畫主持人
109	專題研究計畫 (一般研究計畫)	20200801~ 20210731	結案	計畫主持人
109	專題研究計畫 (新進人員研究計畫)	20200801~ 20230731	結案	計畫主持人
108	專題研究計畫 (一般研究計畫)	20190801~ 20200731	結案	計畫主持人

# 挫折使人發想！

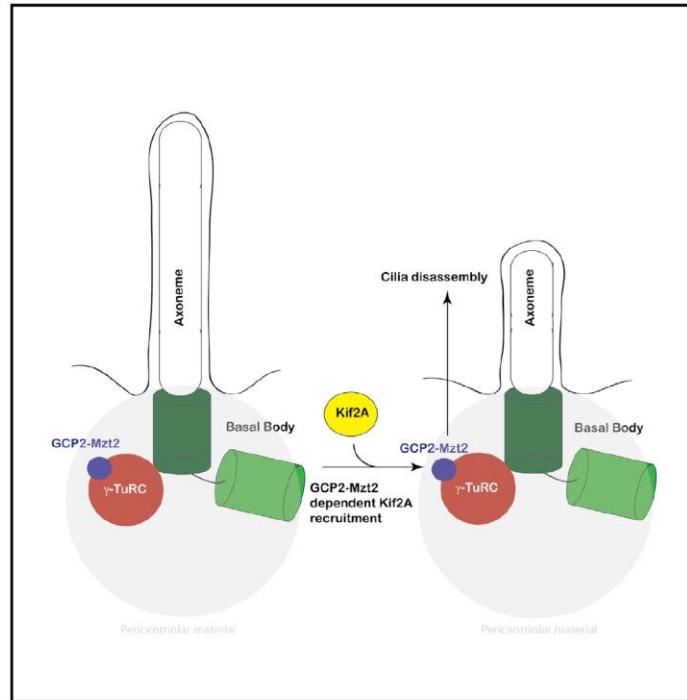
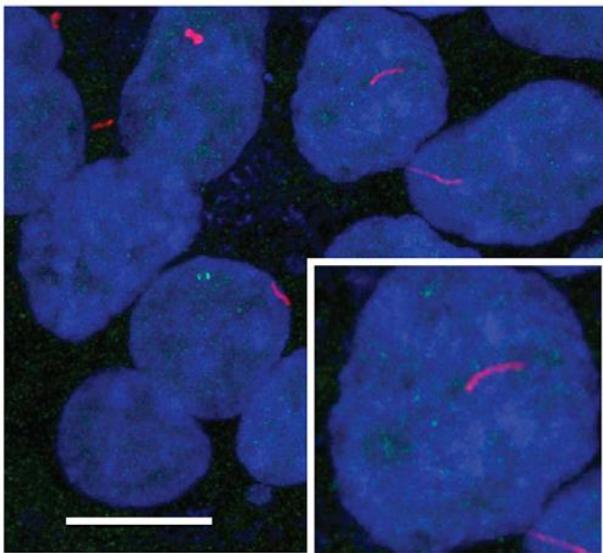
Article

## Cell Reports

### A $\gamma$ -tubulin complex-dependent pathway suppresses ciliogenesis by promoting cilia disassembly

#### Graphical abstract

C  $\Delta$ GCP2 NTS (Kif2A/Arl13b)



#### Authors

Sahana Shankar, Zi-Ting Hsu,  
Artur Ezquerro, ..., Jens Lüders,  
Su-Yi Tsai, Kuo-Chiang Hsia

#### Correspondence

jens.luders@irbbarcelona.org (J.L.),  
suyitsai@ntu.edu.tw (S.-Y.T.),  
khsia@gate.sinica.edu.tw (K.-C.H.)

#### In brief

Shankar et al. show that a kinesin Kif2A bearing microtubule-depolymerizing activity is recruited to the cilium basal body via the  $\gamma$ -TuRC subunits GCP2 and Mzt2. The  $\gamma$ -TuRC-Kif2A-dependent pathway promotes cilia disassembly, preventing ciliogenesis. Functional heterogeneity of  $\gamma$ -TuRC at the basal body facilitates microtubule nucleation and Kif2A recruitment, modulating ciliogenesis.

