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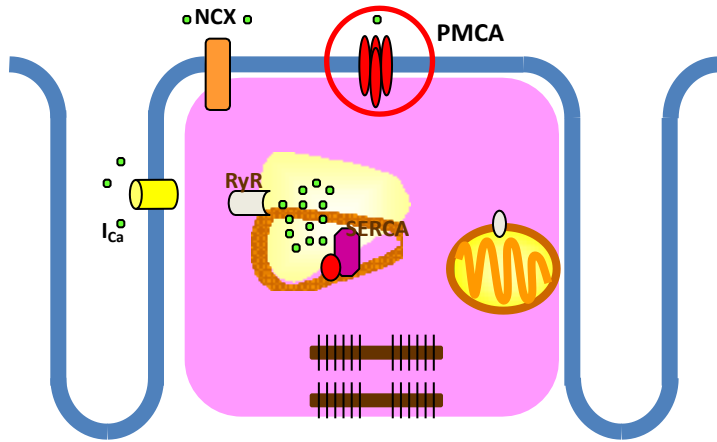
OMICS Group has organized 500 conferences, workshops and national symposiums across the major cities including San Francisco, Las Vegas, San Antonio, Omaha, Orlando, Raleigh, Santa Clara, Chicago, Philadelphia, Baltimore, United Kingdom, Valencia, Dubai, Beijing, Hyderabad, Bengaluru and Mumbai.

# Targeting calcium signaling as a novel therapeutic strategy for cardiac hypertrophy and failure

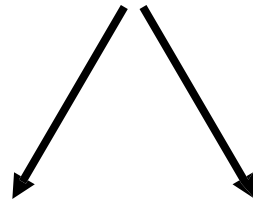
Tamer M A Mohamed, Riham Abou-Leisa, Min Zi, Sukhpal Prehar, Florence Baudoin,  
Elizabeth Cartwright, Ludwig Neyses, Delvac Oceandy

Cardiovascular Research Group, The University of Manchester, United Kingdom.

# Ca<sup>2+</sup> in myocardial (patho-)physiology



Ca<sup>2+</sup>



**Contraction/  
Relaxation**

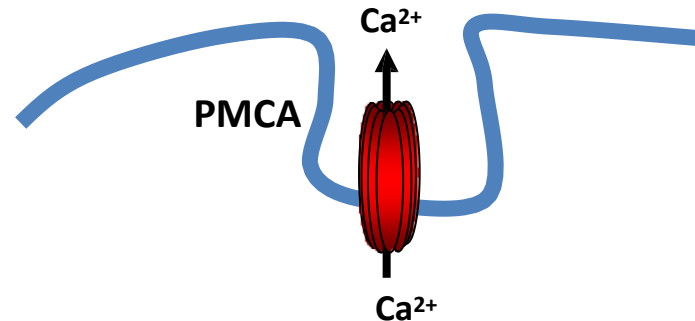
**LTCC & RYR /  
SERCA & NCX**

**Signal  
Transduction**

**PMCA4/  
TRPCs & IP3R**

# Plasma Membrane Calcium ATPase pump (PMCA)

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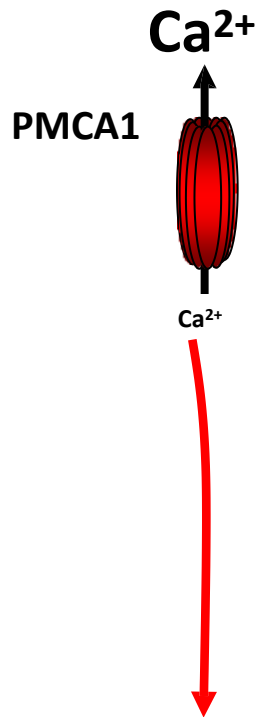


- ❖ PMCA is a calcium extrusion pump.
- ❖ There are 4 different isoforms of PMCA pump encoded by 4 different genes.
- ❖ PMCA1 and 4 are expressed in the heart.

**Whether PMCA4 regulates cardiac hypertrophy and how?**

# Human Relevance of Plasma Membrane Calcium ATPase pump isoforms (PMCAs)

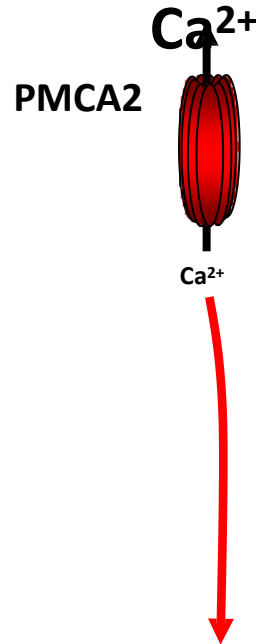
## PMCA1



**Blood Pressure**

*(Cho et al., Nat. Gen., 2009 & Levy et al., Nat. Gen., 2009)*

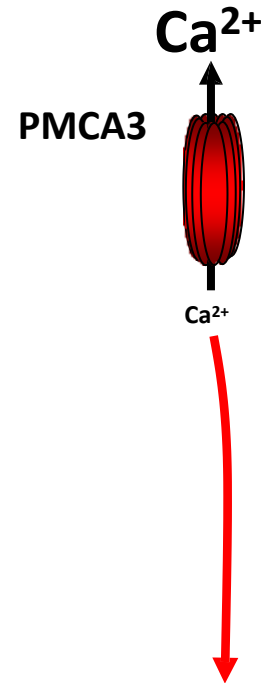
## PMCA2



**Deafness**

*(Schultz et al., NEJM, 2005)*

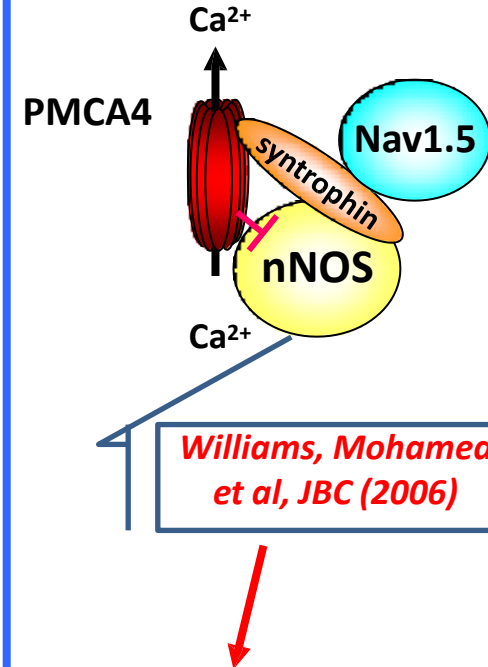
## PMCA3



**Ataxia**

*(Zanni et al., PNAS, 2012)*

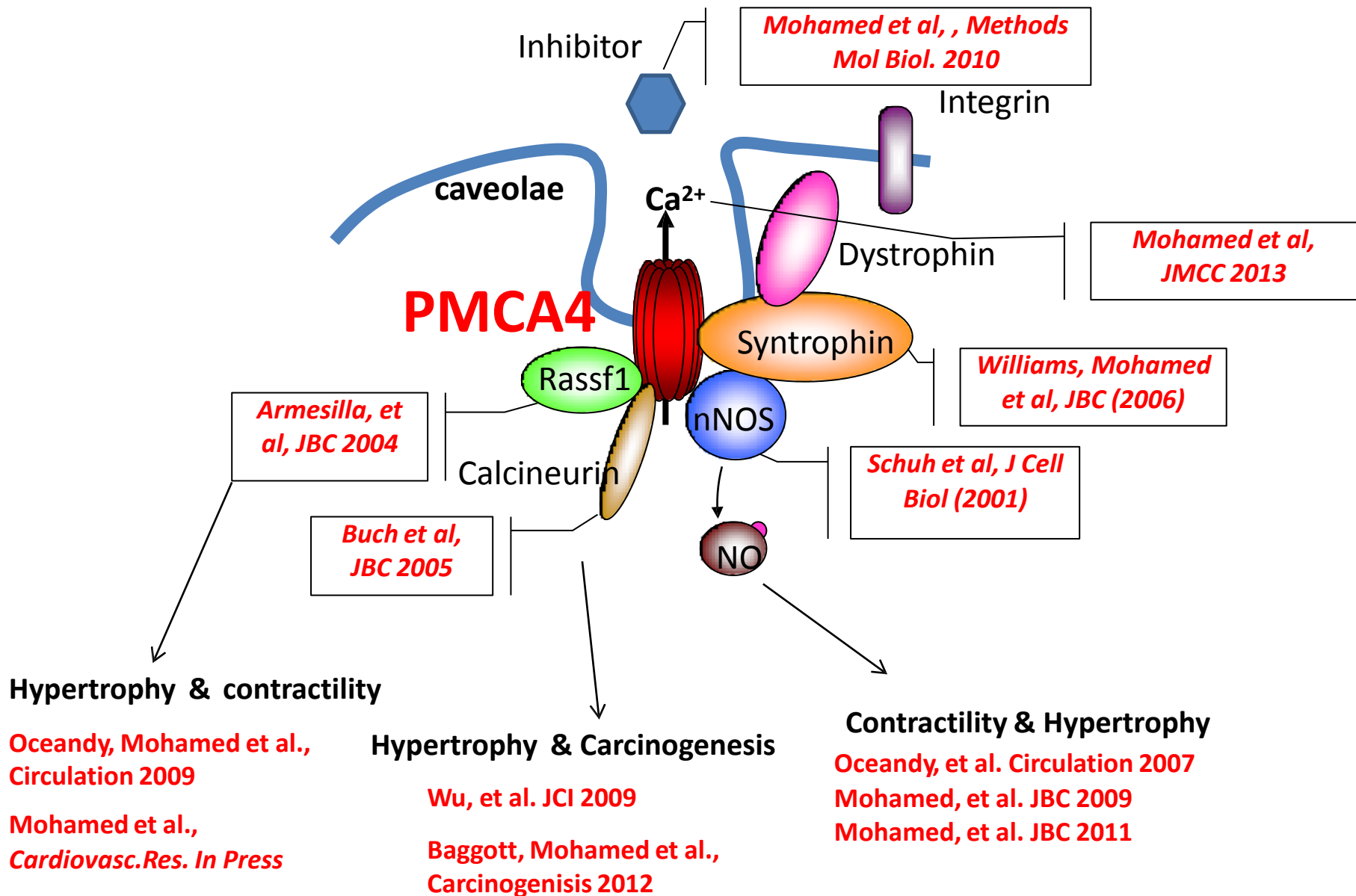
## PMCA4



**Long QT Syndrome**

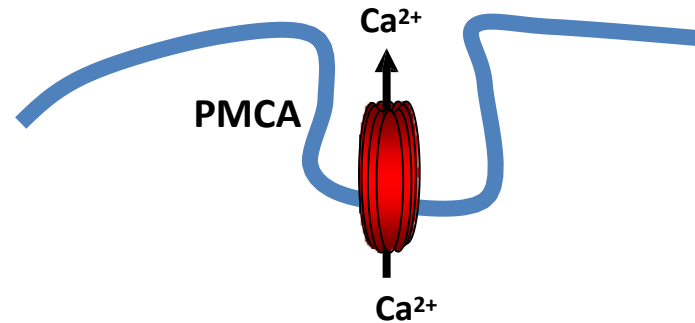
*(Ueda et al., PNAS, 2008)*

# PMCA4 Molecular complex



# Plasma Membrane Calcium ATPase pump (PMCA)

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**Whether PMCA4 regulates cardiac hypertrophy and how?**



