# Signaling in cardiomyocyte hypertrophy

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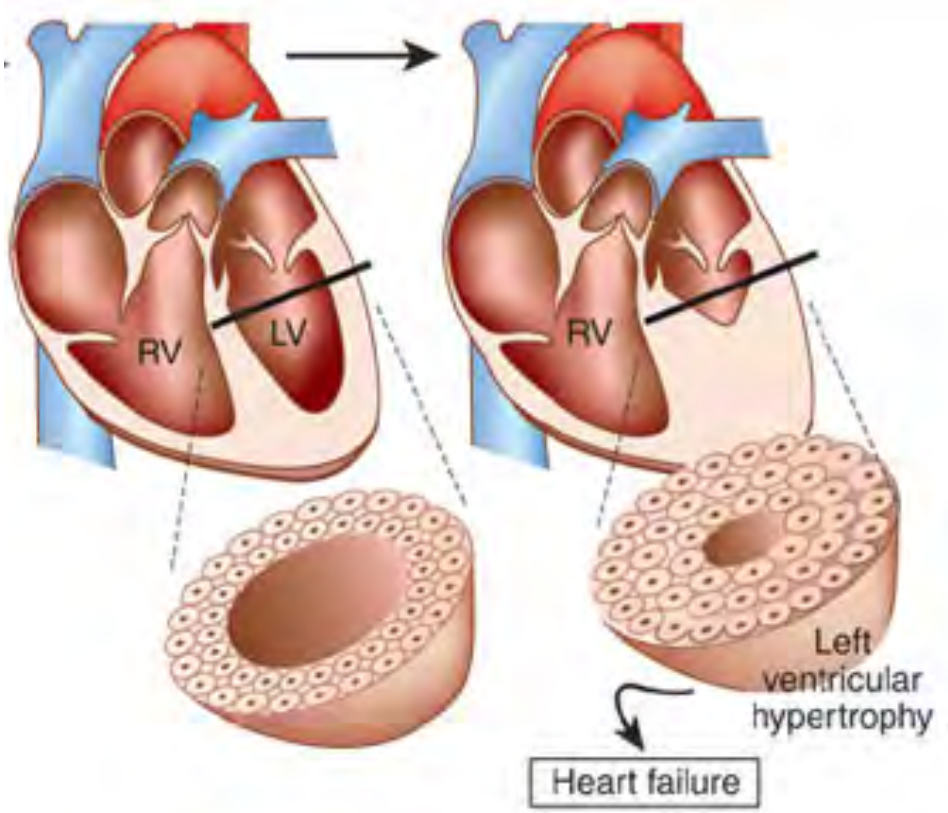
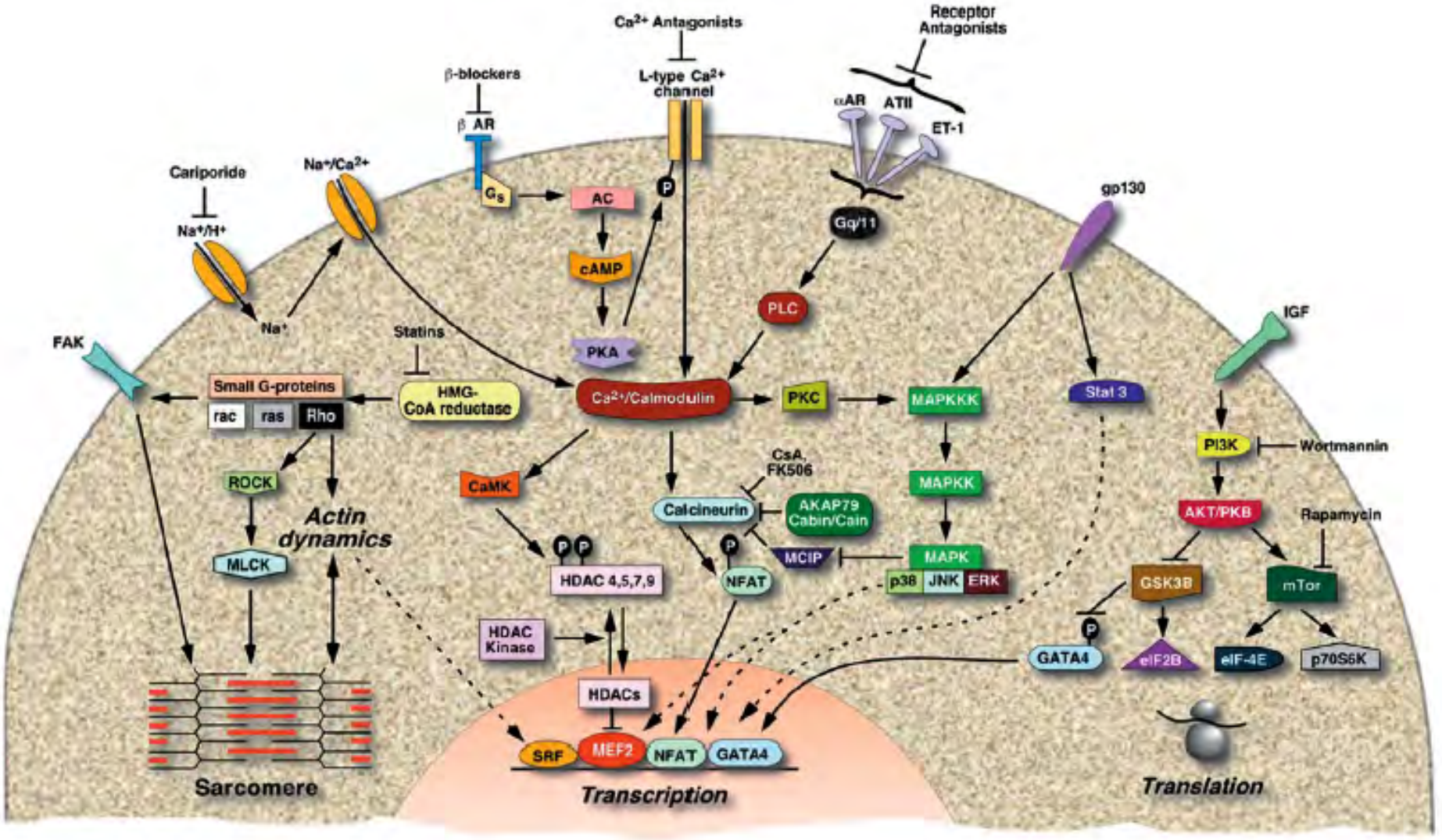
Royal Netherlands Academy of Sciences


RV
LV
RV
Left
ventricular
hypertrophy
Heart failure


LVH
NORMAL
METRIC 1 2 3 4 5 6 7 8 9 10




Frey N. and Olson E.N. (2003) Annu. Rev. Physiol.

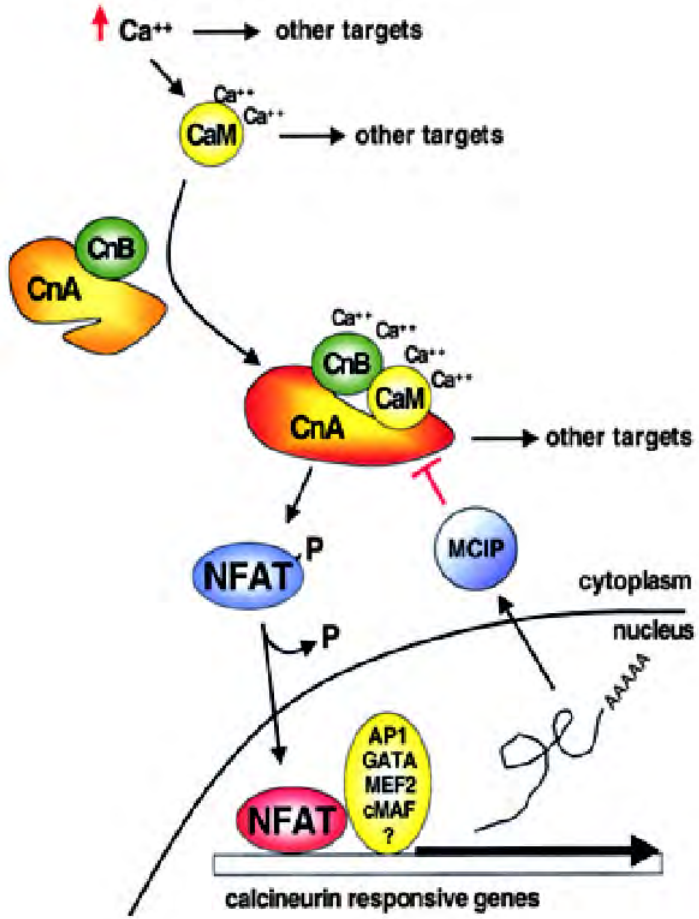
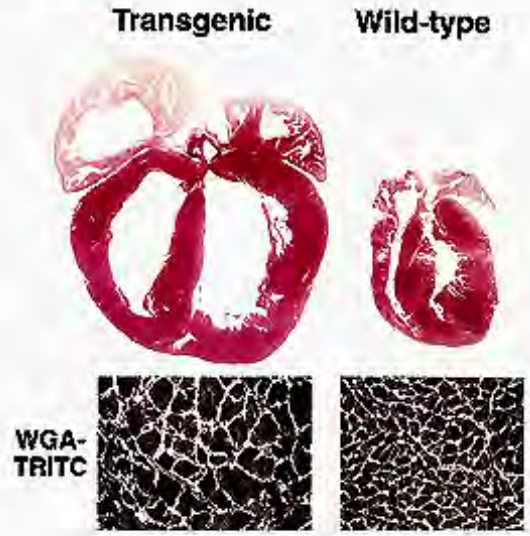