# Never Give up!

--充實自己

Article

## Cell Reports

### A $\gamma$ -tubulin complex-dependent pathway suppresses ciliogenesis by promoting cilia disassembly

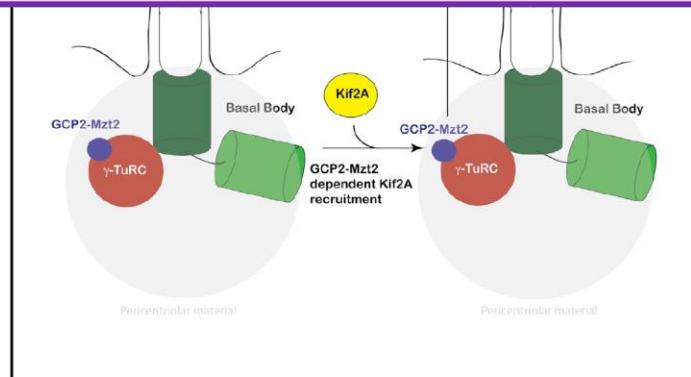
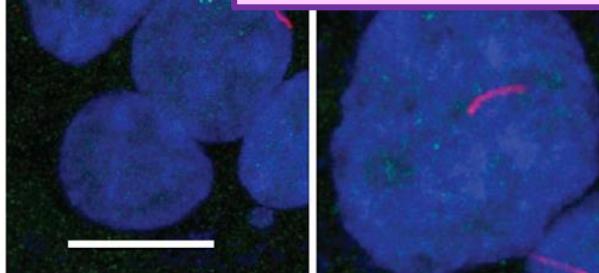
Graphical abstract

Authors

Sahana Shankar, Zi-Ting Hsu,  
Artur Ezquerro, ..., Jens Lüders,

C  $\Delta$ GCP2 NTS (Kif2A/Arl13b)

努力不一定會成功-  
但不努力就一定不會成功！

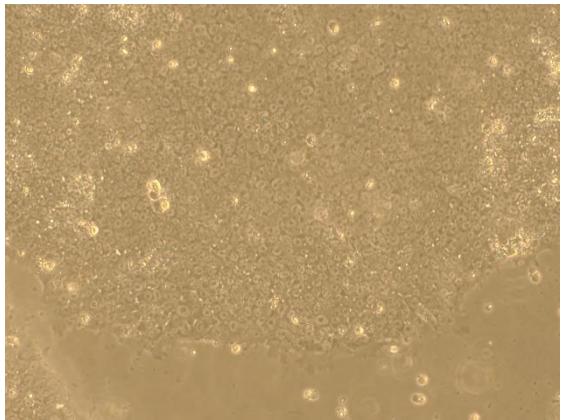


Shankar et al. show that a kinesin Kif2A bearing microtubule-depolymerizing activity is recruited to the cilium basal body via the  $\gamma$ -TuRC subunits GCP2 and Mzt2. The  $\gamma$ -TuRC-Kif2A-dependent pathway promotes cilia disassembly, preventing ciliogenesis. Functional heterogeneity of  $\gamma$ -TuRC at the basal body facilitates microtubule nucleation and Kif2A recruitment, modulating ciliogenesis.