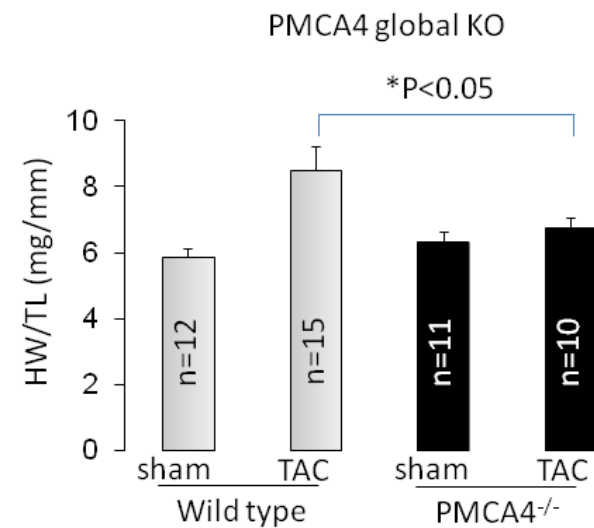
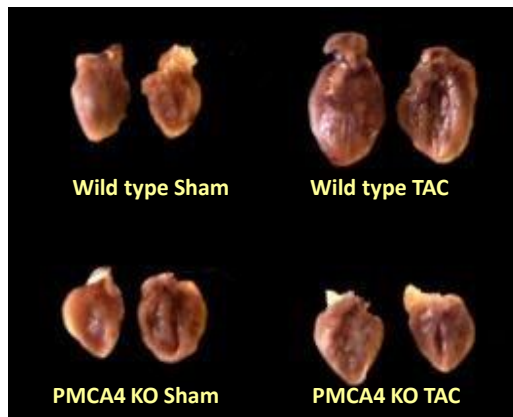
# PMCA4 KO



Mohamed et al., JBC 2011



Protected from pathological hypertrophy



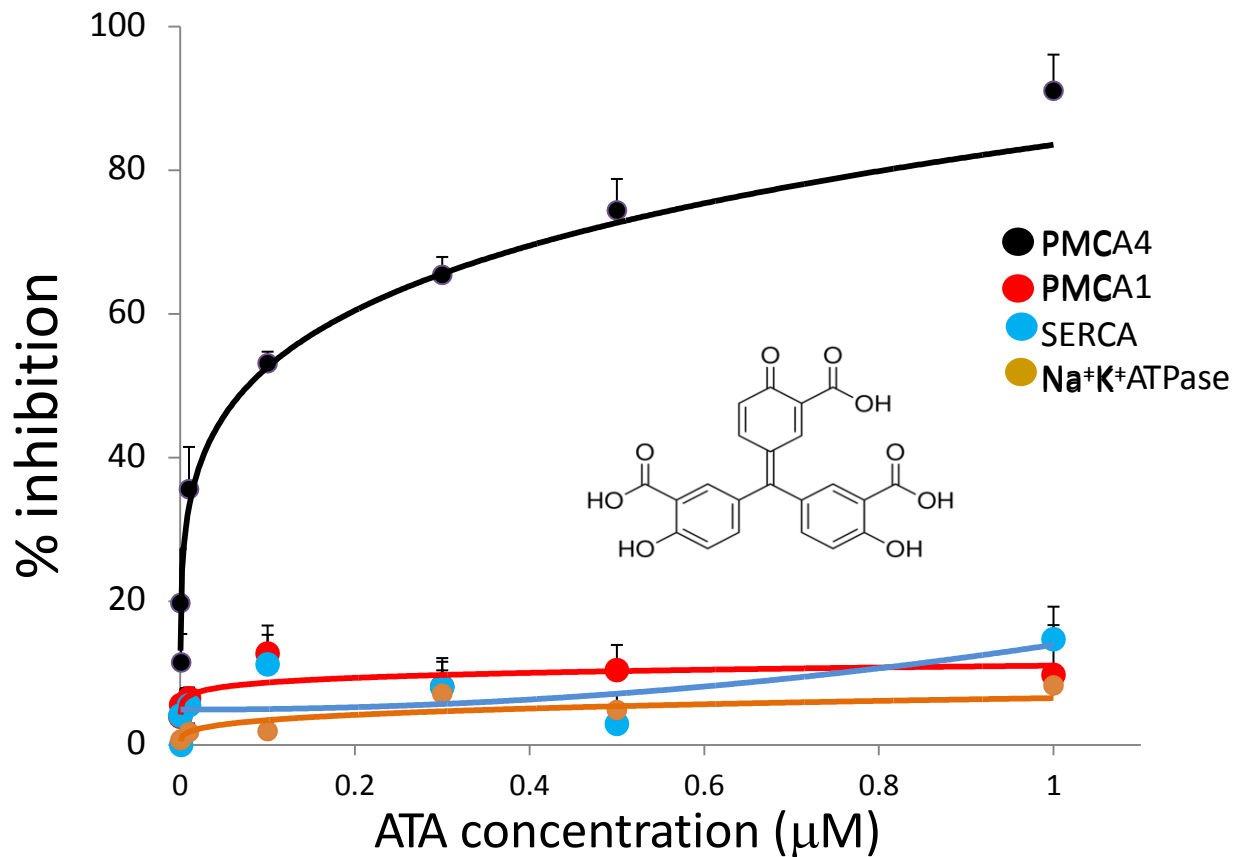
# Identification of the first PMCA4 specific inhibitor



Coupled enzyme assay on membrane microsomes from PMCA4 overexpressing cells

Screened 1300 compounds of medically optimised drug library

# Aurintricarboxylic acid (ATA) is the first PMCA4 specific inhibitor

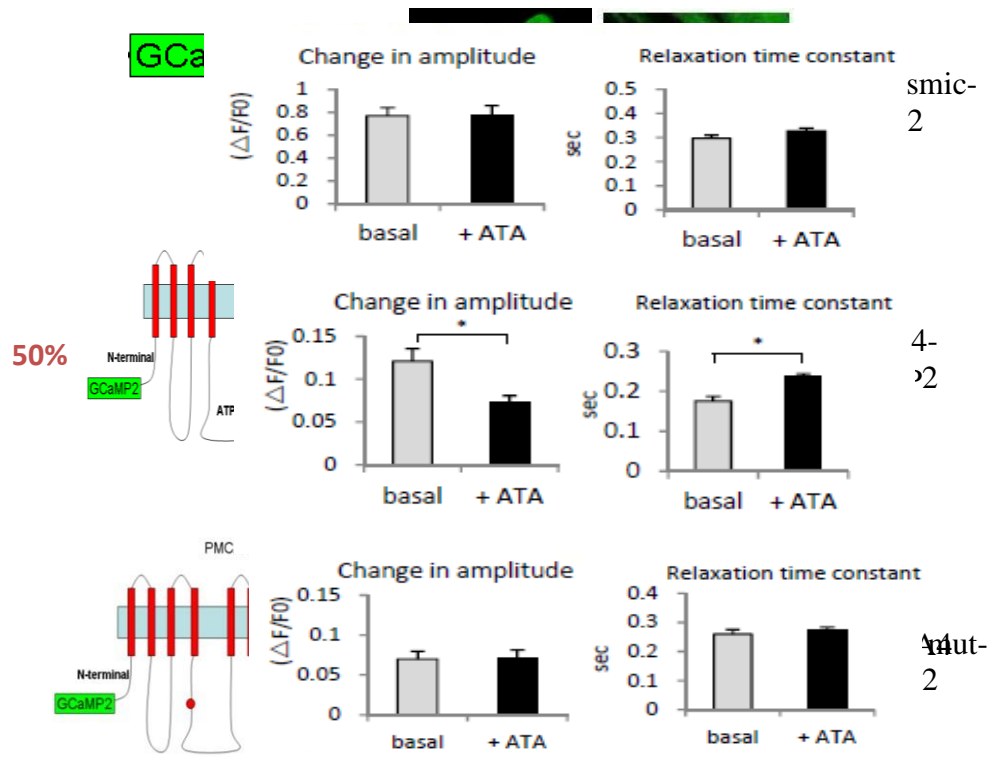
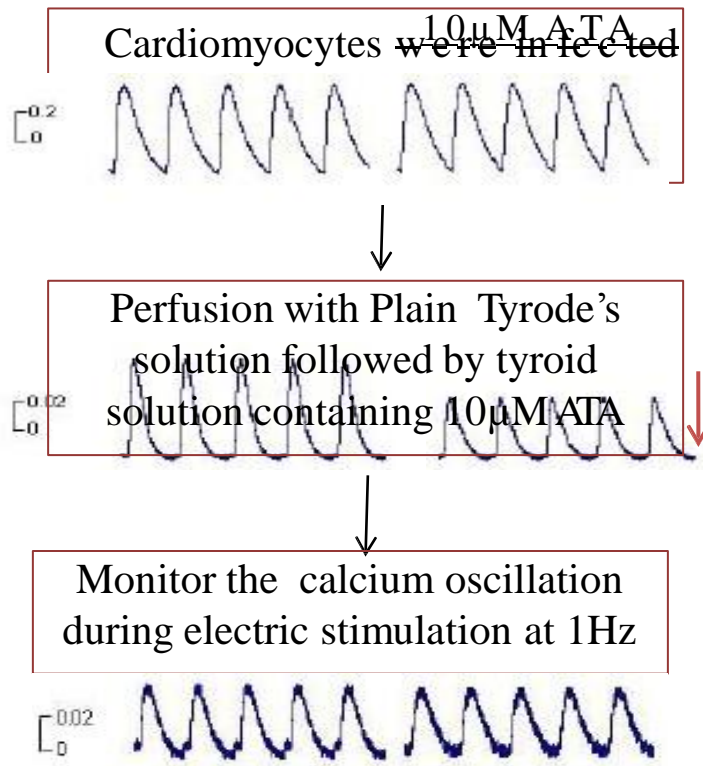
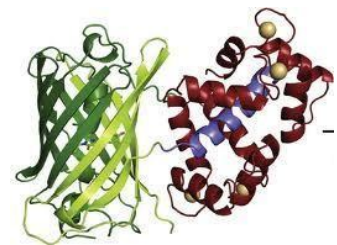