Ca++
other targets
Ca++
Ca++
CaM
other targets
CnB
CnA
Ca++
Ca++
CnB
Ca++
Ca++
CaM
CnA
other targets
NFAT
P
MCIP
cytoplasm
nucleus
P
AAAAA
AP1
GATA
MEF2
cMAF
?
NFAT
calcineurin responsive genes

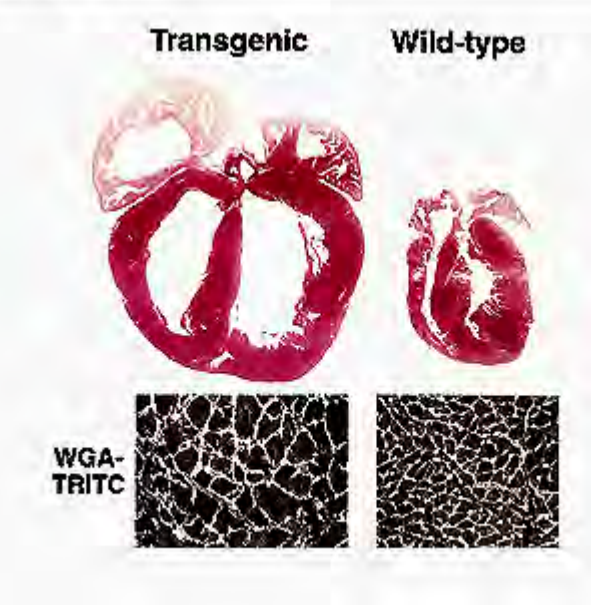
Table 1. Summary of α-MHC-Calcineurin Transgenic Lines

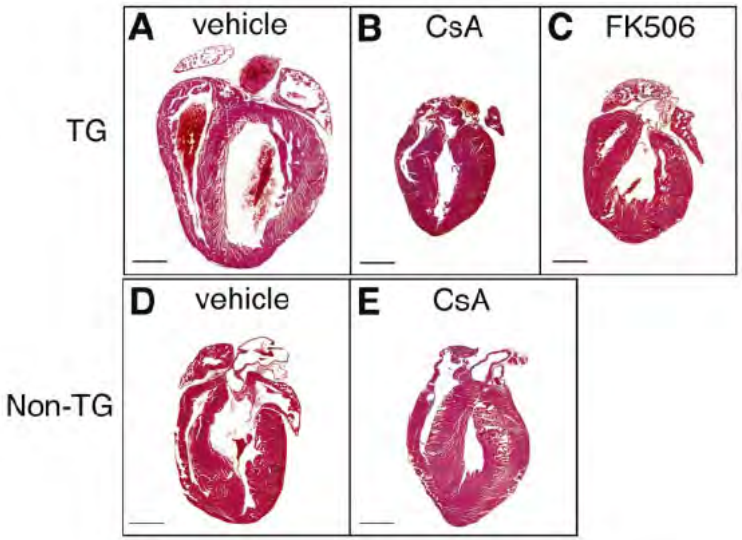
| Transgenic Line | Transgene Copy # | Cause of Death | Age at Death | Heart Weight Tg./Control | Cardiac Phenotype |
|---|---|---|---|---|---|
| 46 | 8 | Sacrificed | 18 days | 2.2 | Hypertrophic |
| 22 | 22 | Sudden | 10 weeks | 2.3 | Dilated |
| 110 | 3 | Sudden | 4 weeks | 2.6 | Hypertrophic |
| 105 | 2 | Sudden | 9 weeks | ND | ND |
| 108 | 3 | Still alive | (14 weeks) | — | — |
| 41 | 68 | Still alive | (24 weeks) | — | — |
| 37 | 15 | Still alive | (23 weeks) | — | — |
| 37-1 | 15 | Sacrificed | 5 weeks | 2.3 | Hypertrophic |
| 37-2 | 15 | Sudden | 4 weeks | ND | Hypertrophic |
| 37-3 | 15 | Sudden | 3 weeks | 2.5 | Hypertrophic |
| 37-4 | 15 | Still alive | (8 weeks) | — | — |
| 37-5 | 15 | Still alive | (8 weeks) | — | — |
| 37-6 | 15 | Sudden | 12 weeks | 2.9 | Dilated |
| 39 | 3 | Sudden | 11 weeks | 2.7 | Hypertrophic |
| 39-1 | 3 | Sudden | 3 weeks | ND | Hypertrophic |
| 39-2 | 3 | Sudden | 4 weeks | ND | ND |
| 39-3 | 3 | Still alive | (10 weeks) | — | — |

Heart weights were determined and are expressed as the relative weight of the transgenic heart compared to nontransgenic litter mates. Ages of mice that are still alive are shown in parentheses as of 2/18/98. 37 and 39 were founder transgenics and, mice designated as 37- and 39- were their offspring. ND, not determined.