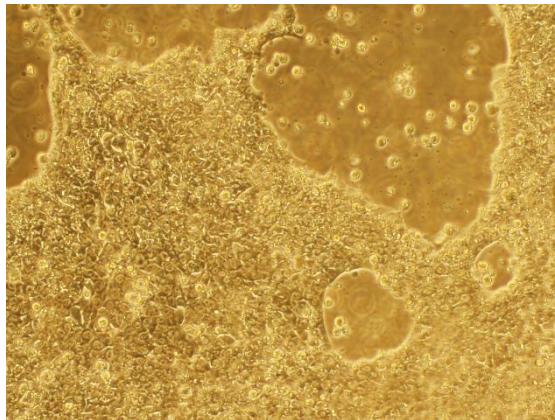
# 成長的過程是艱辛的！



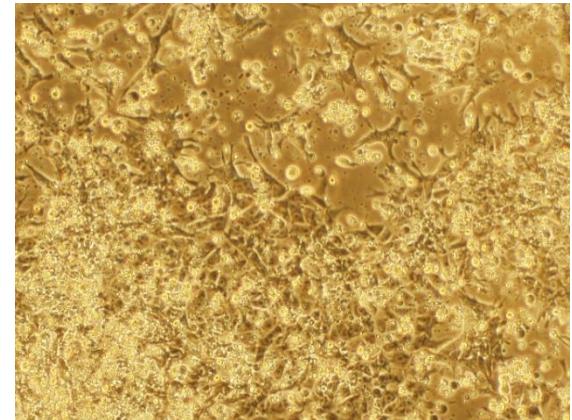
# Differentiation Day0



## Differentiation Day1



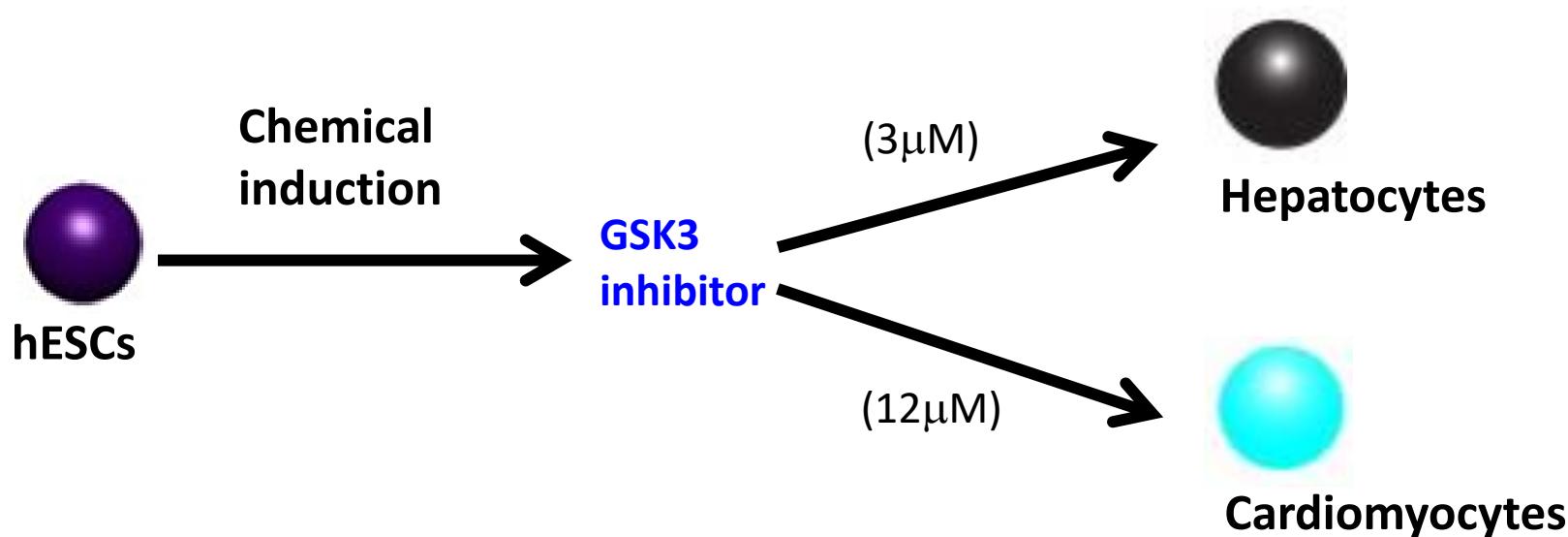
## Differentiation Day4



# 選擇（人生的十字路口）

## Cell differentiation $\Rightarrow$ Cell Fate (細胞的命運)

- 選擇的重要性
- 不要害怕選擇
- 選擇你選愛，愛你所選擇



贏在起跑點？

我的三不政策(不出國、不唸博班、不當PI)