$IC_{50} = 0.1\mu M$

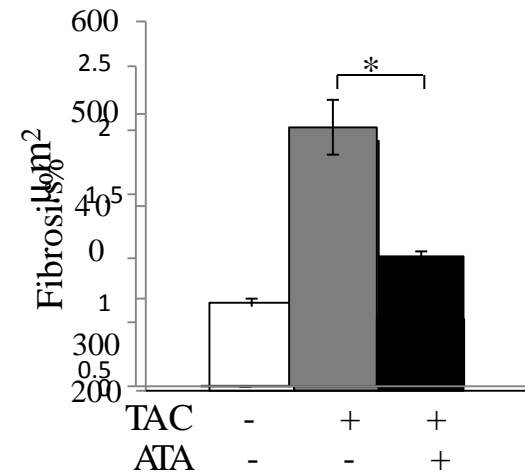
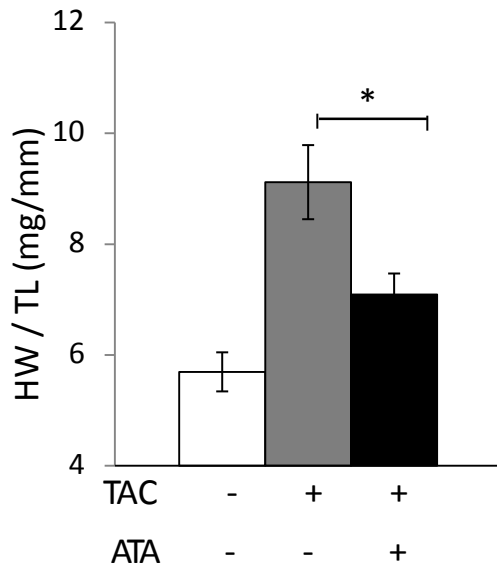
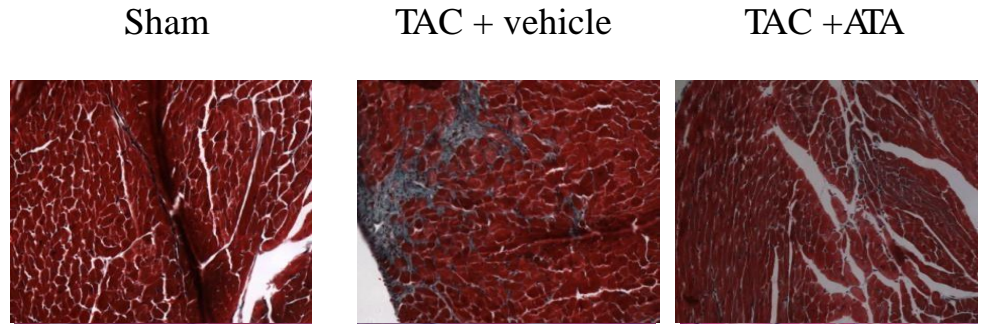
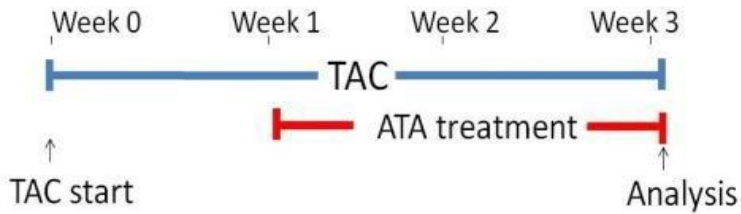
# ATA inhibits PMCA4 activity *in situ*



GCaMP2

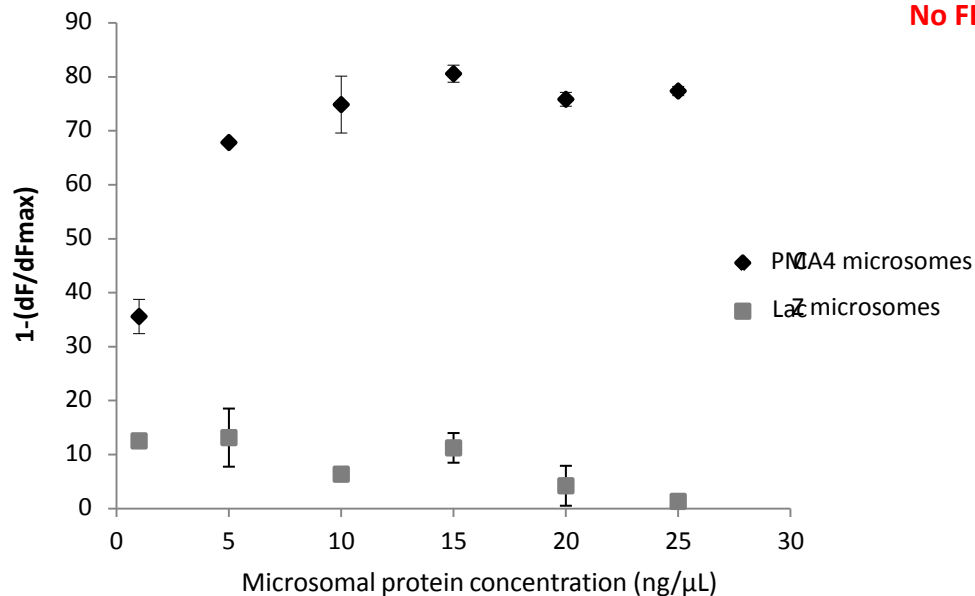
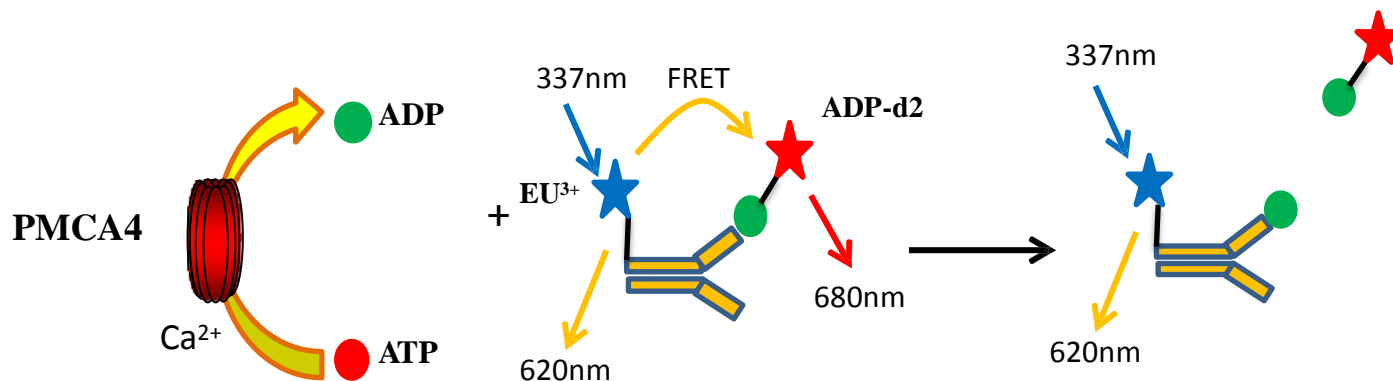