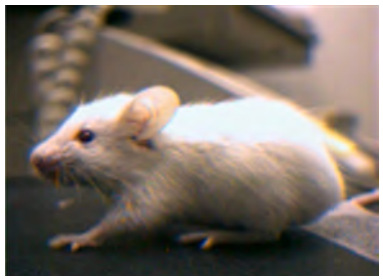


# calcineurin activation in the postnatal myocardium provokes heart failure




Wildtype



Transgenic

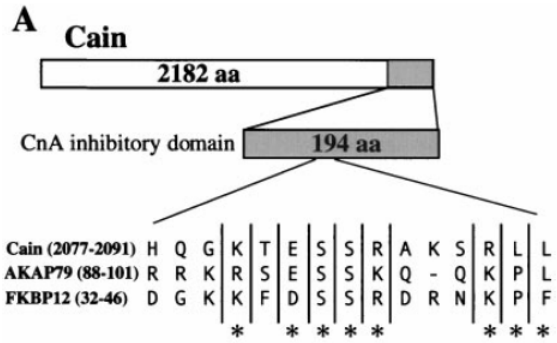
Shortness of breath
Lethargy
Mortality

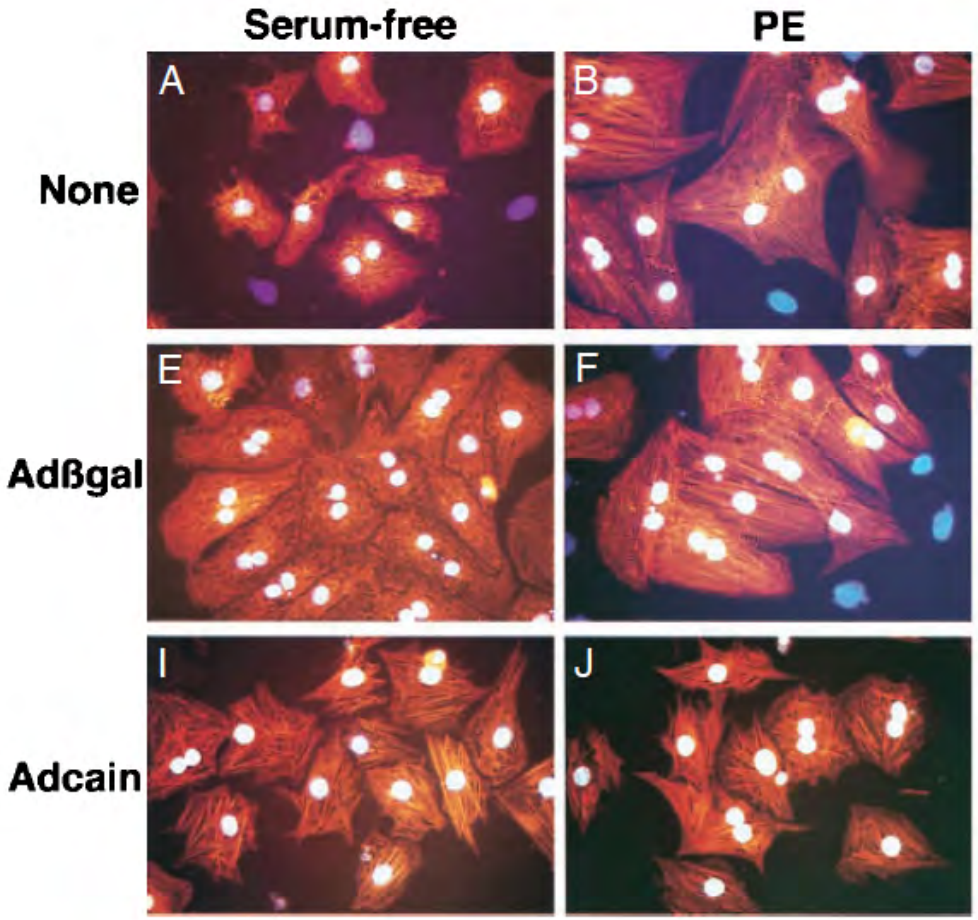
Molkentin *et al*. *Cell* 1998;93:215

**Summary of Animal Models of Cardiac Hypertrophy Treated With CsA and FK506**

| Study | Model | Drug (Dosage, Times per Day) | % Increase | % Increase+Drug | Significant |
|---|---|---|---|---|---|
| Luo et al[31] | Rat abdominal AC | CsA* ? | 42 | 27 | No |
| Müller et al[32] | Mouse transverse AC | CsA 25 mg/kg, 2 | ... | ... | No |
| Ding et al[29] | Mouse ascending AC | CsA 25 mg/kg, 2 | 53 | 52 | No |
| Zhang et al[28] | Rat abdominal AC | CsA 20 mg/kg, 1 | 47 | 21† | No‡ |
| Zhang et al[28] | SHR+high salt | CsA 5 mg/kg, 1 | ... | ... | No |
| Sussman et al[22] | TG mice with HCM | CsA 15 mg/kg, 2 | 120 | 0 | Yes |
| Sussman et al[22] | Rat abdominal AC | CsA 20 mg/kg, 1 | 27 | 0 | Yes |
| Shimoyama et al[25] | Rat abdominal AC | FK506 1 mg/kg, 1 | ≈33 | 0 | Yes |
| Lim et al[24] | Rat abdominal AC | CsA 10 mg/kg, 2 | 34 | 6 | Yes |
| Hill et al[34] | Mouse transverse AC | CsA 25 mg/kg, 2 | 45§ | 0§ | Yes |
| Meguro et al[33] | Mouse transverse AC | CsA 25 mg/kg, 1 | 44 | 33 | Yes |
| Eto et al[26] | Rat transverse AC | CsA 40 mg/kg, 1 | 33 | 18 | Yes |
| Eto et al[26] | Rat exercise | CsA 40 mg/kg, 1 | 15 | 0 | Yes |
| Mervaala et al[35] | Ang II/renin TG rat | CsA 5 mg/kg, 1 | ≈45 | ≈19 | Yes |
| Øie et al[36] | Rat infarction/failure | CsA 50 mg/kg | ... | ... | Yes‖ |
| Mende et al[37] | Gαq TG mice | CsA 15 mg/kg, 2 | ... | ... | Yes |

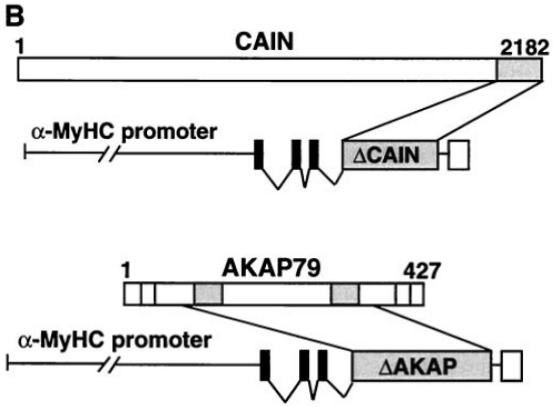
# targeted inhibition of calcineurin attenuates cardiac hypertrophy

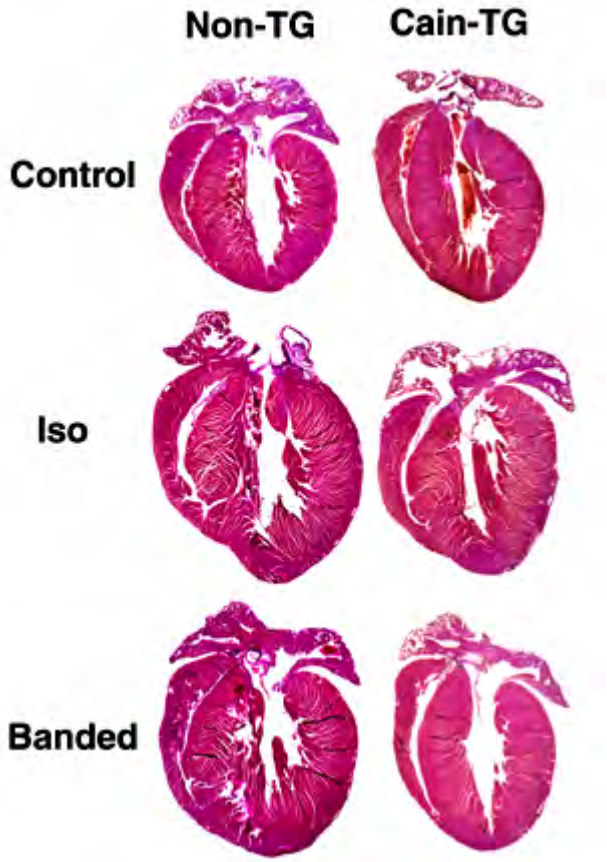



Taigen *et al*. *PNAS* 2000;97:1196

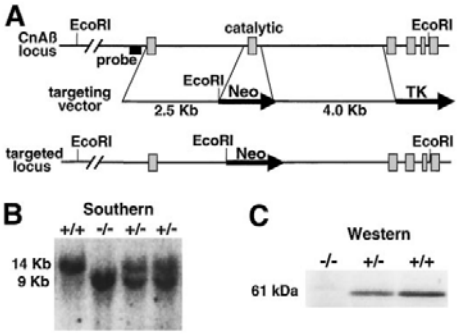
# Targeted inhibition of calcineurin attenuates cardiac hypertrophy

