Histone Deacetylase Inhibition in Cardiovascular Diseases

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Contents

① HDAC & HDAC inhibitors

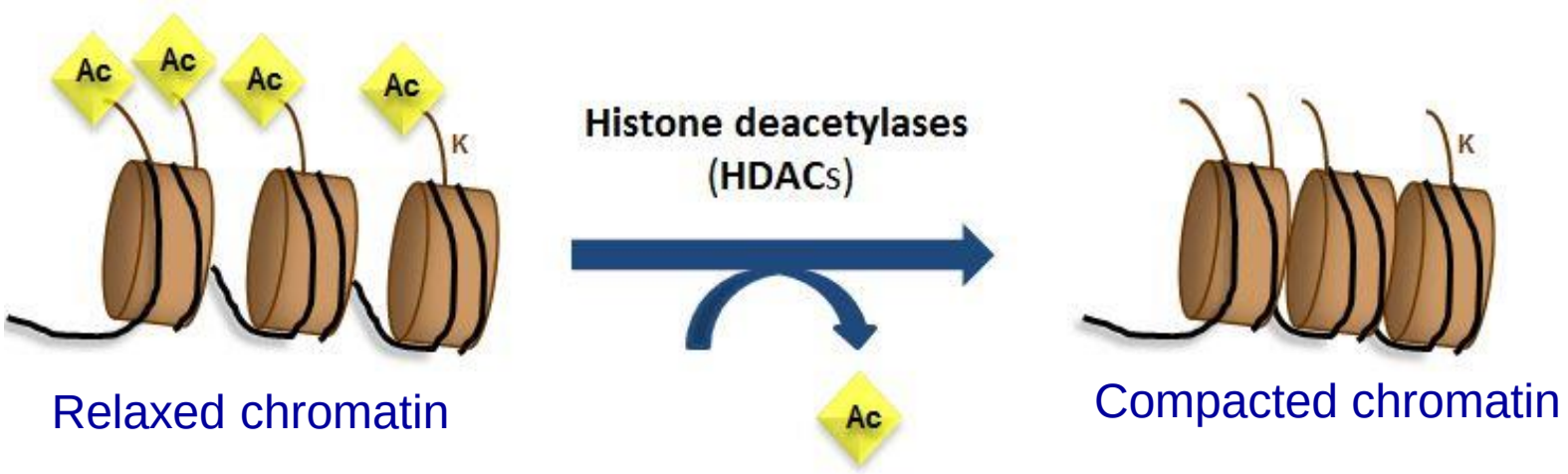
② Cardiac hypertrophy and fibrosis

③ Hypertension

Part 1

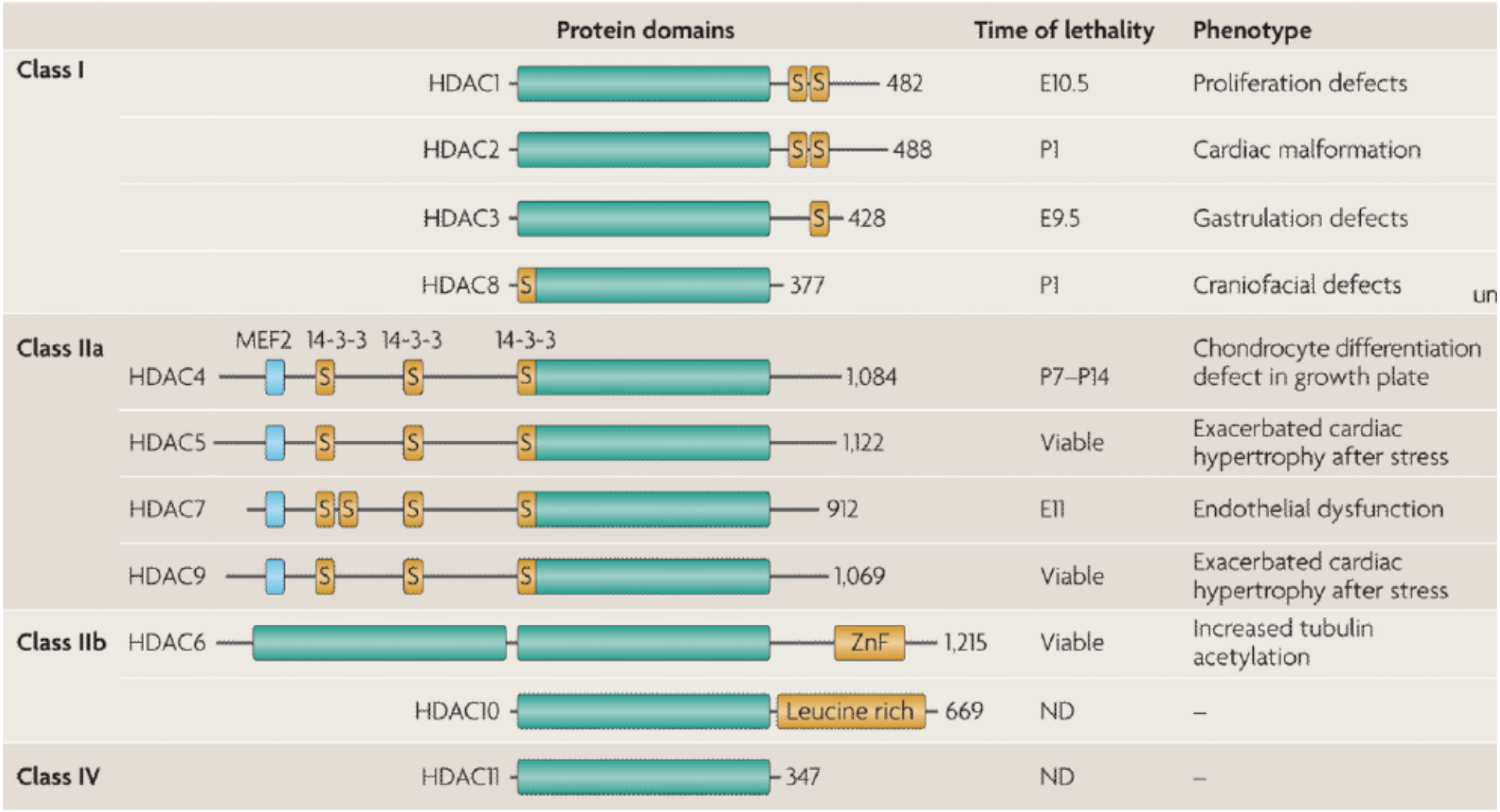
- ✓ Histone deacetylases (HDACs)
- ✓ HDAC inhibitors (chemicals)
- ✓ HDAC inhibitors (natural products)

Histone deacetylase (HDAC) = Lysine deacetylase (KDAC)



- Removes acetyl groups from histones
- Represent gene expression
- Recently HDACs are called lysine deacetylases (KDAC) to describe their function rather than their targets.