# ATA reverses existing hypertrophy in mice

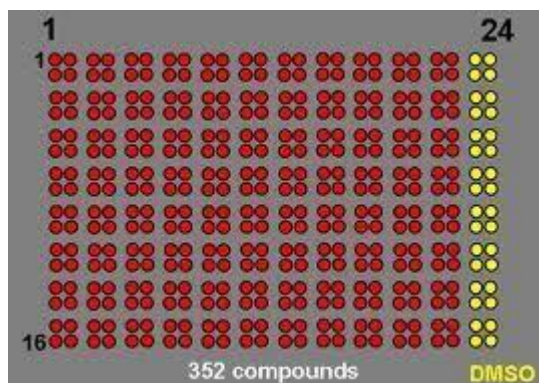


# New high-throughput screening assay for PMCA4

## Homogeneous Time Resolved Fluorescence (HTRF)



# High-throughput screening for PMCA4 inhibitors

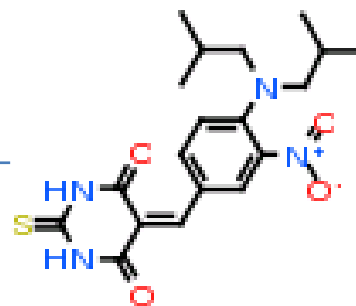


Screened 25000 compounds and identified 112 primary hits



77 confirmed hits from the original solid

Currently under testing for efficiency and specificity



Best inhibitor

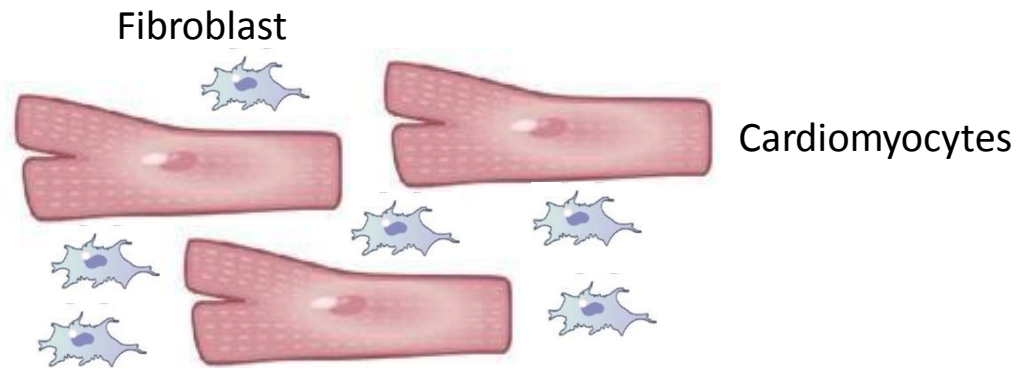
# Conclusion 1

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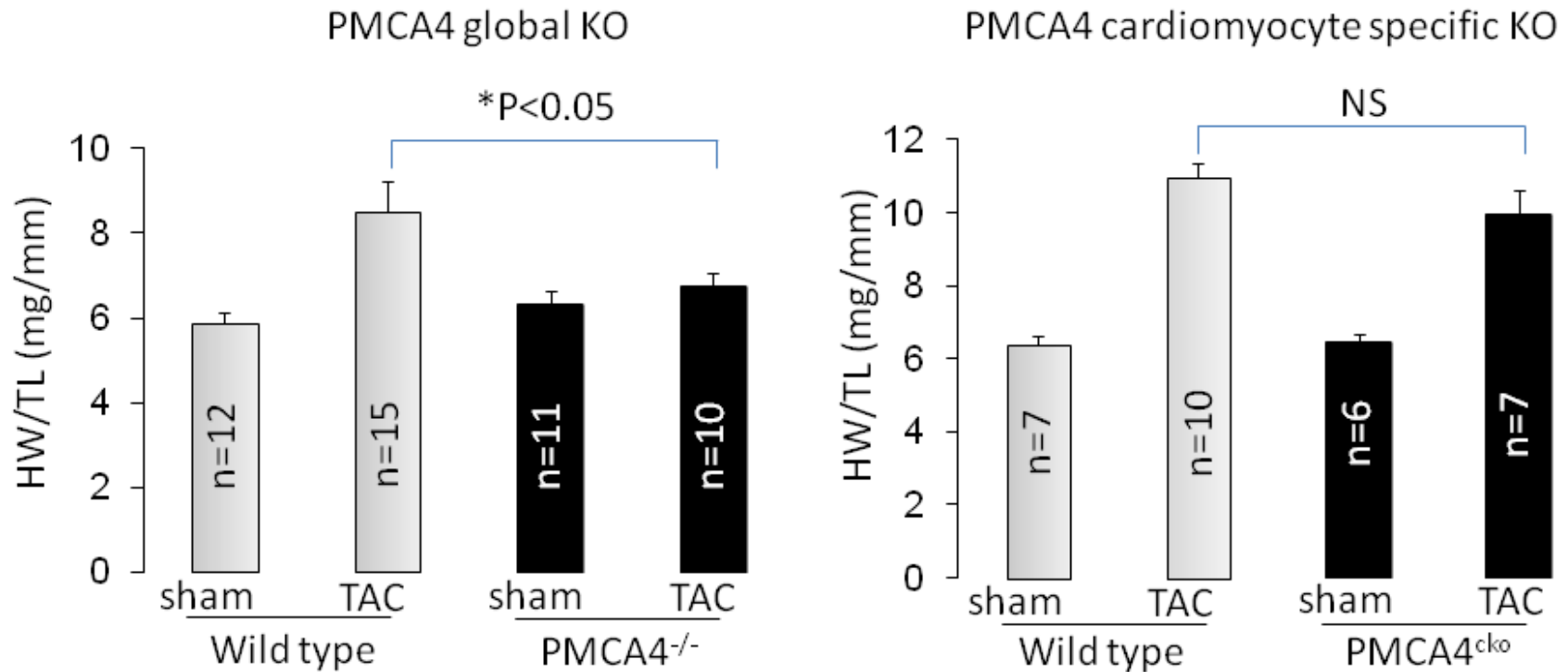
**PMCA4 inhibitor emulates the effect of PMCA4 knockout on cardiac hypertrophy**



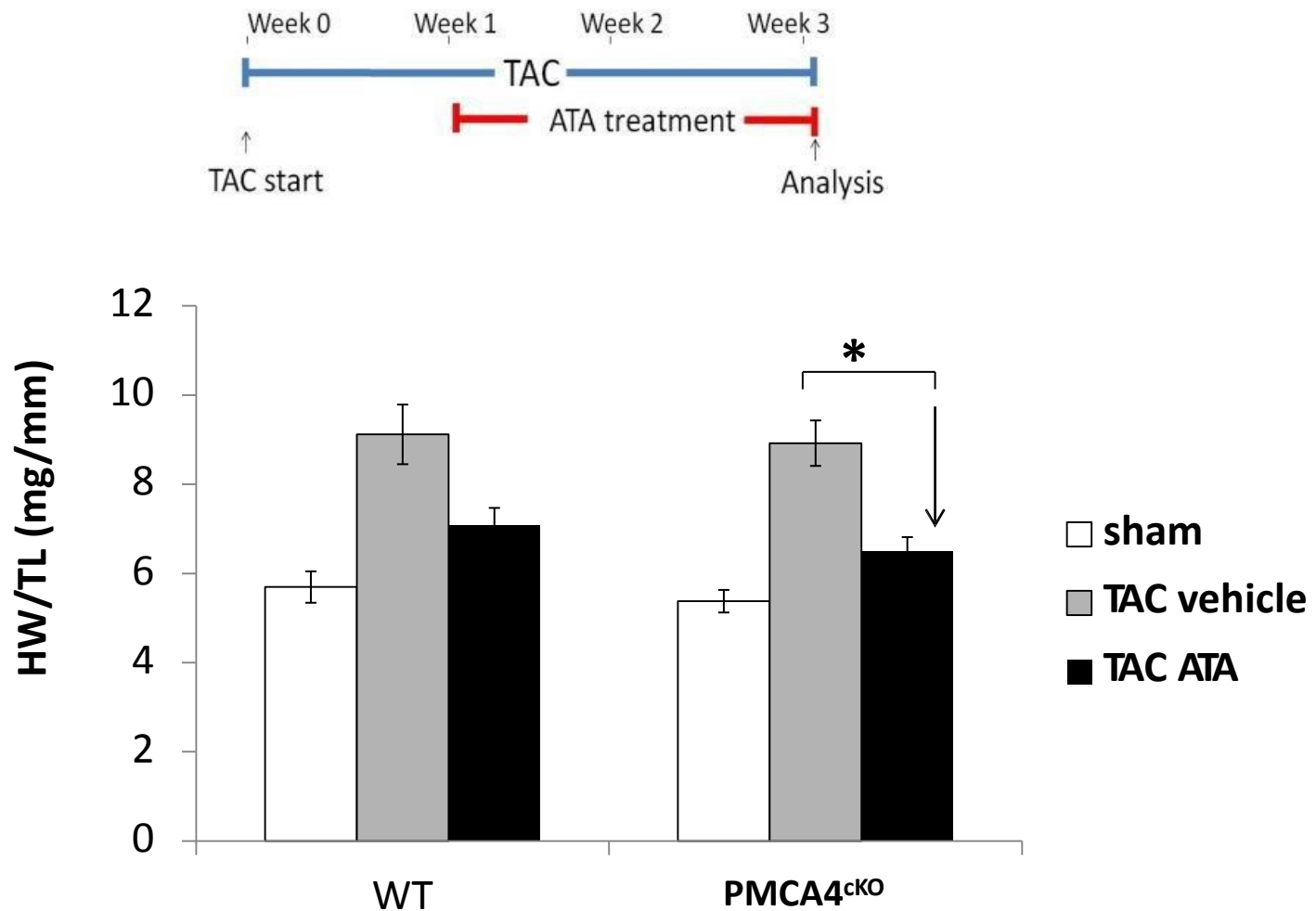
# Cardiomyocytes Vs Fibroblasts



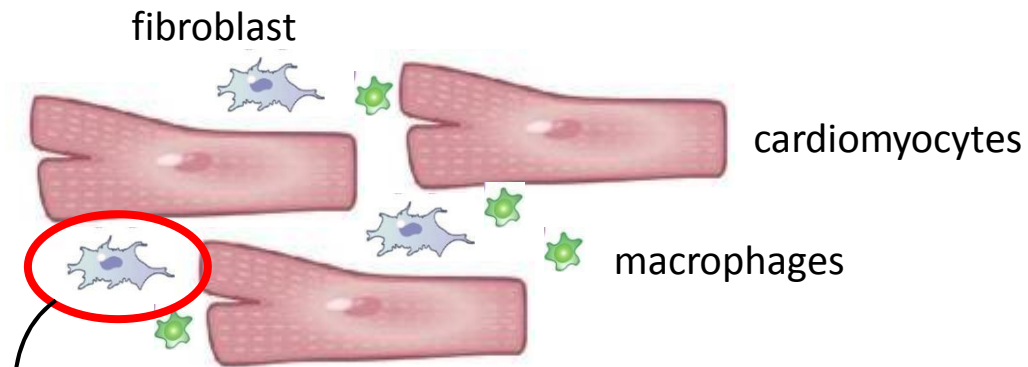
# PMCA4 cardiomyocyte specific knockout did not show protection against pathological hypertrophy