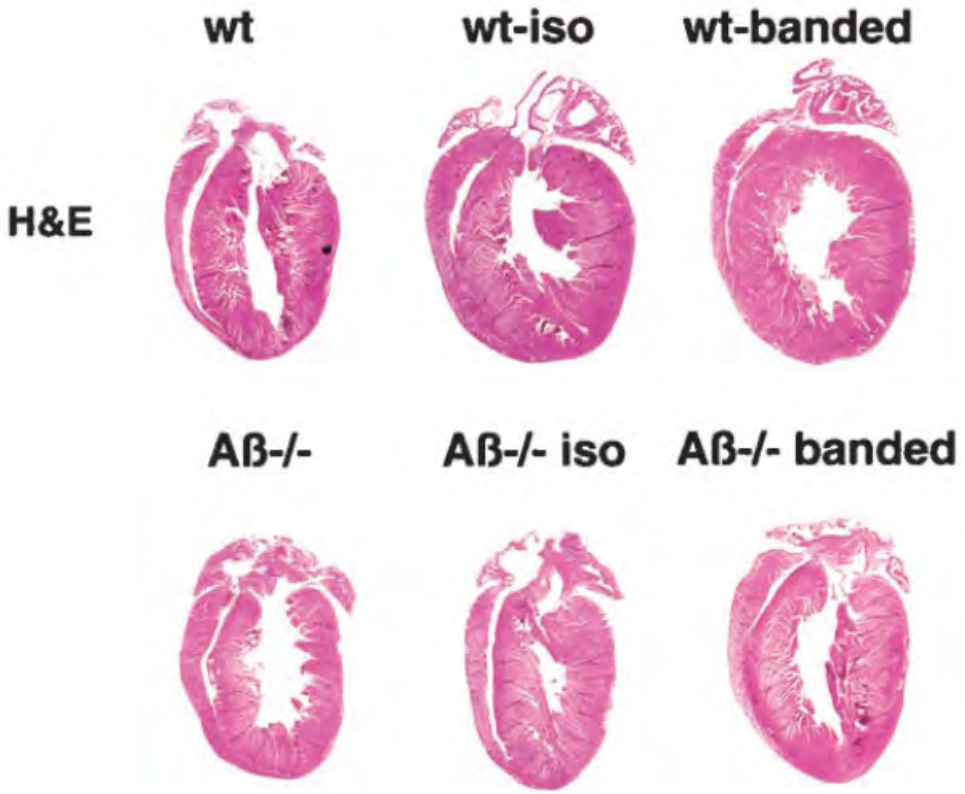



De Windt *et al*. *PNAS* 2001;98:3322

# Targeted deletion of calcineurin Aβ attenuates cardiac hypertrophy



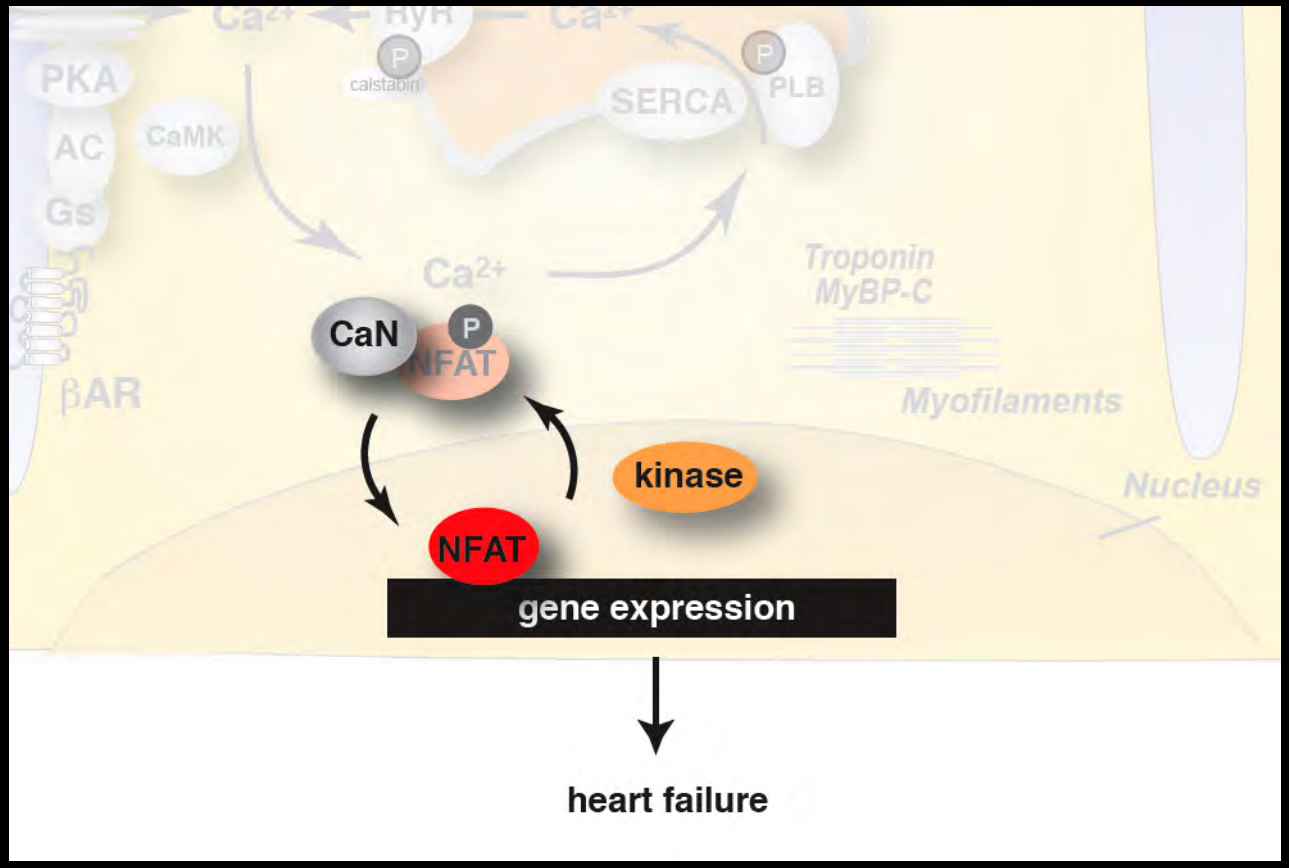

De Windt *et al*. *PNAS* 2002;99:4586

# Editorial

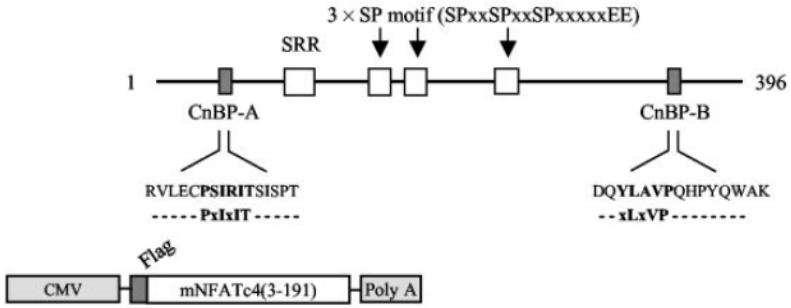
## Calcineurin Inhibition in Hypertrophy
### Back From the Dead!

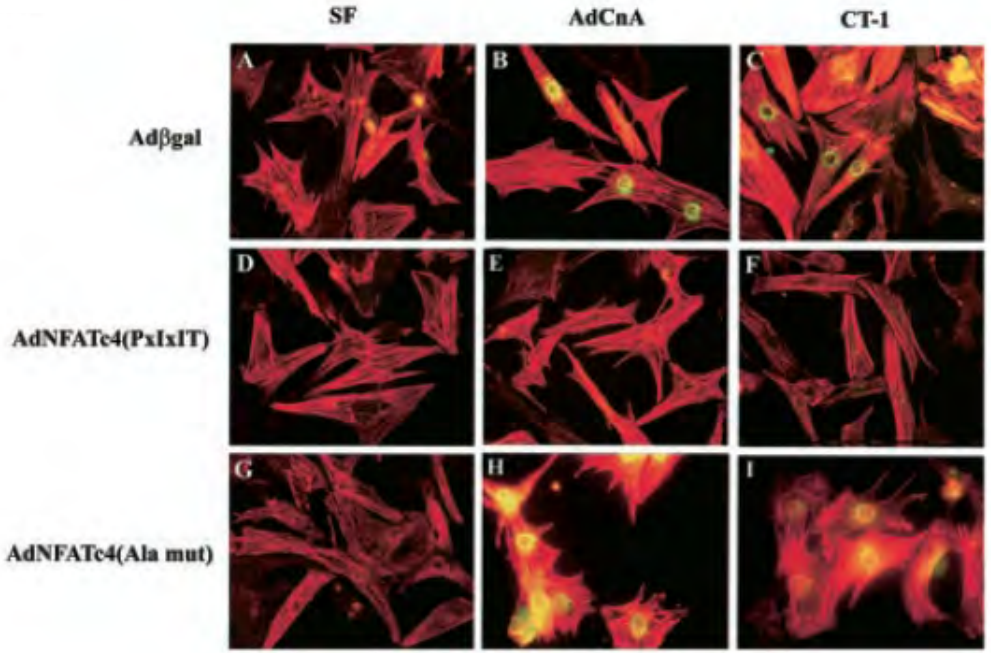
Gerald W. Dorn II, MD

(*Circulation* 2001;104:9-11.)


PKA
AC
Gs
βAR
CaMK
P
calstabin
SERCA
P
PLB
Ca2+
Troponin
MyBP-C
CaN
P
NFAT
Myofilaments
kinase
Nucleus
NFAT
gene expression
heart failure

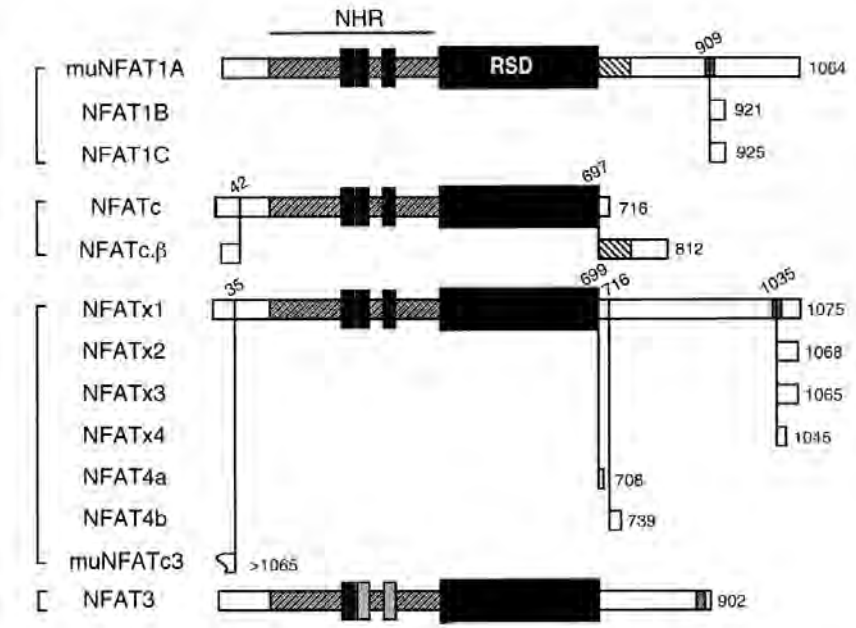
# Involvement of NFAT in cardiomyocyte hypertrophy