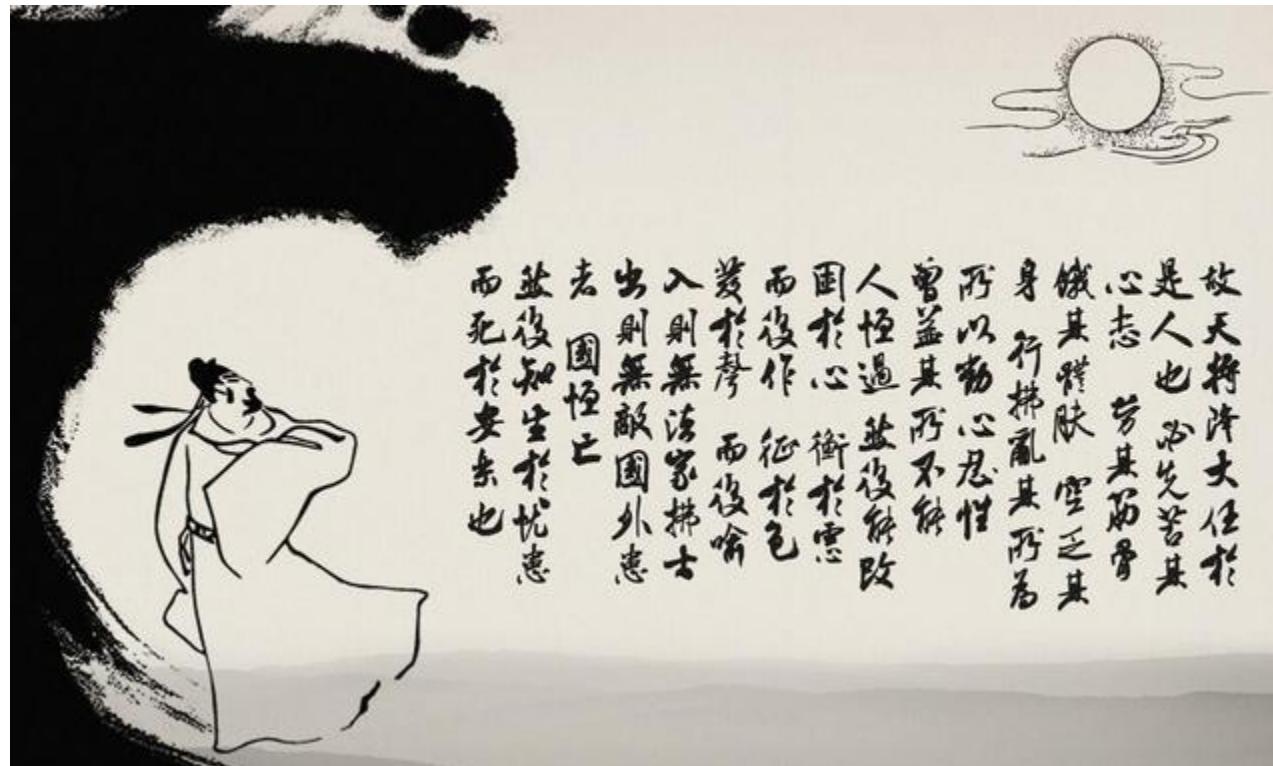


輸在起跑點！

我的三不政策(不出國、不唸博班、不當PI)