# ATA reverses existing hypertrophy in PMCA4<sup>ckO</sup> mice

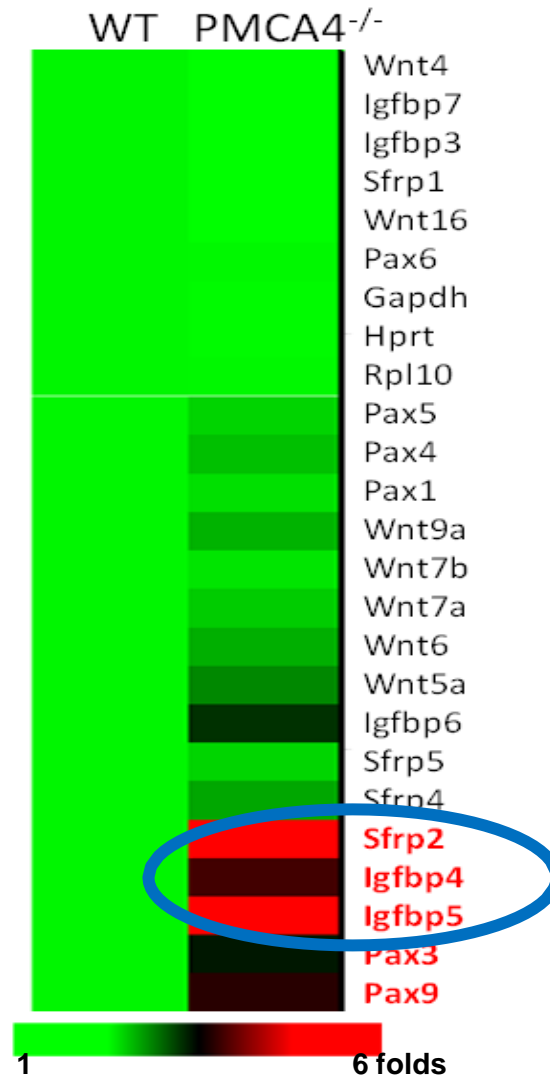


# What is the Mechanism?

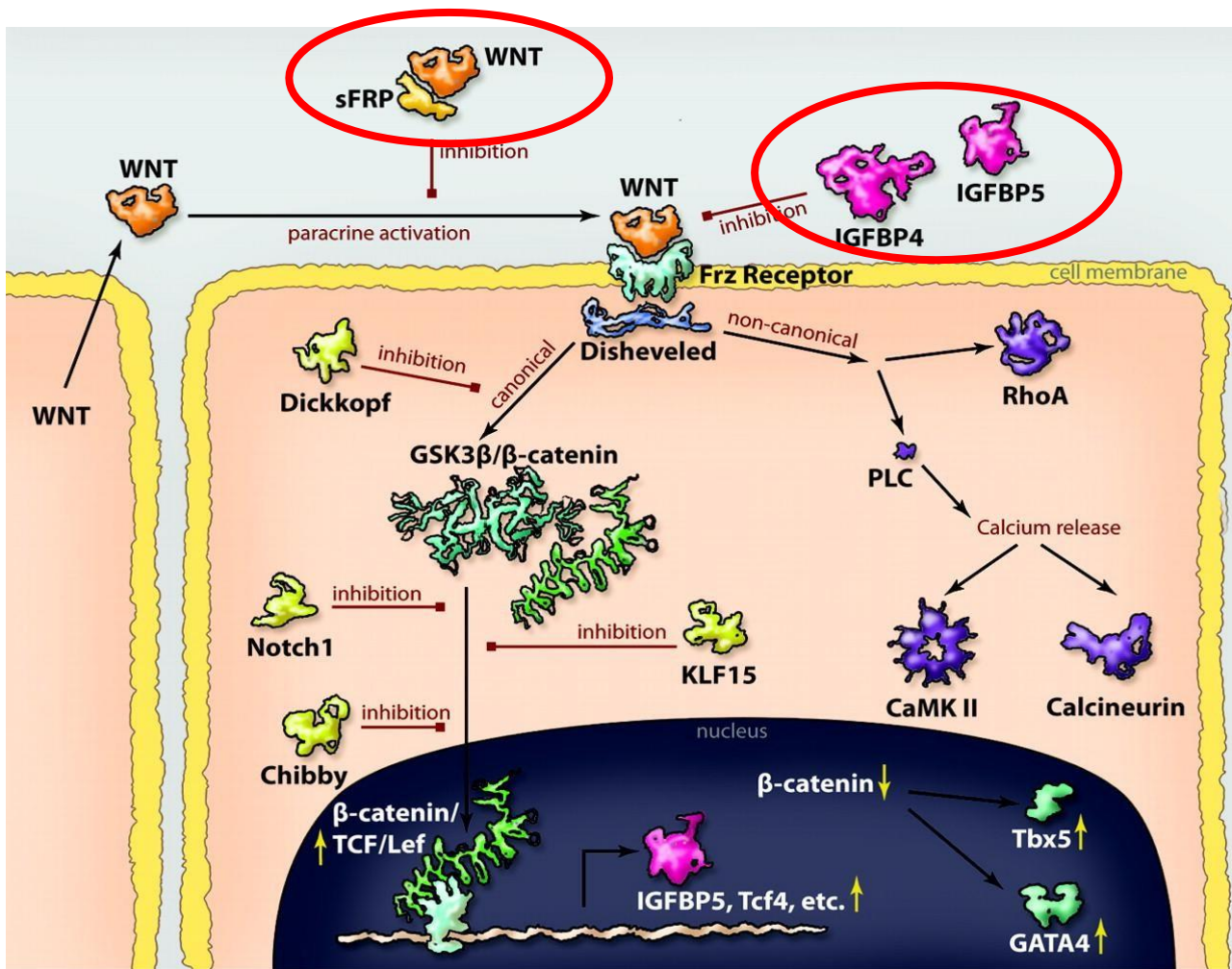


Microarray analysis:  
PMCA4<sup>-/-</sup> vs Wild type  
fibroblasts

# Microarray in PMCA4 KO skin and cardiac fibroblasts showed increased expression of Wnt inhibitors (SFRP2, IGFBP4 & IGFBP5)

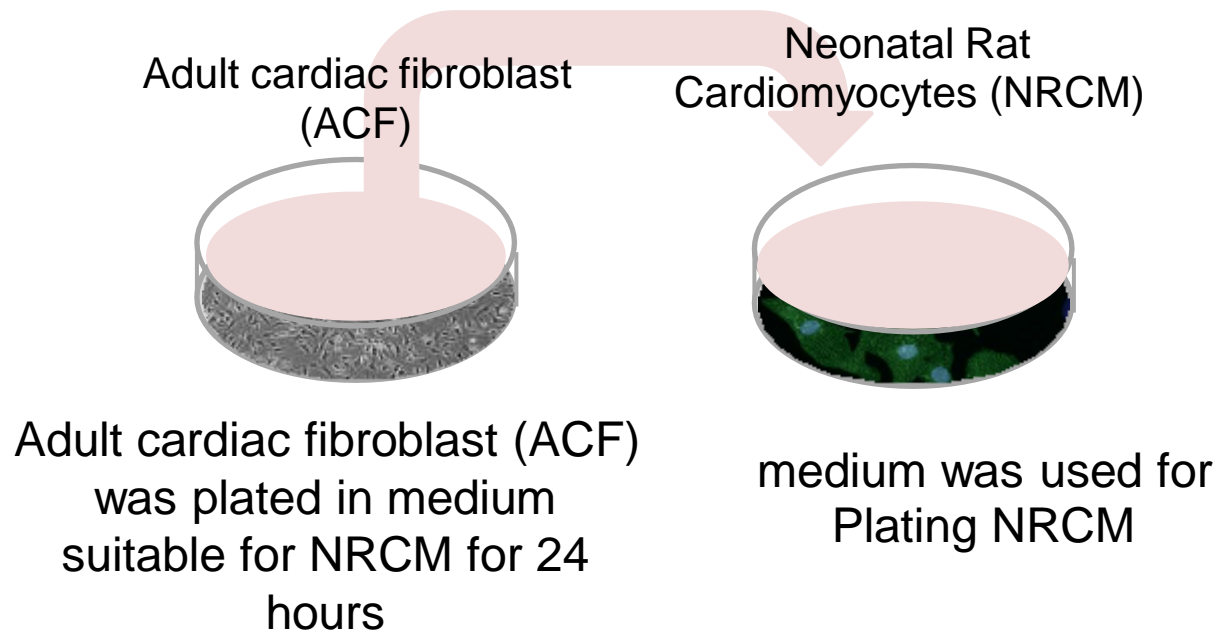


# Schematic summary of signaling molecules described to inhibit Wnt/ $\beta$ -catenin signaling in the cardiac compartment.

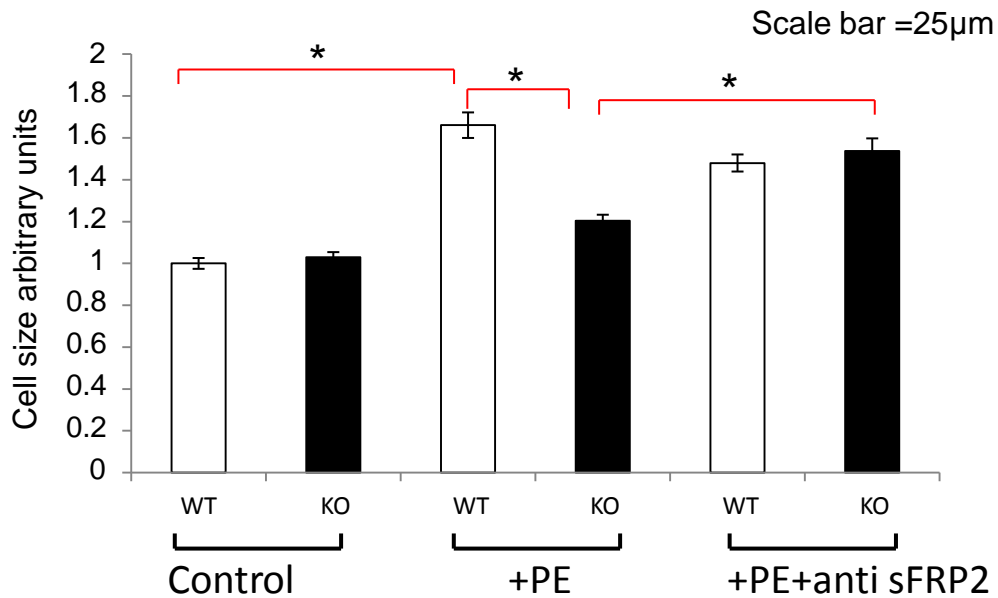
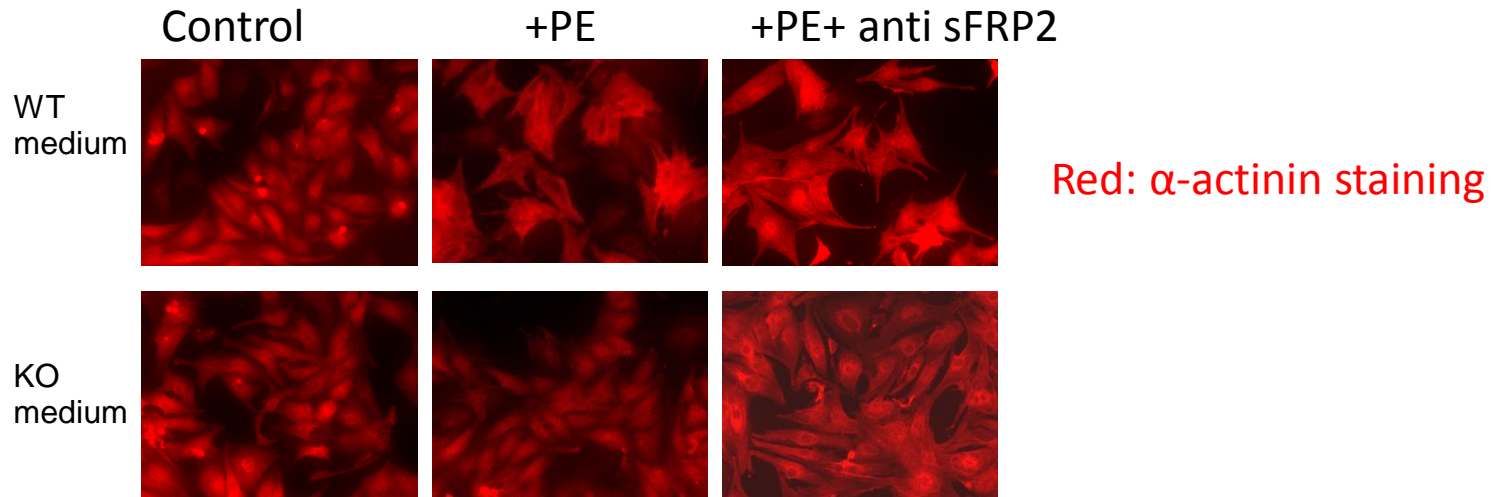


Bergmann M W Circulation Research 2010;107:1198-1208

- **Does PMCA4<sup>-/-</sup> fibroblast reduce the hypertrophic response in WT cardiomyocyte?**
- **Is this phenotype through upregulation of secreted sFRP2?**