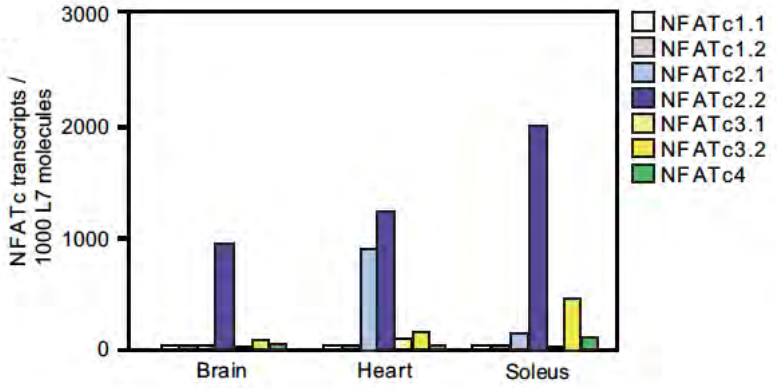



Van Rooij *et al*. J Biol Chem 2002;277:48617

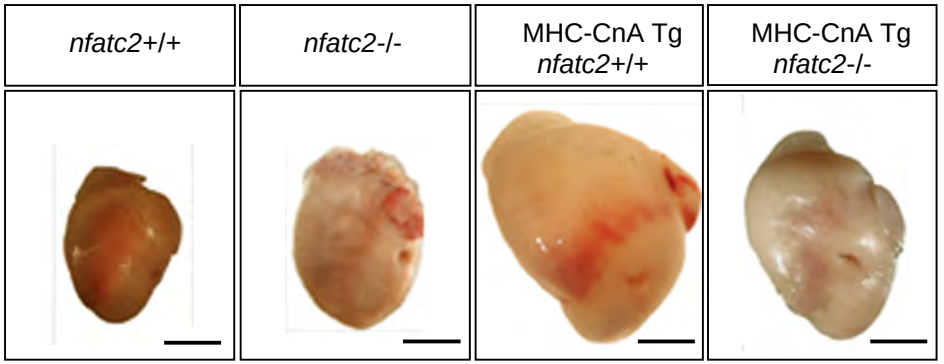
# cardiac NFAT (splice)isoforms

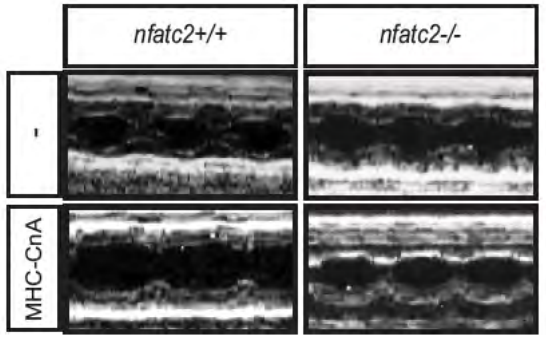



Bourajjaj *et al*. *J Biol Chem* 2008;283:22295-22303

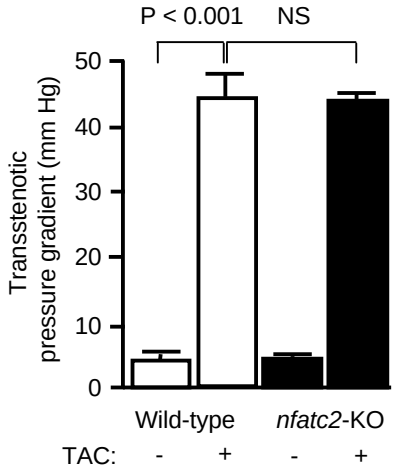
# NFATc2 ablation rescues calcineurin-induced heart failure