# 輸在起跑點！

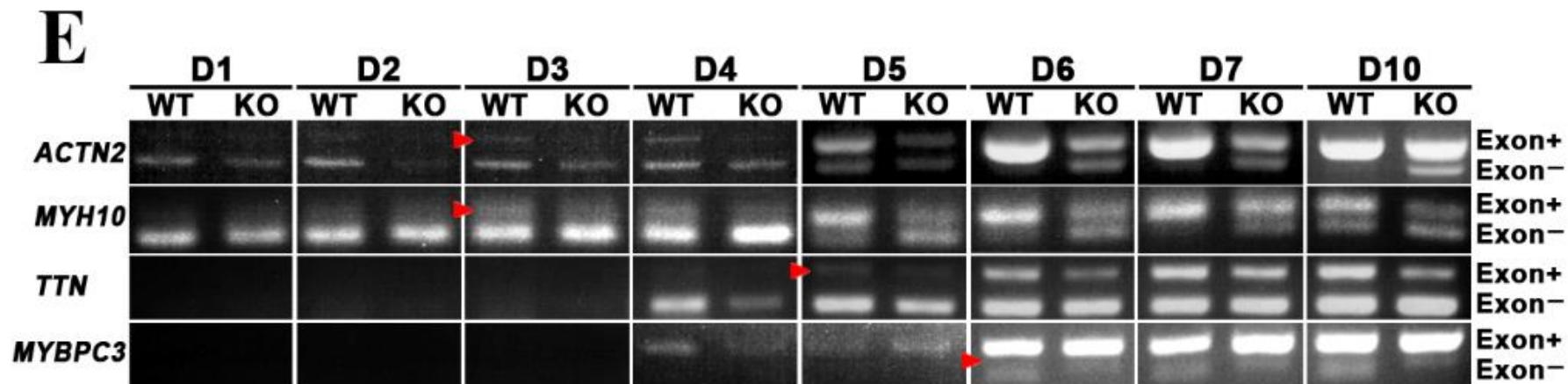
我的三不政策(不出國、不唸博班、不當PI)  
生於憂患，死於安樂(跌倒挫折是好事!)



# Alternative splicing of cardiac genes is mediated by RBM24 in a temporal-dependent manner

每個人開竅的時間不同，潛伏期不同，把握當下！

努力就對了！



# 人生就像一場馬拉松

- 選擇你選愛，愛你所選擇
- 是一種磨心的過程
- 不要在意別人的速度

人生，能不能堅持到終點！



2024國家地理雜誌路跑

# 不被看好，有關係嗎？

Cell

## Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors

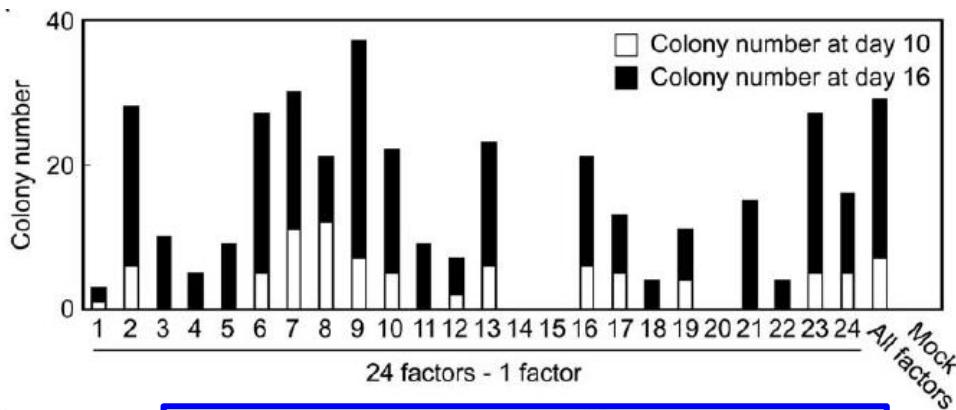
Kazutoshi Takahashi<sup>1</sup> and Shinya Yamanaka<sup>1,2,\*</sup>

<sup>1</sup>Department of Stem Cell Biology, Institute for Frontier Medical Sciences, Kyoto University, Kyoto 606-8507, Japan

<sup>2</sup>CREST, Japan Science and Technology Agency, Kawaguchi 332-0012, Japan

\*Contact: [yamanaka@frontier.kyoto-u.ac.jp](mailto:yamanaka@frontier.kyoto-u.ac.jp)

DOI 10.1016/j.cell.2006.07.024



4 factors:Oct4, Sox2, cMyc, Klf4



Dr. Shinya Yamanaka

2012 Nobel Laureate

# 不被看好，有關係嗎？

Karikó received the Nobel Prize in Physiology or Medicine in 2023 for her work, along with American immunologist Drew Weissman.