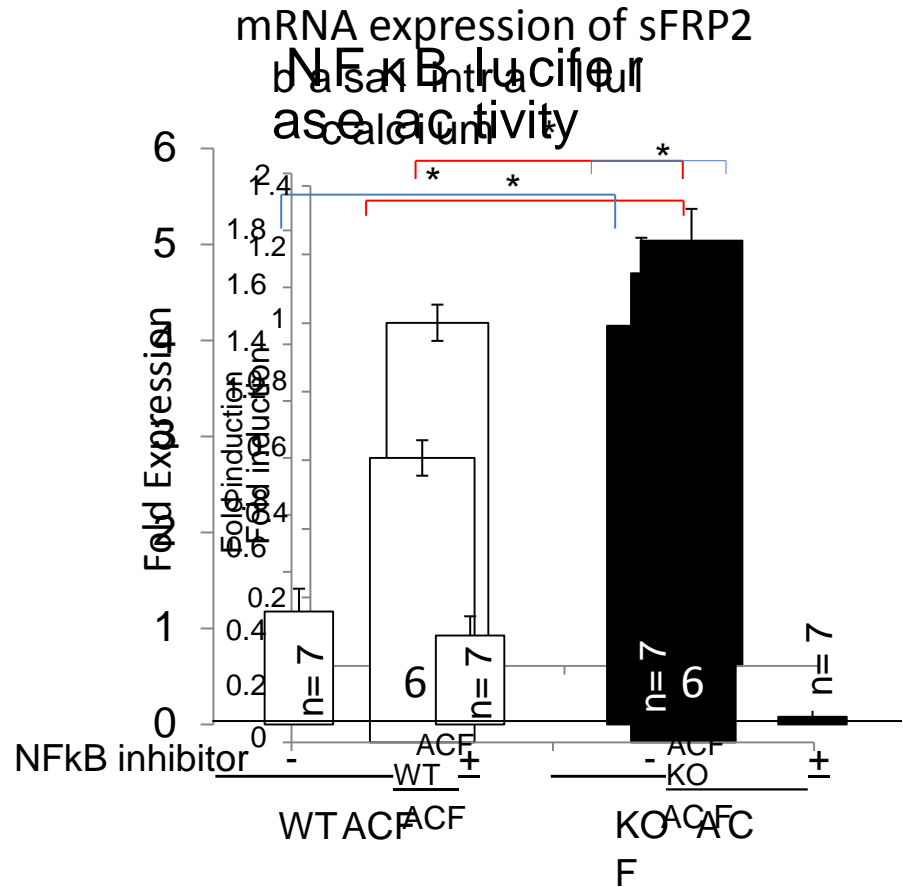
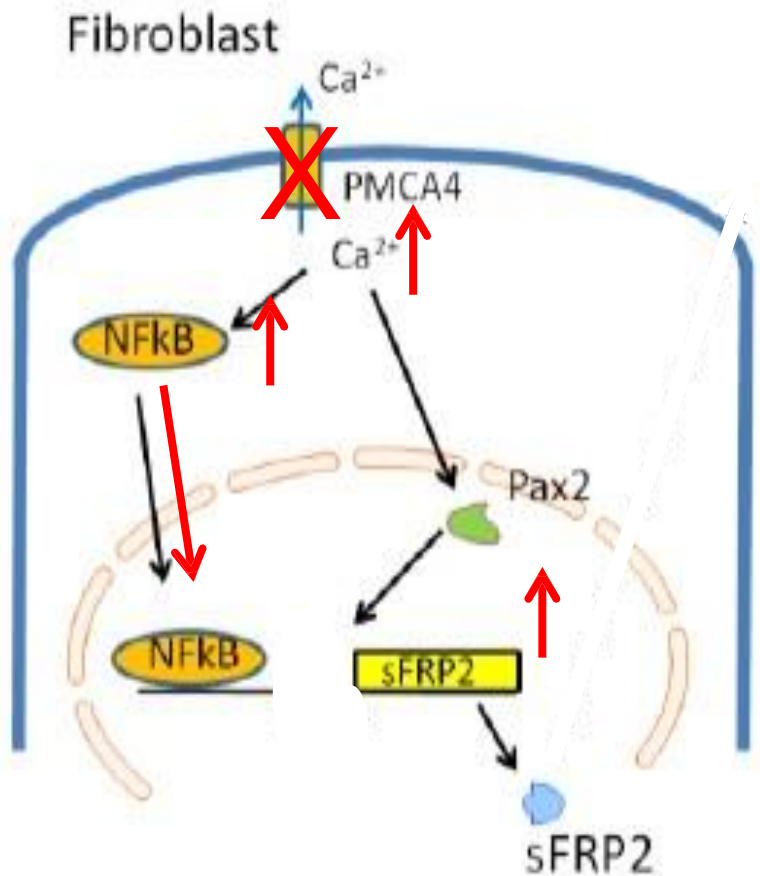
# Treatment of NRCM with conditioned medium of WT or PMCA4<sup>-/-</sup> cardiac fibroblasts



PE: Phenylephrine



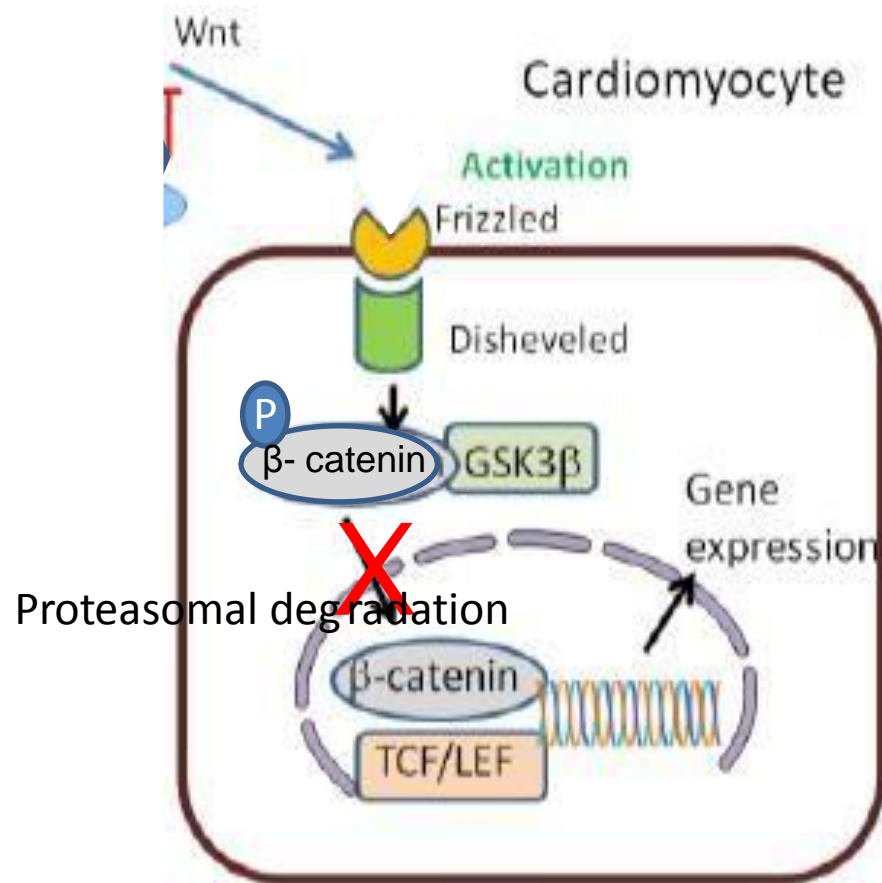
# Cross talk mechanism between fibroblast and cardiomyocytes



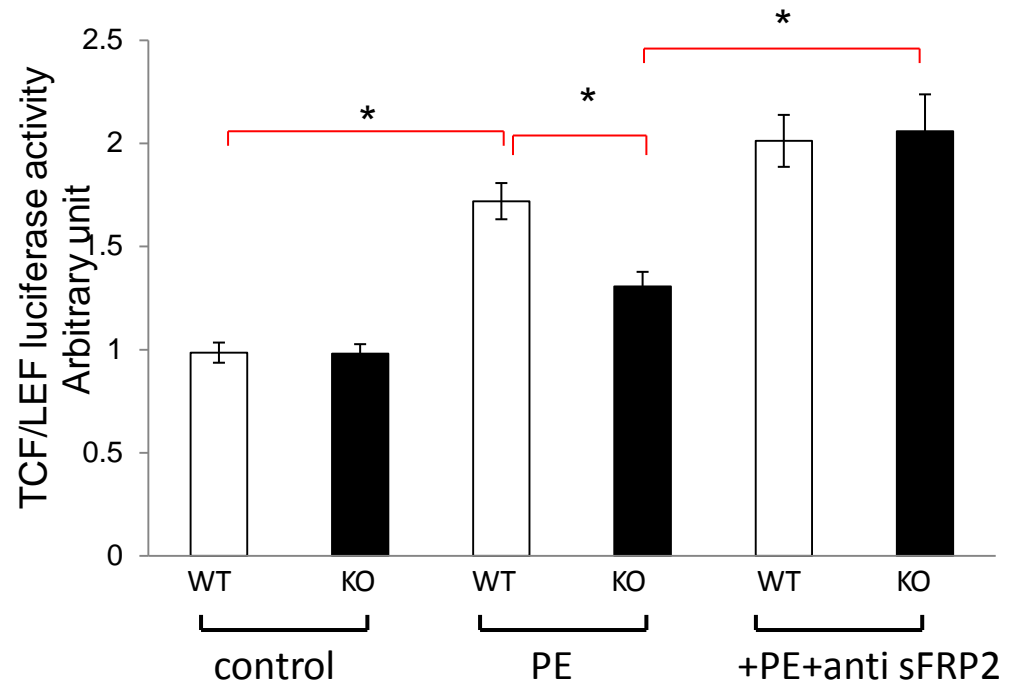
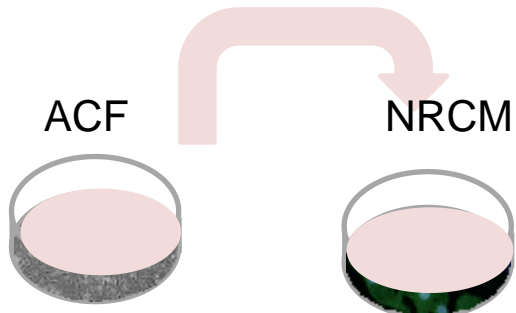
ACF: Adult Cardiac Fibroblasts