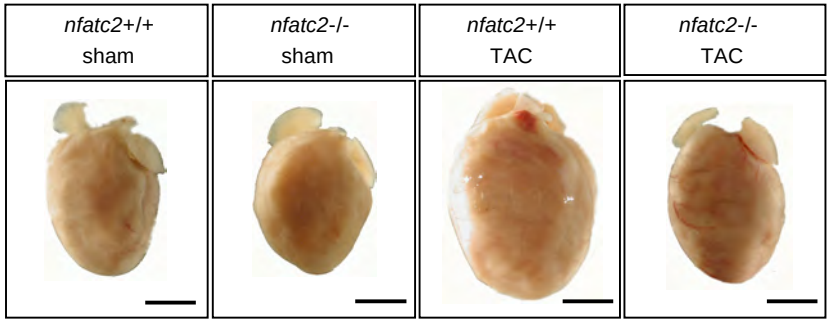


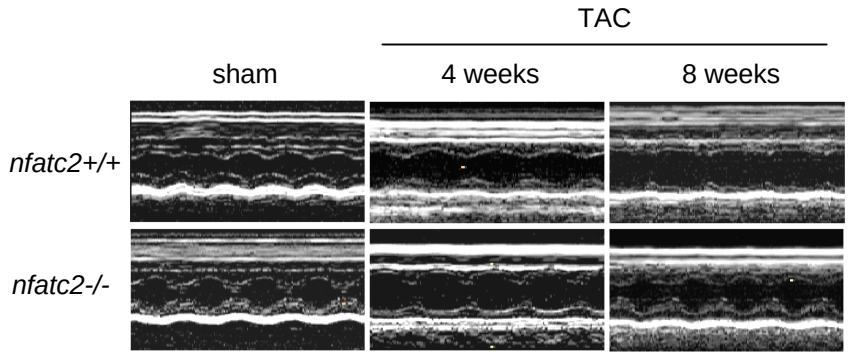




Bourajjaj *et al*. *J Biol Chem* 2008;283:22295-22303

# NFATc2 ablation rescues pressure overload-induced cardiac dysfunction

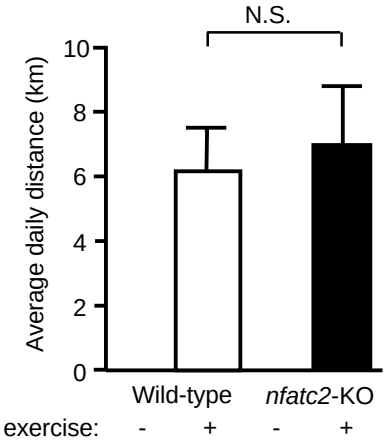


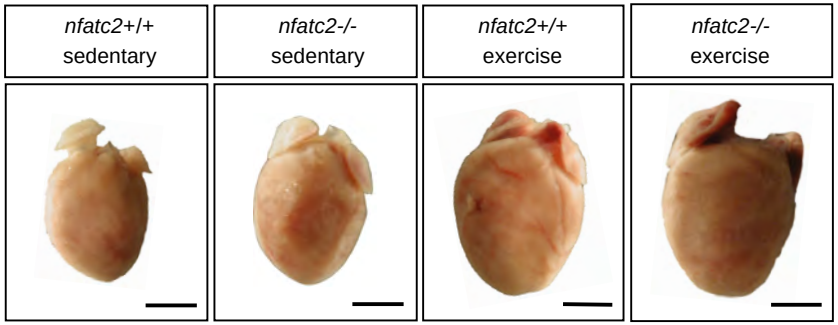



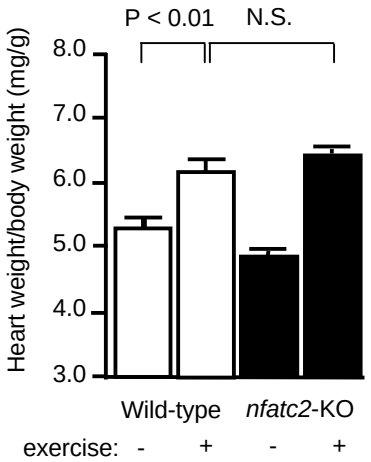




Bourajjaj *et al*. *J Biol Chem* 2008;283:22295-22303

# NFATc2 is not involved in exercise-induced cardiac growth

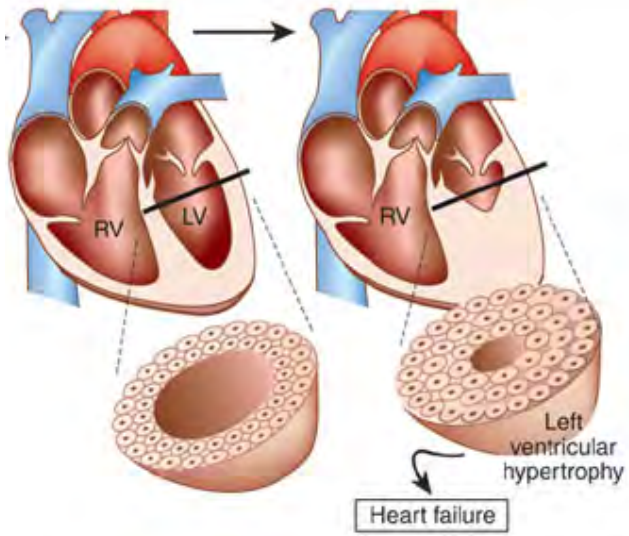


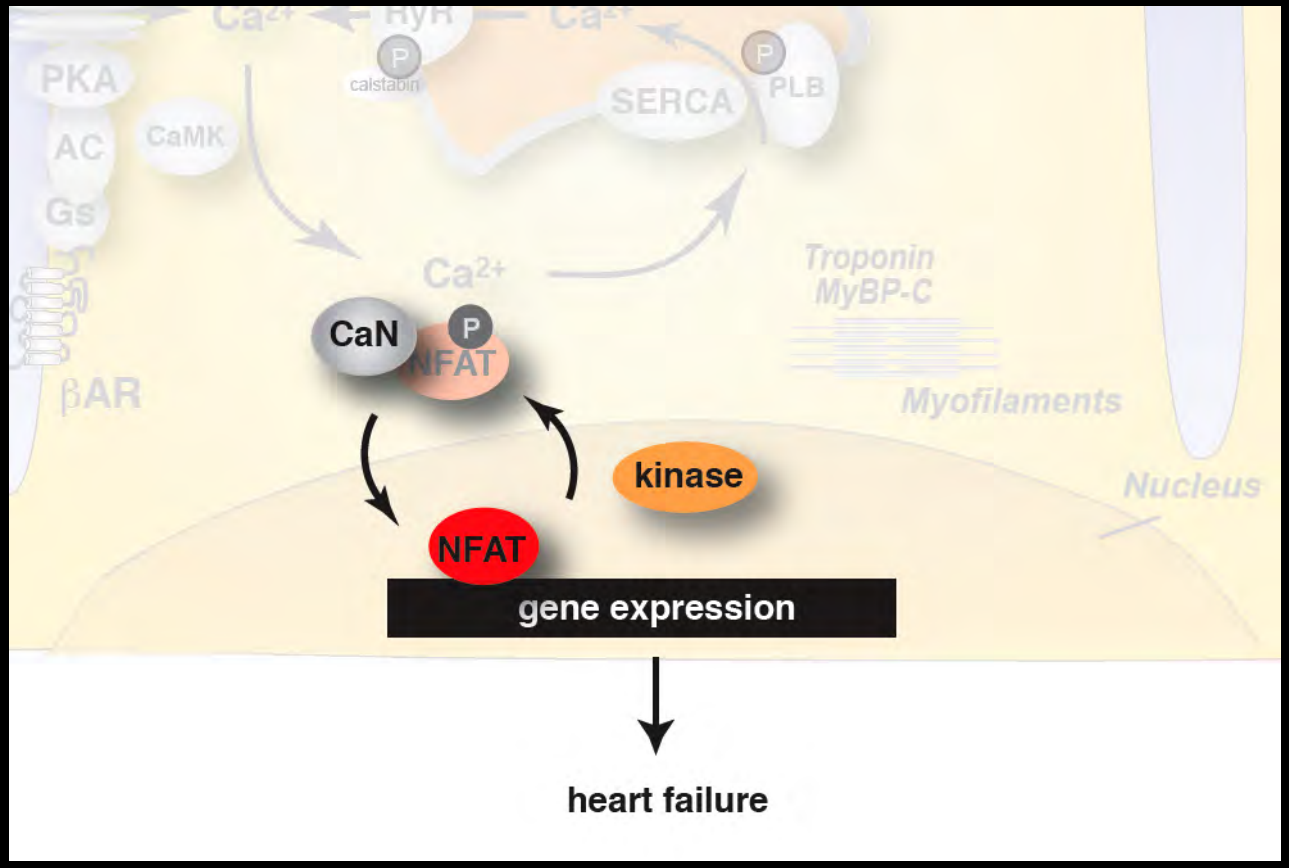



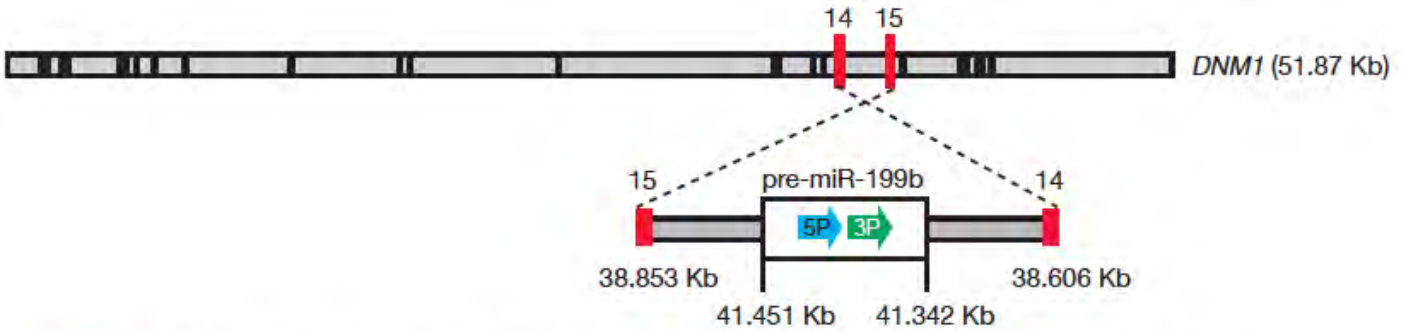

Bourajjaj *et al*. *J Biol Chem* 2008;283:22295-22303

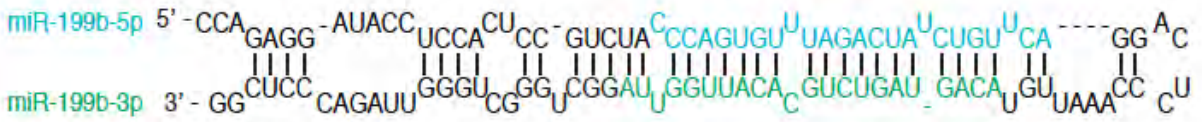
| *nfatc2*+/+ sham | *nfatc2*-/- sham | *nfatc2*+/+ TAC | *nfatc2*-/- TAC |
|---|---|---|---|
|  |  |  |  |

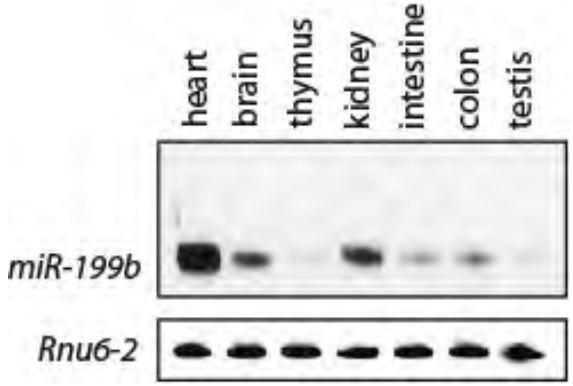



PKA
AC
Gs
βAR
CaMK
P
calstabin
SERCA
P
PLB
Ca2+
Troponin
MyBP-C
CaN
P
NFAT
Myofilaments
kinase
Nucleus
NFAT
gene expression
heart failure

# microRNA-199b




| | 5' | 3' |
|---|---|---|
| Human | CCCAGUGUUUAGACUAUCUGUUC | |
| Orangutan | GUGUUUAGACUAUCUGUUC | |
| Horse | CCCAGUGUUUAGACUAUCUGUUC | |
| Cow | CCCAGUGUUUAGACUAUCUGUUC | |
| Pig | CCCAGUGUUUAGACUAUCUGUU | |
| Mouse | CCCAGUGUUUAGACUACCUGUUC | |
| Frog | CCCAGUGUUCAGACUACGUGUUC | |

Da Costa Martins, Salic *et al*. *Nature Cell Biol* 2010.

**Dyrk1a:** **D**ual-specificity t**y**rosine-(Y)-phosphorylation **r**egulated **k**inase **1a**

## A genome-wide *Drosophila* RNAi screen identifies DYRK-family kinases as regulators of NFAT

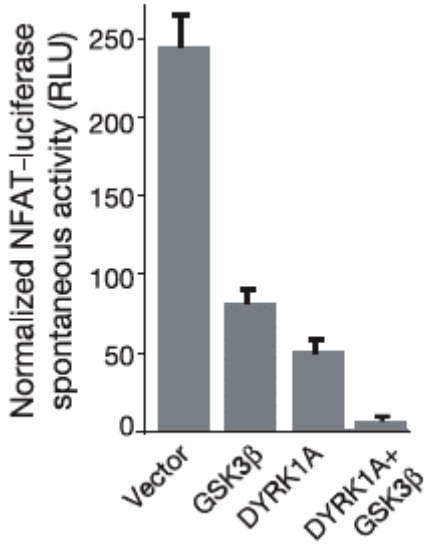
Yousang Gwack[1,2*], Sonia Sharma[1,2*], Julie Nardone[1†], Bogdan Tanasa[1], Alina Iuga[1,2], Sonal Srikanth[1,2], Heidi Okamura[1,2†], Diana Bolton[1†], Stefan Feske[1,3], Patrick G. Hogan[1] & Anjana Rao[1,2]

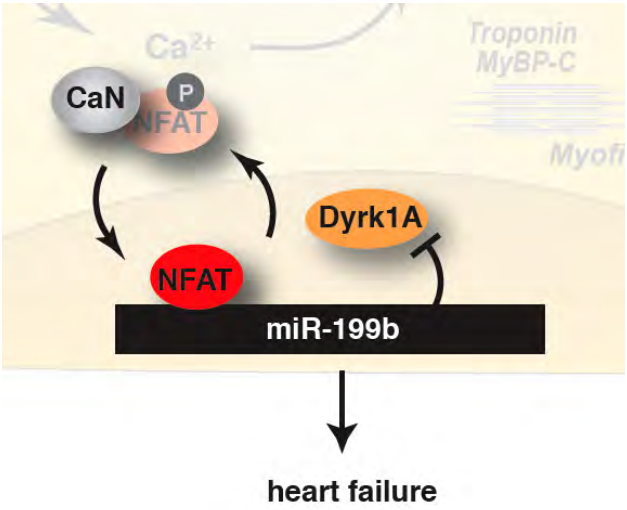
Vol 441|1 June 2006|doi:10.1038/nature04631