Karikó spent more than twenty years as a poorly supported researcher at the University of Pennsylvania.

She was described as "not of faculty quality"

From wikipedia



Katalin Karikó

2023 Nobel Laureate

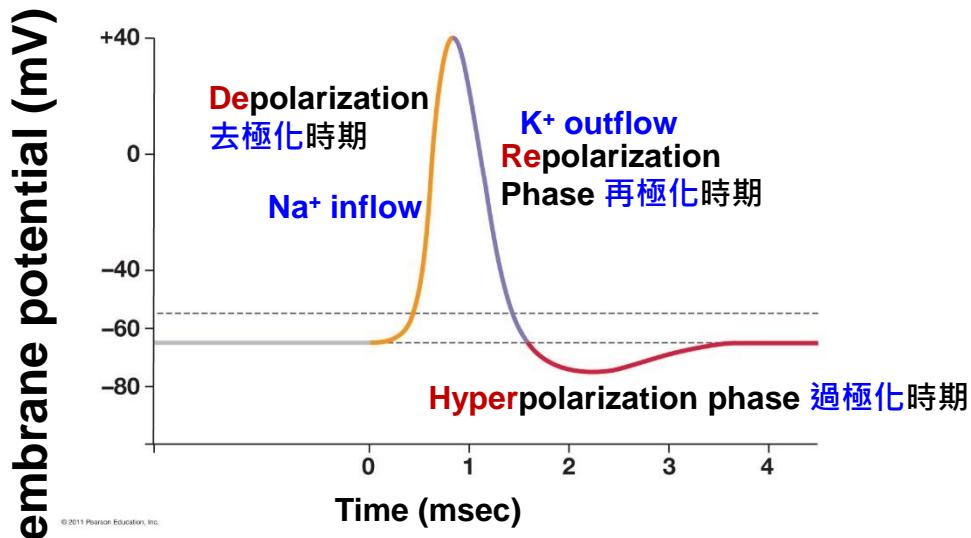
# 人生就像一場馬拉松

- 選擇你選愛，愛你所選擇
- 是一種磨心的過程
- 不要在意別人的速度
- 學習欣賞別人



2024國家地理雜誌路跑

# Action potential 動作電位

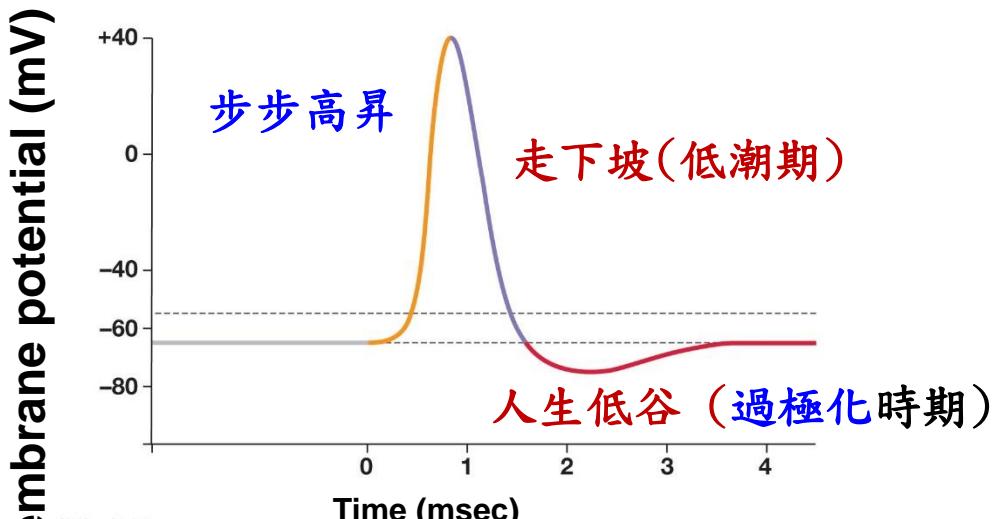