# Cross talk mechanism between fibroblast and cardiomyocytes

During hypertrophic response



# TCF/LEF luciferase activity ( $\beta$ -catenin activity reporter)



PE: Phenylephrine

## Conclusion 2

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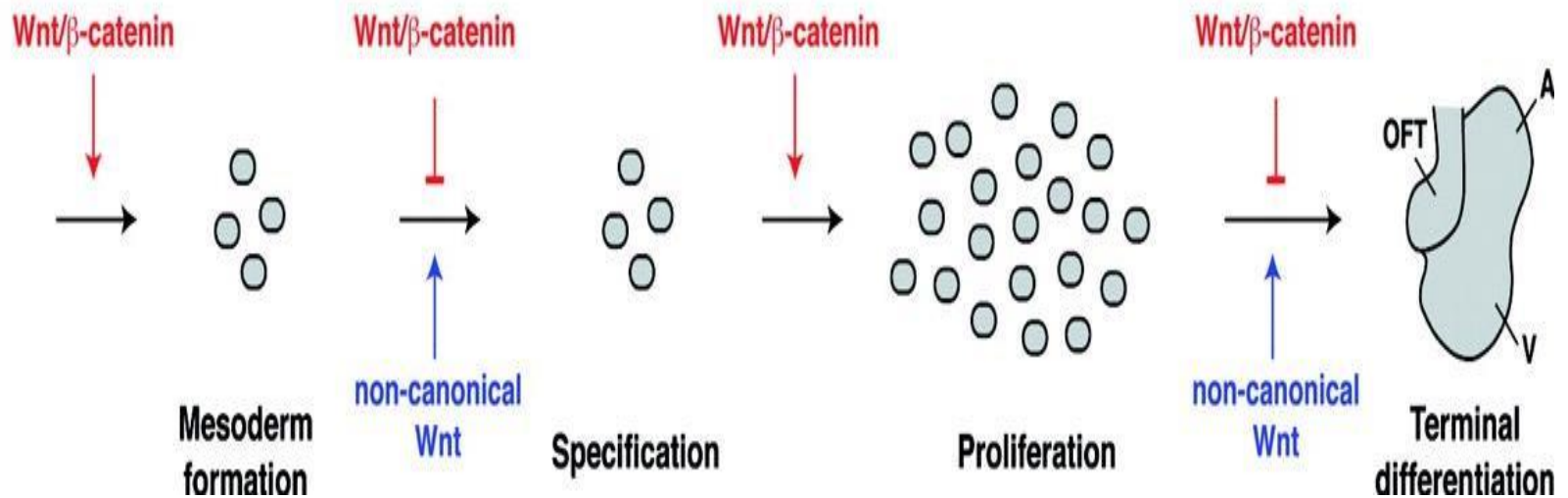
- Cardiac fibroblasts lacking PMCA4 produces higher levels of sFRP2 which inhibits the hypertrophic response in the neighbouring cardiomyocytes.

# Current work

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- PMCA4 KO Stem cell derived cardiomyocytes are potentially for better stem cell therapy for heart failure

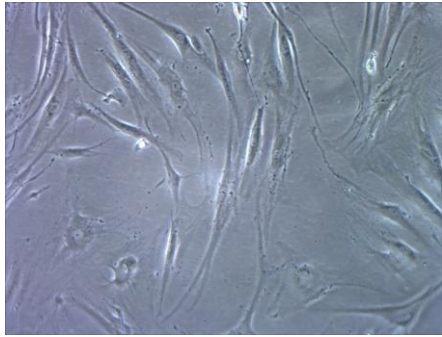
# The multiple faces of Wnt signaling during early cardiac development.



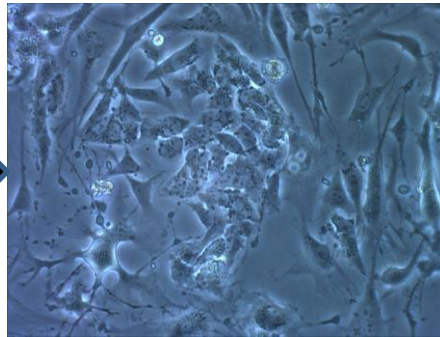
PMCA4 KO Stem cells for better stem cell therapy for heart failure

Gessert S , Kühl M *Circulation Research* 2010;107:186-199

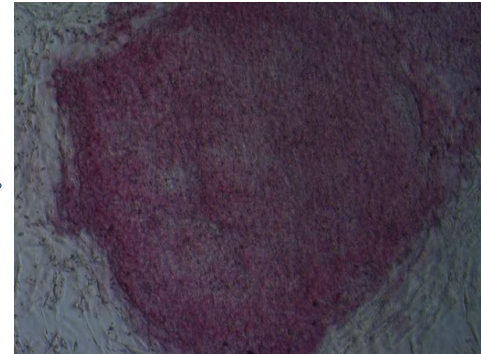
# Generation of hiPS-CM



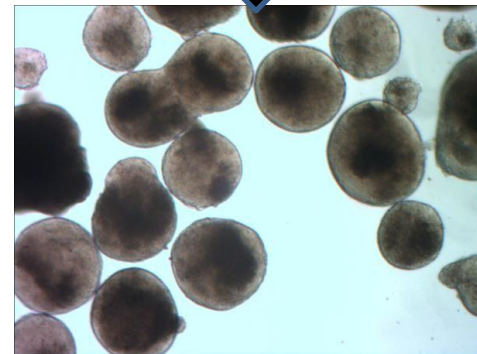
Human Skin  
Fibroblasts



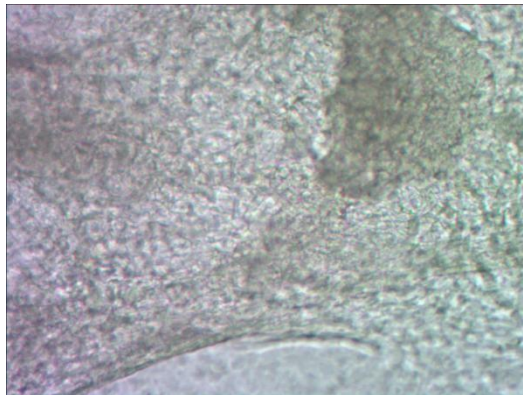
Emerging iPS  
colony



iPS colony



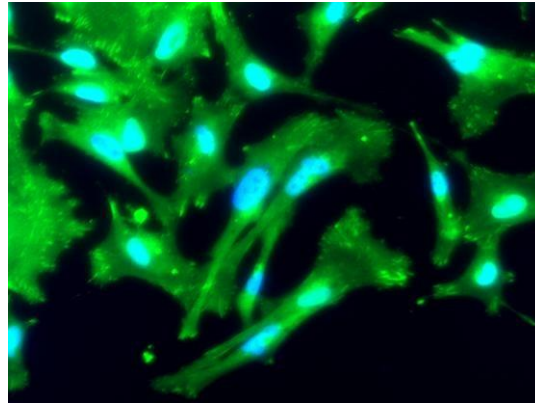
Embryonic  
bodies



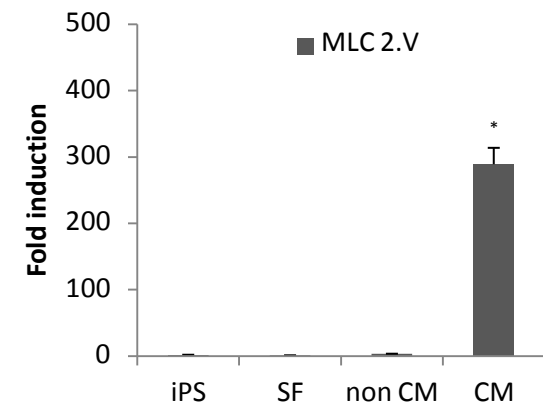
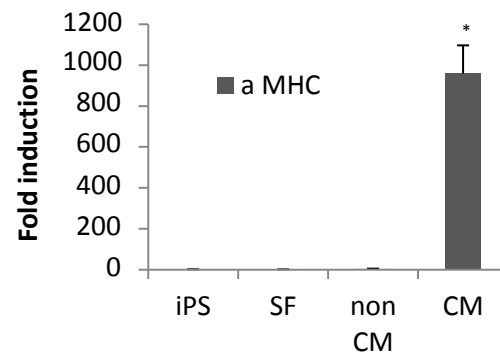
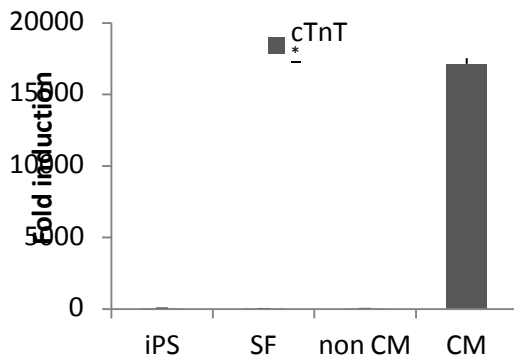
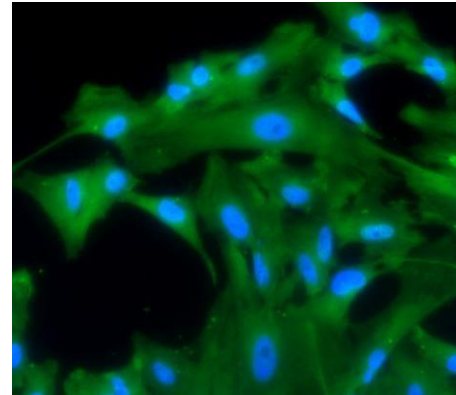
Beating cardiac  
colonies

# hiPSC-CMs

Nkx-2.5



cTnT





# What is the relation between the heart and the male reproductive system?

Viagra may prevent and improve heart failure

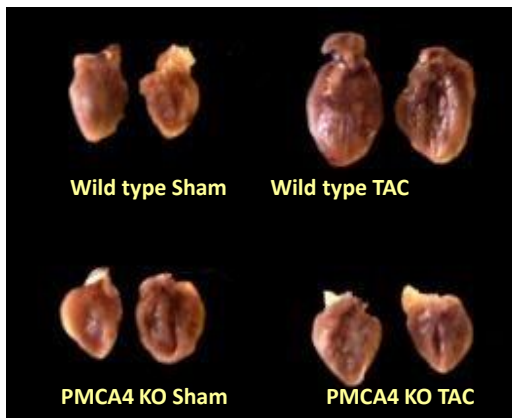


# PMCA4 KO

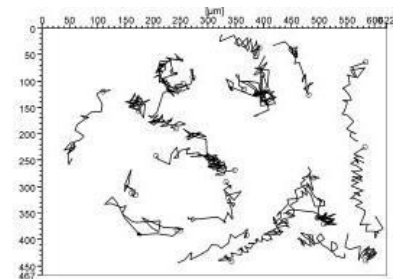
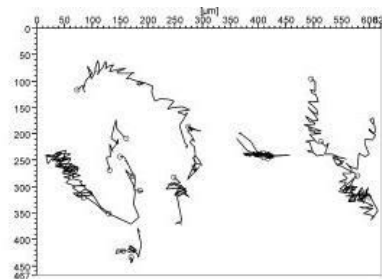