HDAC classification

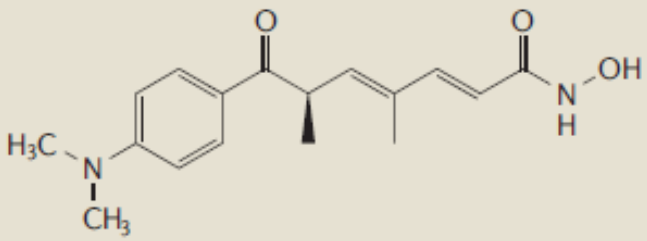


Haberland, M. et al. Nat Rev Genet 2009

HDAC inhibitors : Four classes

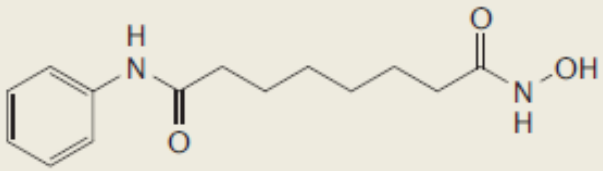
Hydroxamate

TSA

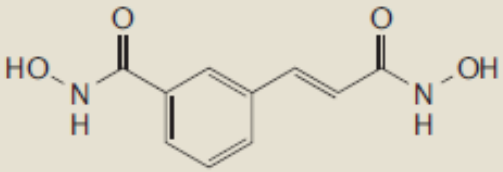


SAHA

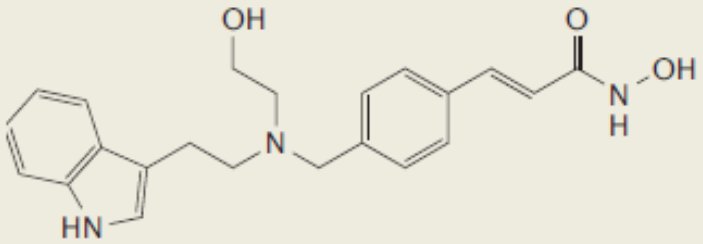
FDA approval



CBHA

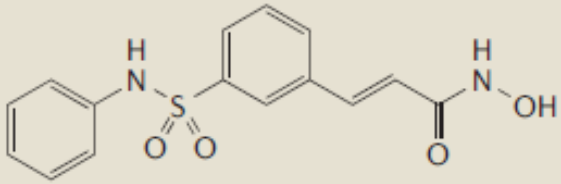


LAQ-824



PXD-101

FDA approval

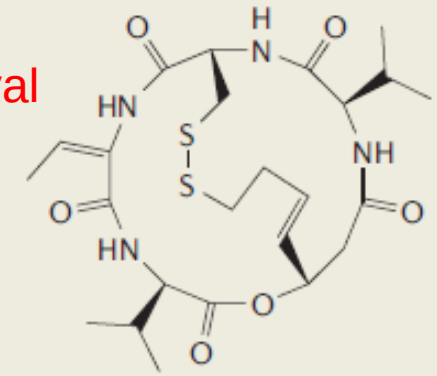


Classes of HDAC inhibitors

Cyclic peptide

Depsipeptide

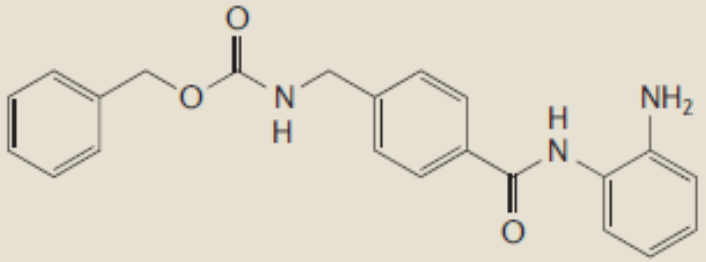
FDA approval



Benzamide

MS-275

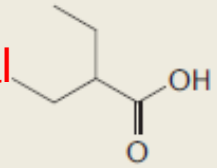