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By Freeman

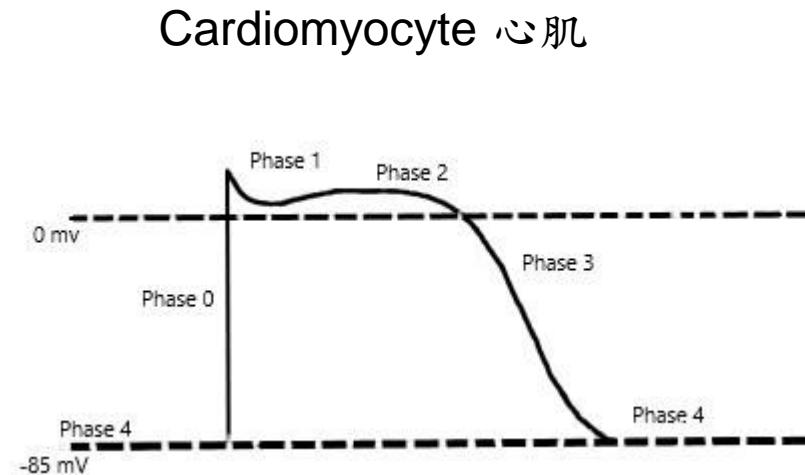
# 人生就像是一連串的動作電位

## Action potential 動作電位



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By Freeman

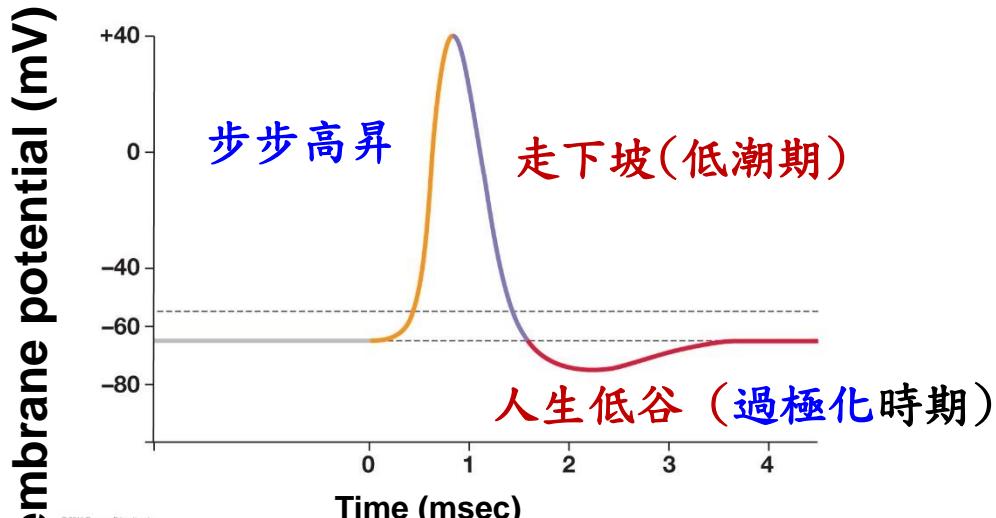


Singh et. al., 2023

# 人生就像是一連串的動作電位

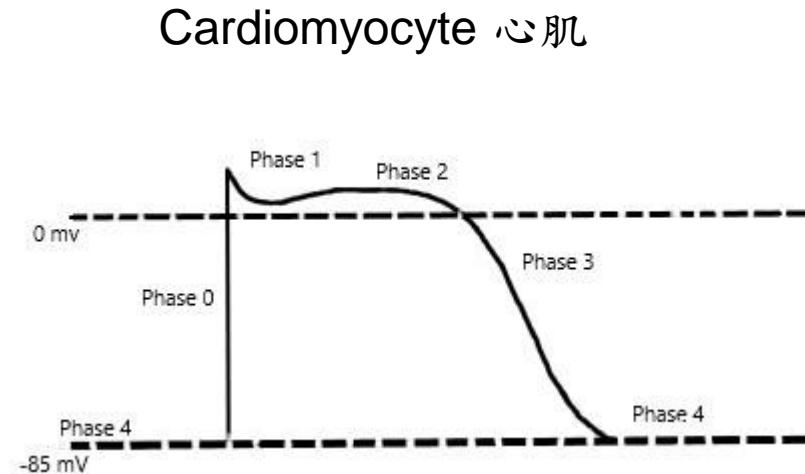
—當你爬到高點時，別忘了關心還在低谷的人！