Immotile sperms

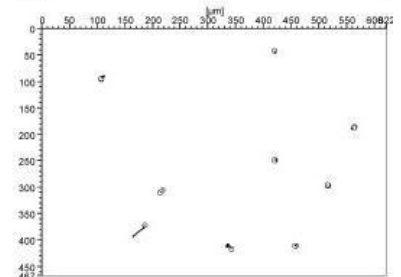
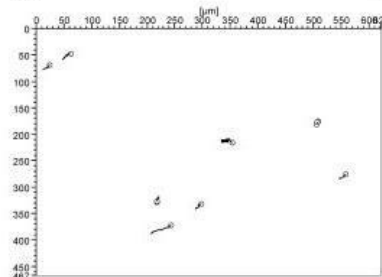
Protected from pathological hypertrophy



WT



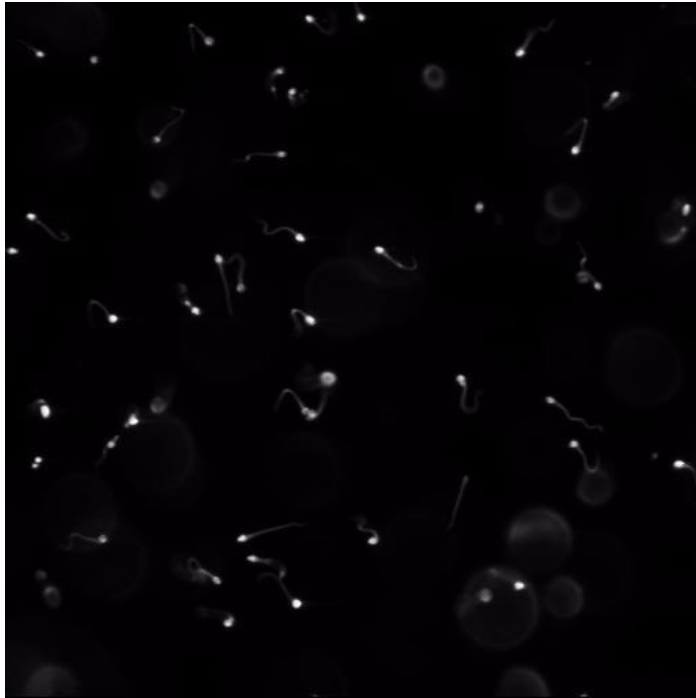
KO



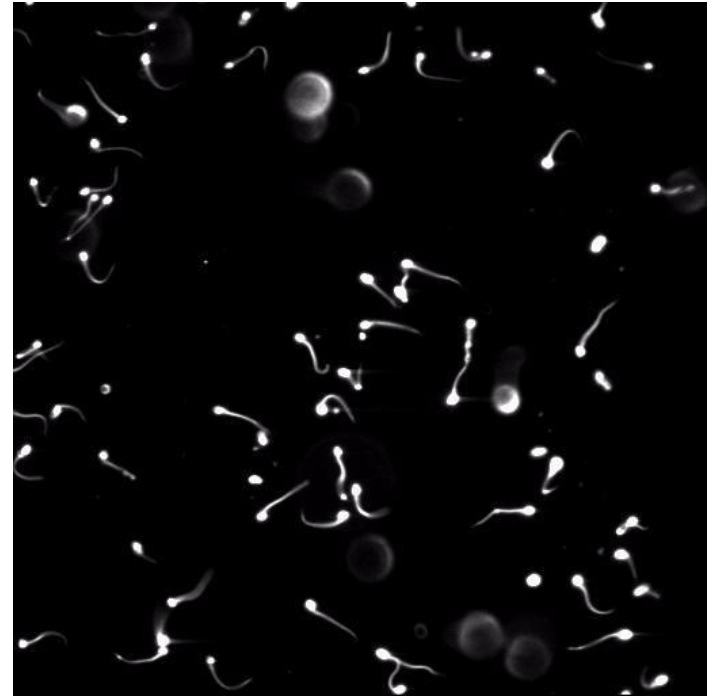
# Effect of ATA on sperm motility

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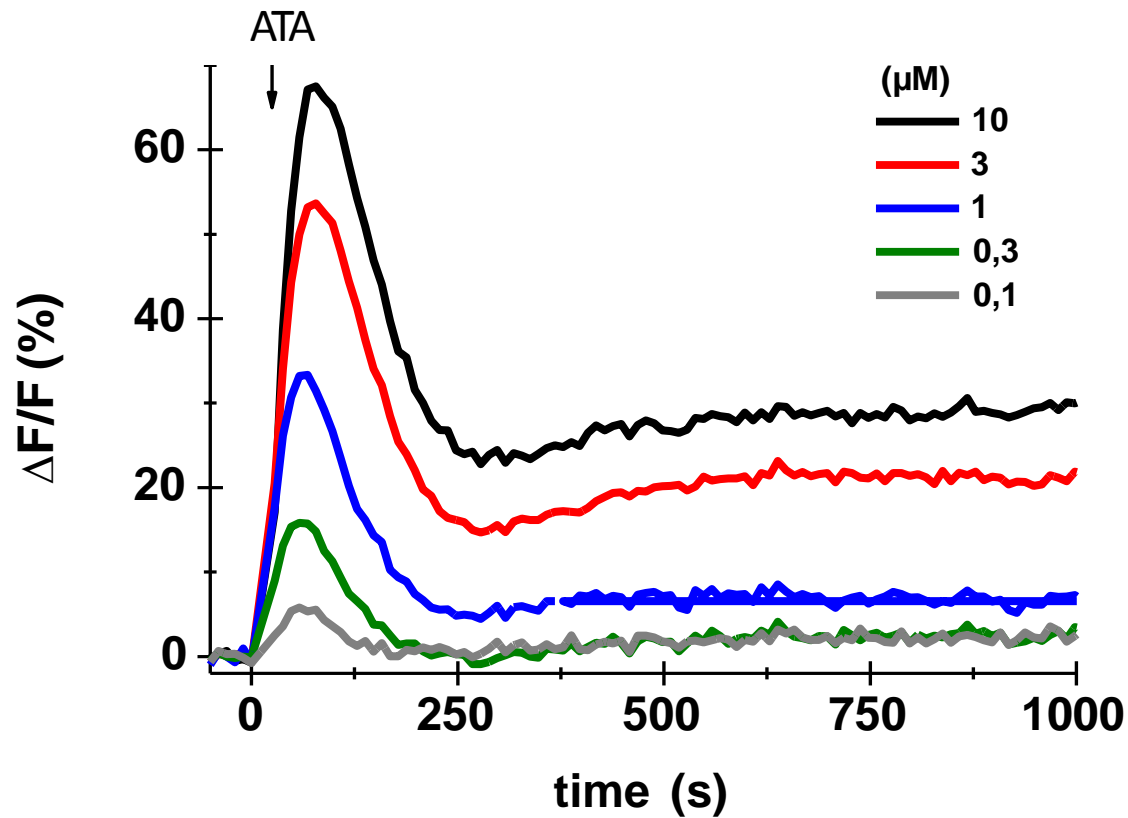
Control



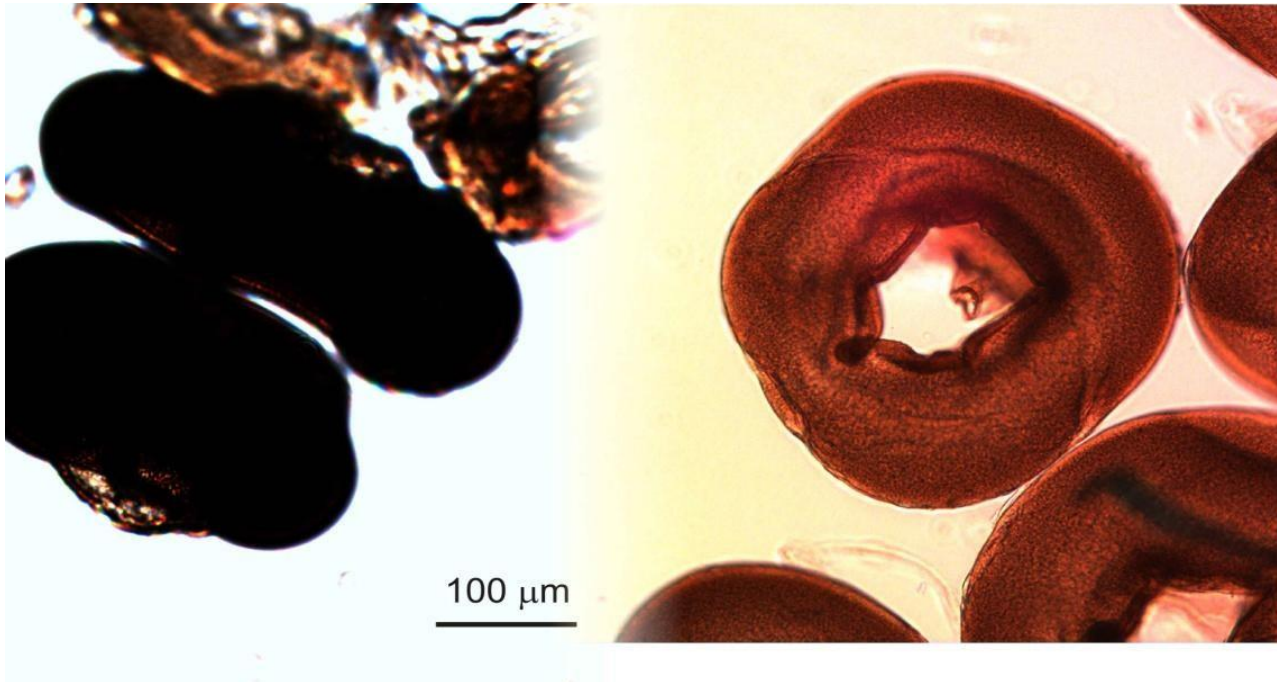
+ 30uM ATA



# ATA inhibits sperm motility through elevation of intracellular calcium in the sperm



# Doughnut microspheres for local non-hormonal contraception



Awarded \$100,000

## Conclusion 3

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**PMCA4 inhibitor emulates the effect of PMCA4 knockout on sperm motility and could be a potential non hormonal contraceptive**

# Acknowledgements

## Cardiovascular Research Group, Manchester

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of Gottingen

**Dr. Sheraz Gul** European  
Screening port

**Prof. U. B Kaupp** MaxPlanck  
Institute, Germany

**Prof. Deepak Srivastava**  
J David Gladstone Research  
Institutes UCSF



**Thanks' for your kind attention!!!!!!**





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