FDA approval



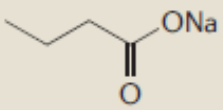
Aliphatic acids

Valproic acid

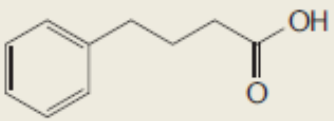
FDA approval



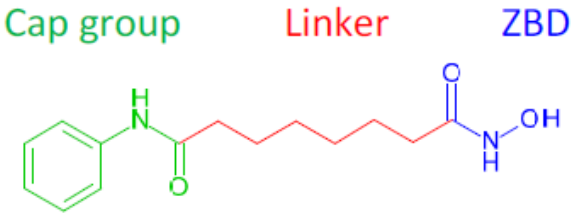
Sodium butyrate



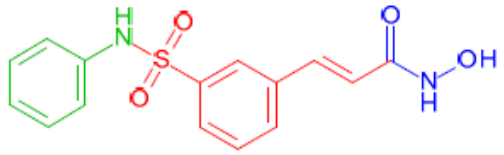
Phenyl butyrate



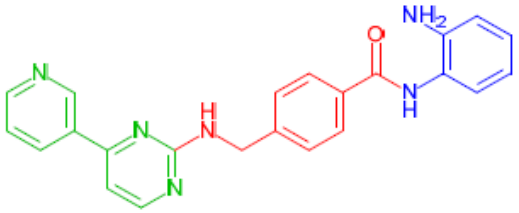
Pharmacophores of HDAC inhibitors



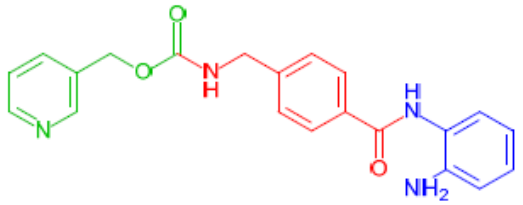
Vorinostat (SAHA)



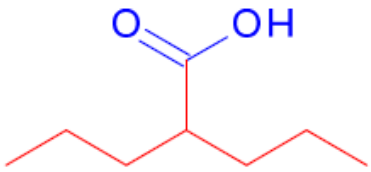
Belinostat (PXD-101)



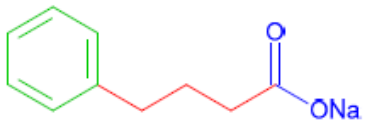
Mocetinostat (MGCD0103)



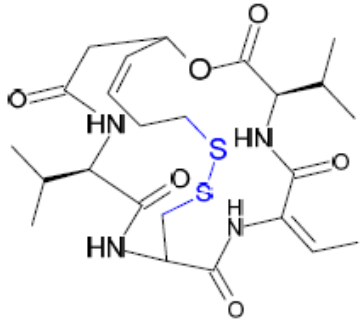
Entinostat (MS-275)