## Action potential 動作電位



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Singh et. al., 2023

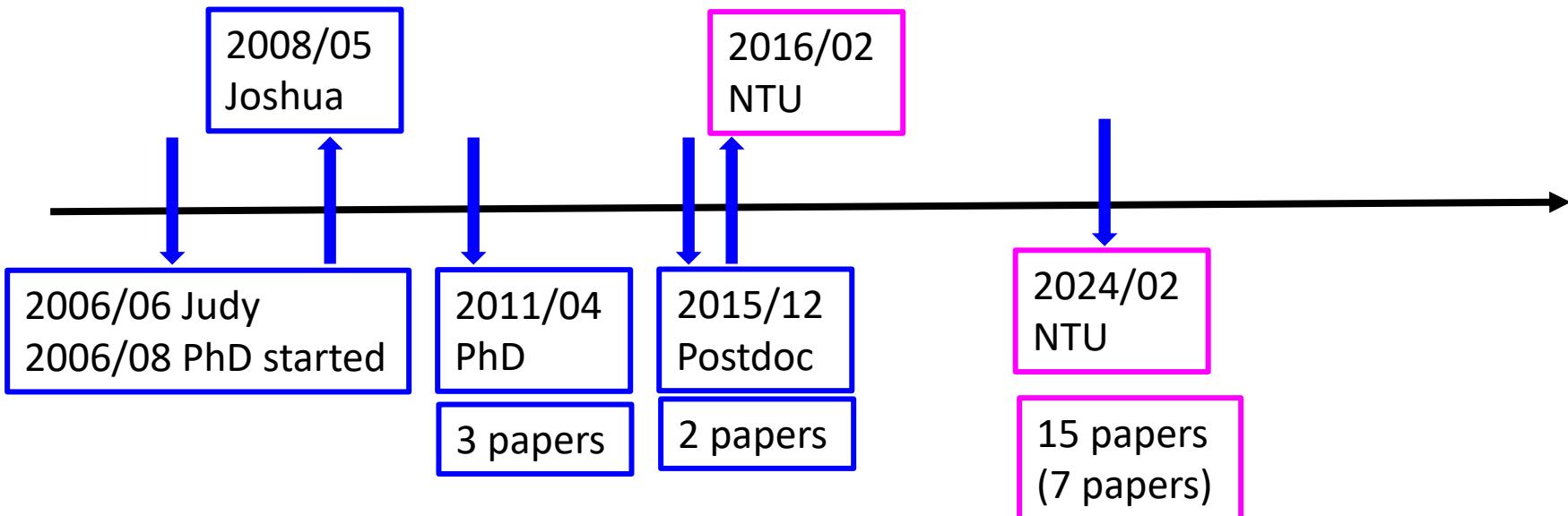
# 貴人?!

一個人可以跑得快，但一群人可以跑得遠(學習欣賞別人)



# 如果有時光機?!

韌性!!



選擇你選愛，愛你所選擇!!

# Summary (總結)

1. 可以迷惘，但要努力
2. 錢不是最重要的，但興趣是！
3. 年輕要勇於去探險，凡走過必留下痕跡
4. 選擇了，就不要抱怨
5. 不在勝人，在自勝



人生真苦，所以一定要做自己最喜歡的事

# Summary (總結)



人生真苦，所以一定要做自己最喜歡的事



# Acknowledgments