## NFAT dysregulation by increased dosage of *DSCR1* and *DYRK1A* on chromosome 21

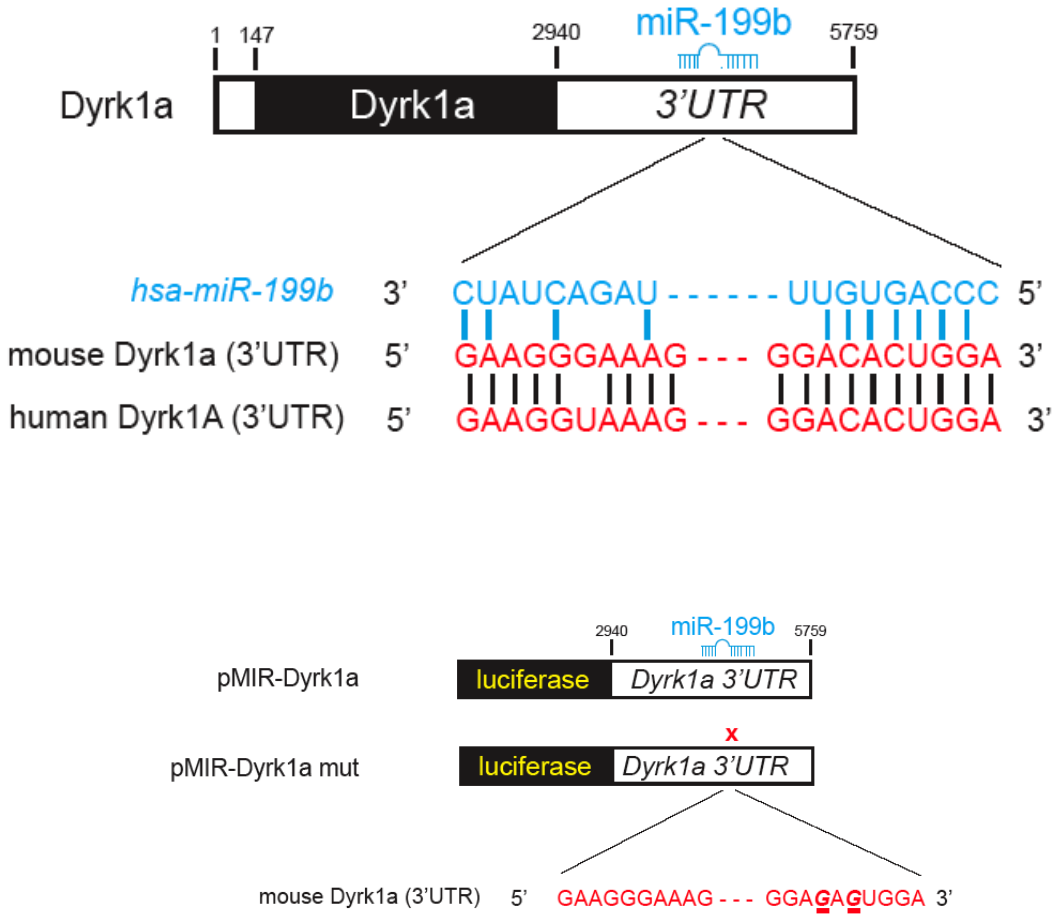
Joseph R. Arron[1*], Monte M. Winslow[2*], Alberto Polleri[1*], Ching-Pin Chang[3], Hai Wu[1], Xin Gao[1], Joel R. Neilson[2], Lei Chen[1], Jeremy J. Heit[4], Seung K. Kim[4], Nobuyuki Yamasaki[7], Tsuyoshi Miyakawa[7], Uta Francke[5], Isabella A. Graef[1*] & Gerald R. Crabtree[1,4,6]

doi:10.1038/nature04678



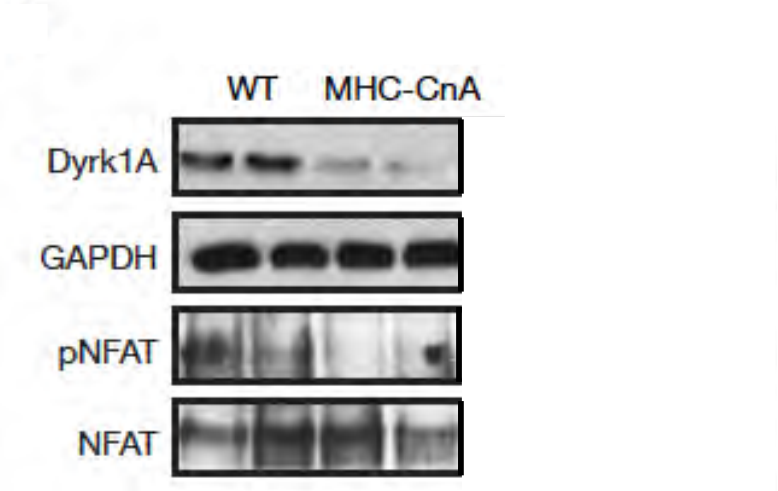



# A conserved seed region in the 3’UTR of Dyrk1a



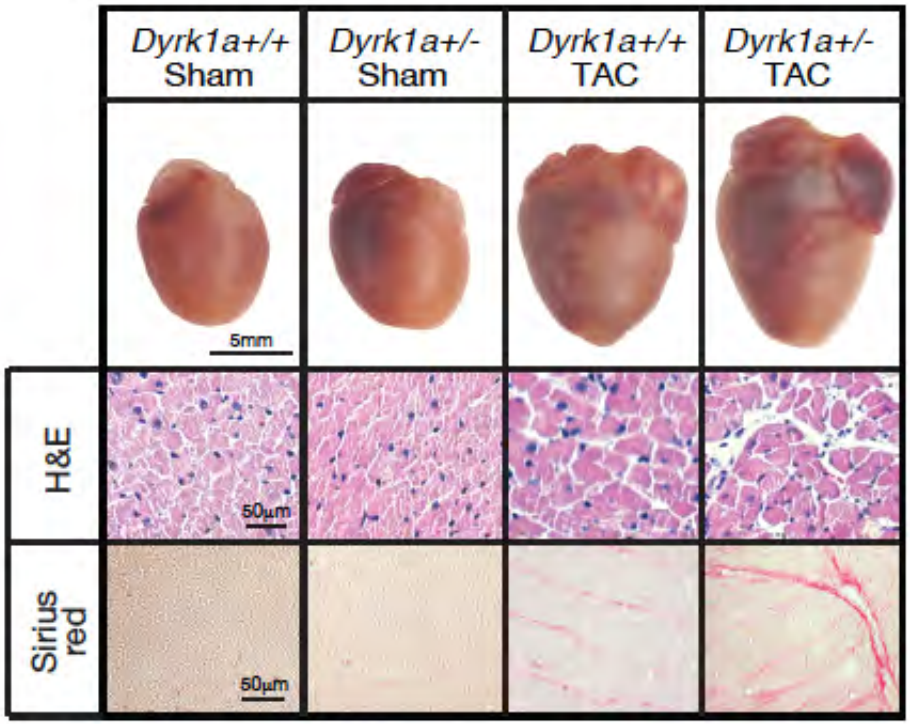

Da Costa Martins, Salic *et al*. *Nature Cell Biol* 2010.

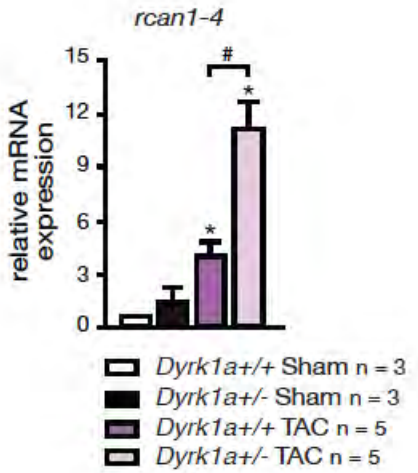
# Dyrk1a and miR-199b expression inversely correlate in the failing mouse heart



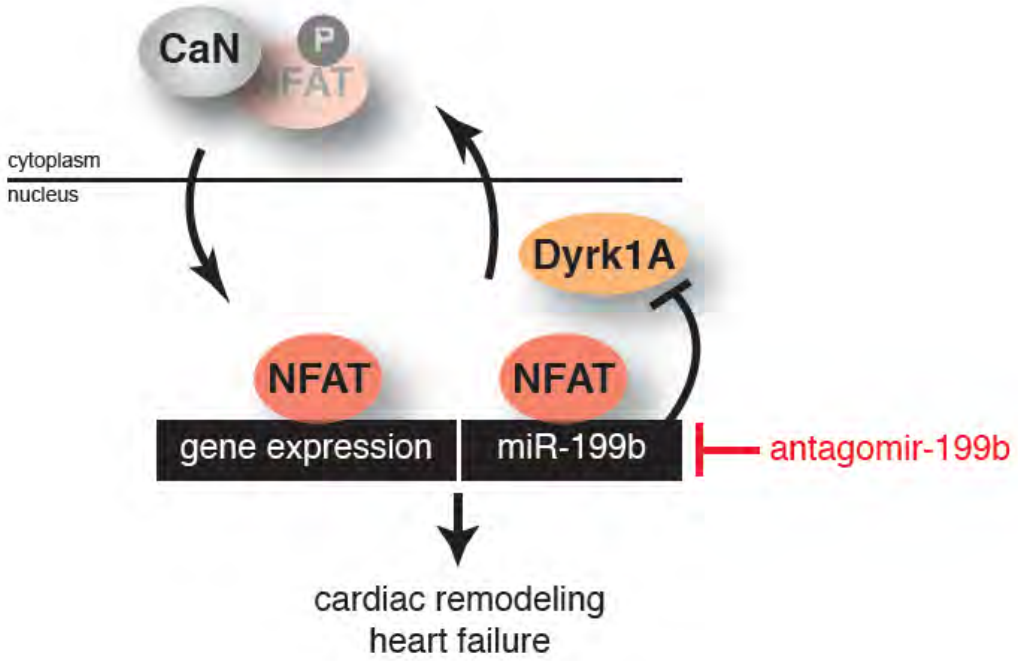

Da Costa Martins, Salic *et al*. *Nature Cell Biol* 2010.