Valproic acid



Sodium phenylbutyrate

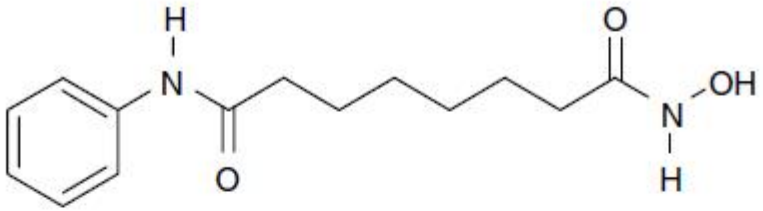


Romidepsin

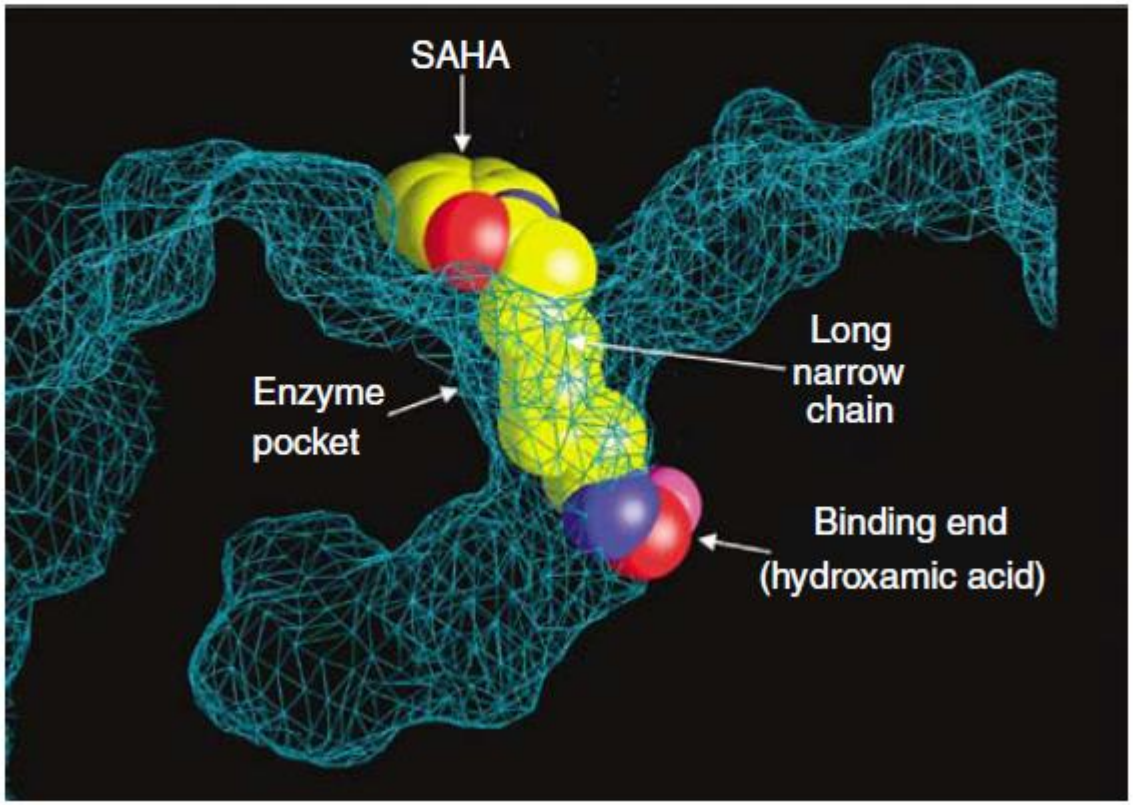
- Zinc-dependent HDAC inhibitors have common pharmacophores consisting of three distinct domains.

SAHA inhibits HDAC activity
by binding to the pocket of the catalytic site.

Vorinostat (suberoylanilide hydroxamic acid, SAHA)



Approved by the USA FDA
Fail to show efficacy in treating leukaemia



SAHA binds to the active site of HDAC

SAHA acts as a chelator for zinc ions

Pink : zinc atom

Richon VM.
British J of Cancer, 2006

Natural HDAC inhibitors

Garlic

Broccoli and broccoli sprouts

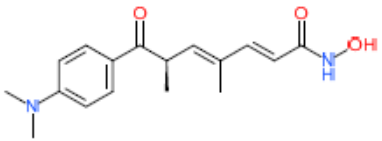
Blueberries

Grapes

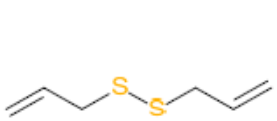
Black tea

Natural product HDAC inhibitors

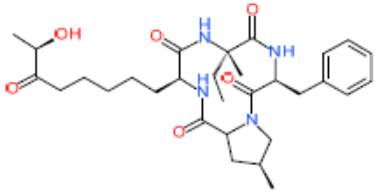
- Many HDAC inhibitors are of natural origin.



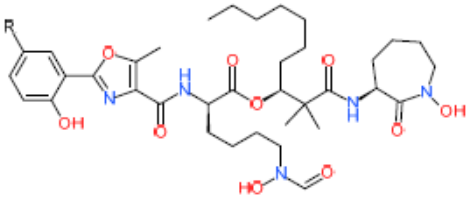
Trichostatin A
Streptomyces Hygroscopicus



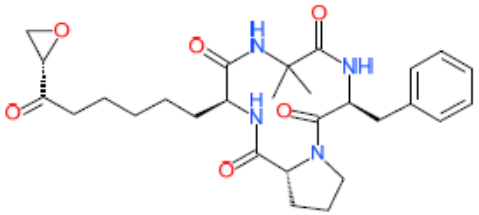
Diallyl disulfide
Garlic



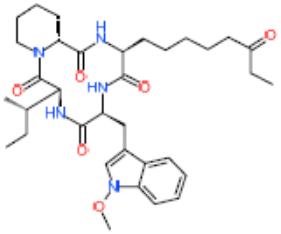
FR235222
Acremonium sp



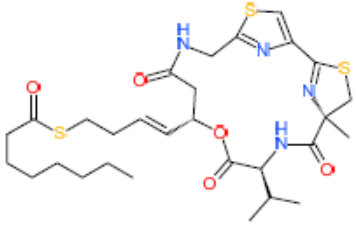
Amamistatin (A) R = OMe, (B) R = H
Nocardia Asteroides