# Dyrk1a haploinsufficient mice are sensitized to stress stimuli



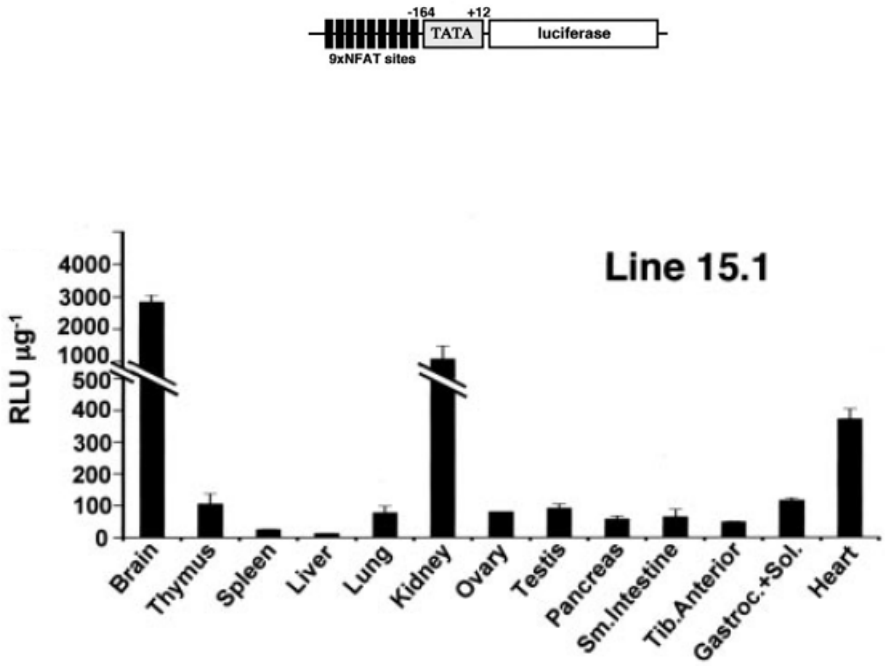



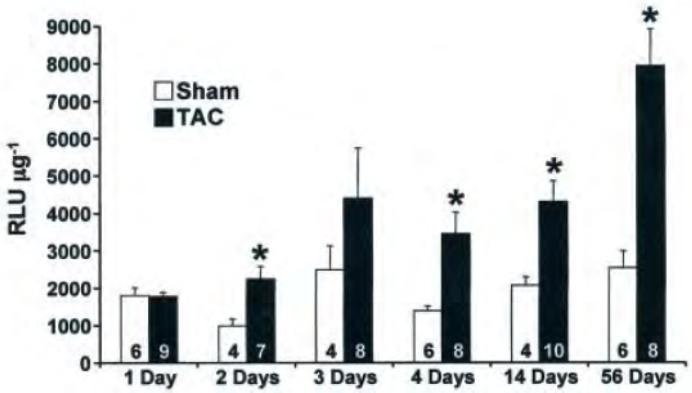

Da Costa Martins, Salic *et al*. *Nature Cell Biol* 2010.


CaN
P
NFAT
cytoplasm
nucleus
Dyrk1A
NFAT
NFAT
gene expression
miR-199b
antagomir-199b
cardiac remodeling
heart failure

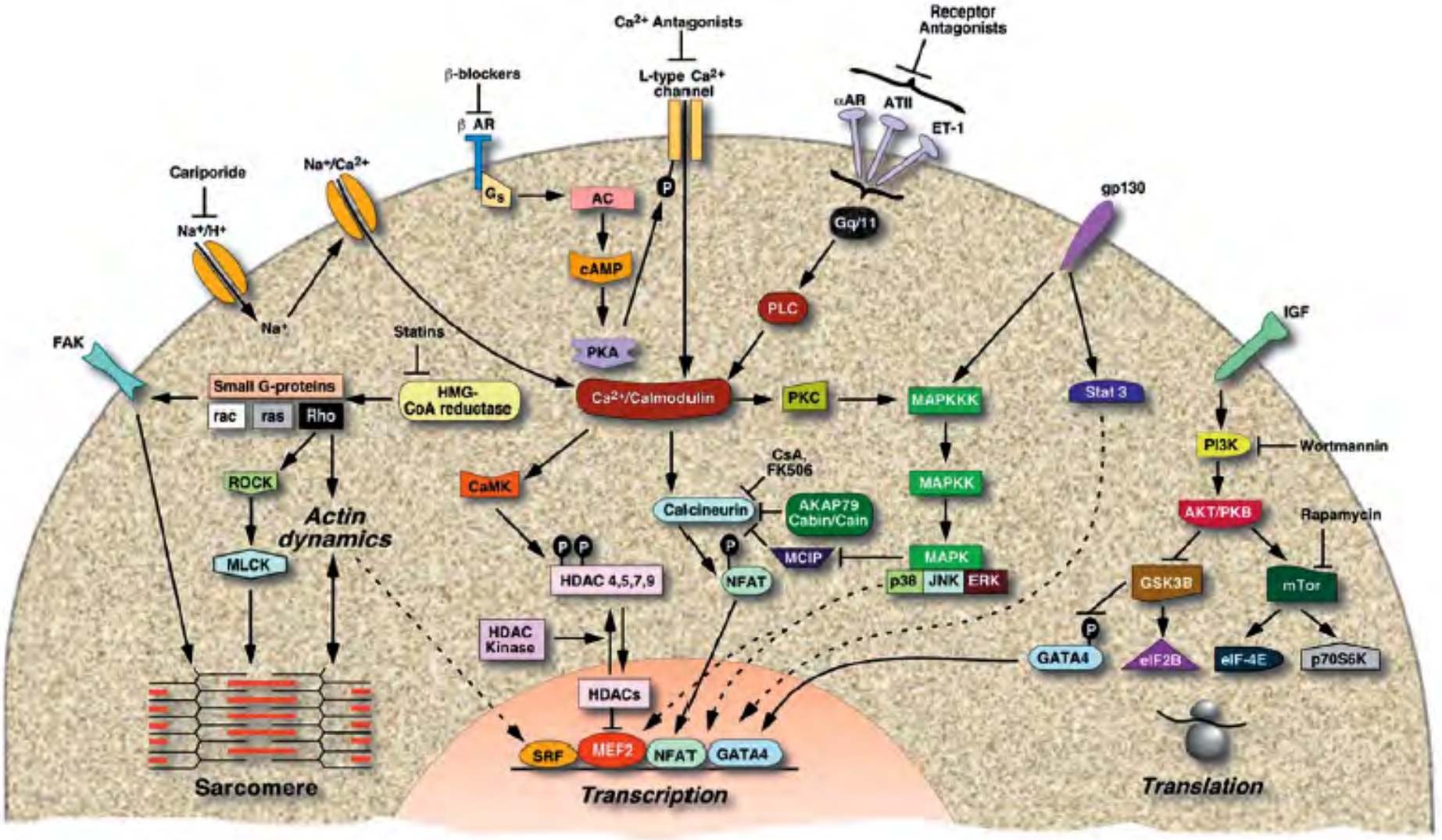
# Calcineurin/NFAT Coupling Participates in Pathological, but not Physiological, Cardiac Hypertrophy

Benjamin J. Wilkins, Yan-Shan Dai, Orlando F. Bueno, Stephanie A. Parsons, Jian Xu,
David M. Plank, Fred Jones, Thomas R. Kimball, Jeffery D. Molkentin




Wilkins *et al*. *Circ Res* 2004;94:110.




Frey N. and Olson E.N. (2003) Annu. Rev. Physiol.

**Dept of Cardiology, Maastricht**

Hamid el Azzouzi

Monika Gladka

Stefanos Leptidis

Leonne Philippen

Kanita Salic

Gustavo da Silva

Natasja Kisters

Serve Olieslagers

Nicole Bitsch

Burcu Duygu

Paula da Costa Martins

**Harvard, Boston**

Laurie Glimcher

**Tulane, New Orleans, USA**

Peter Cserjesi

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