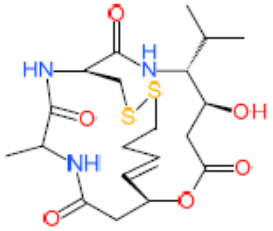
Chlamydocin
Diheterospora Chlamydosporia



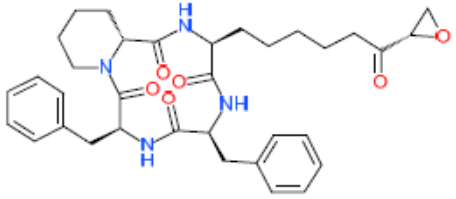
Apicidin
Fusarium sp



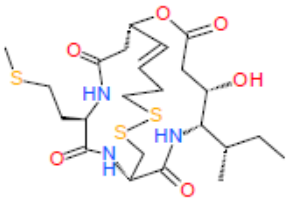
Largazole
Cyanobacterium Symploca sp



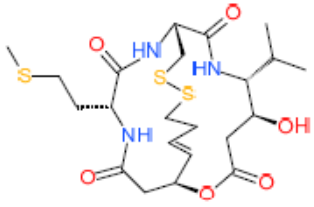
Spiruchostatin A
Pseudomonas



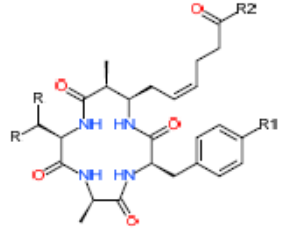
Trapoxin A
Corollospora intermedia



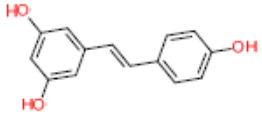
Burkholdac A
Burkholderia Thailandensis



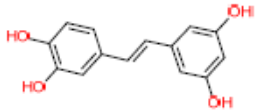
Thailandepsin A
Burkholderia Thailandensis



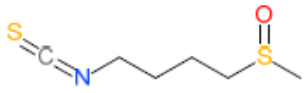
Azumamide (A) $R/R_1/R_2 = CH_3/H/NH_2$; (B) $CH_3/OH/NH_2$;
(C) $CH_3/OH/OH$; (D) $H/H/NH_2$, (E) $CH_3/H/OH$
Marine sponge mycale izuensis



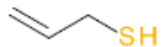
Resveratrol
Grapes/blueberries



Piceatannol
Blueberries

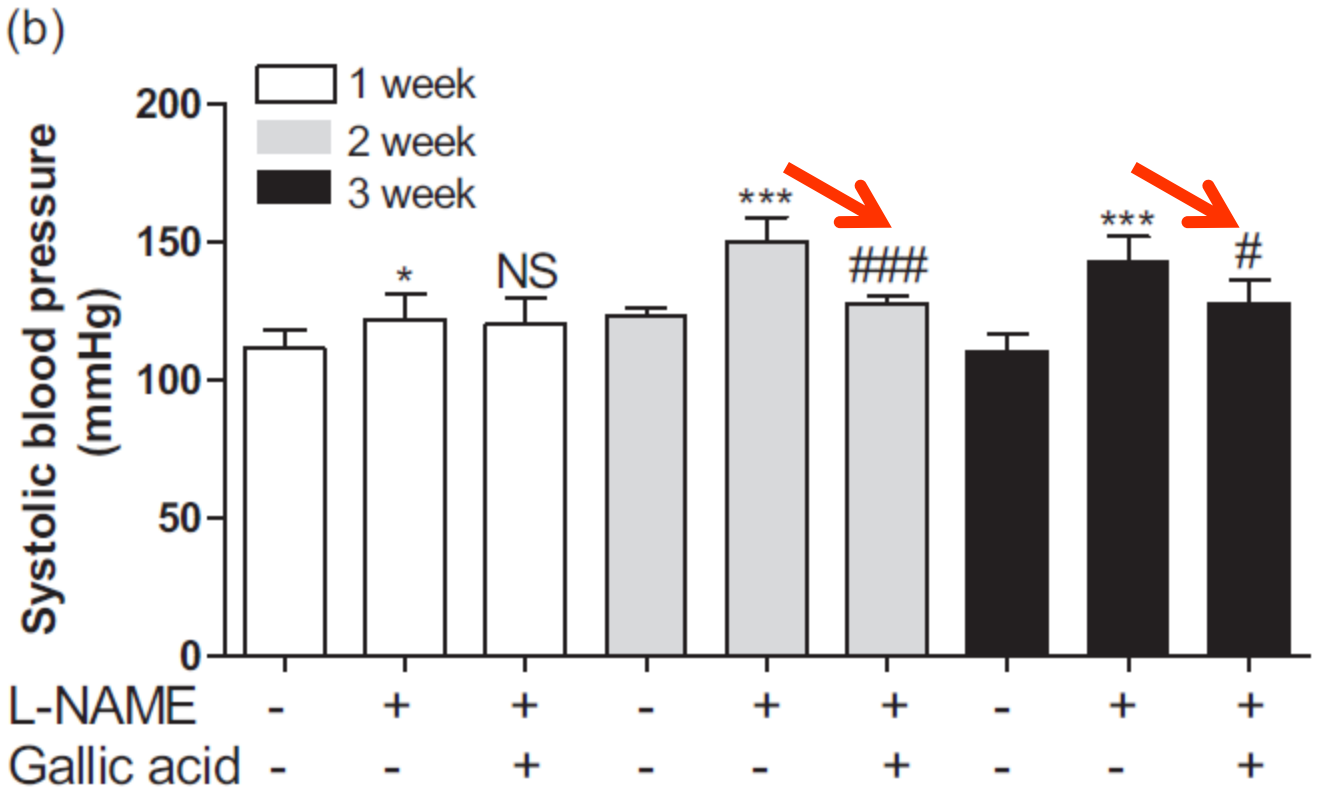


Sulforaphane
Broccoli sprouts



Allyl Mercaptan
Garlic

Gallic acid reduces elevated blood pressure in NAME-induced hypertensive mice



Original Article

Journal of Hypertension, 2017

Gallic acid attenuates hypertension, cardiac remodeling, and fibrosis in mice with N^G-nitro-L-arginine methyl ester-induced hypertension via regulation of histone deacetylase 1 or histone deacetylase 2

Li Jin[a,b,*], Ming Quan Lin[a,c,*], Zhe Hao Piao[d], Jae Yeong Cho[a], Gwi Ran Kim[a], Sin Young Choi[a], Yuhee Ryu[a], Simei Sun[a], Hae Jin Kee[a], and Myung Ho Jeong[a]

Objective: Gallic acid, a natural chemical found in plants, has been reported to show antioxidant, anticancer, and anti-inflammatory effects. We investigated the efficacy of a short-term or long-term treatment with gallic acid in N^G-nitro-L-arginine methyl ester (L-NAME)-induced hypertensive mice and the underlying regulatory mechanism.

Abbreviations: α-SMA, α-smooth muscle actin; ACE1, angiotensin II-converting enzyme; ANP, atrial natriuretic peptide; AT1, angiotensin II receptor; BNP, brain natriuretic peptide; HAT, histone acetyltransferases; HDAC, histone deacetylase; L-NAME, N^G-nitro-L-arginine methyl ester; LV, left ventricular; NOS, nitric oxide synthase; TGF-β, transforming growth factor beta

Part 2

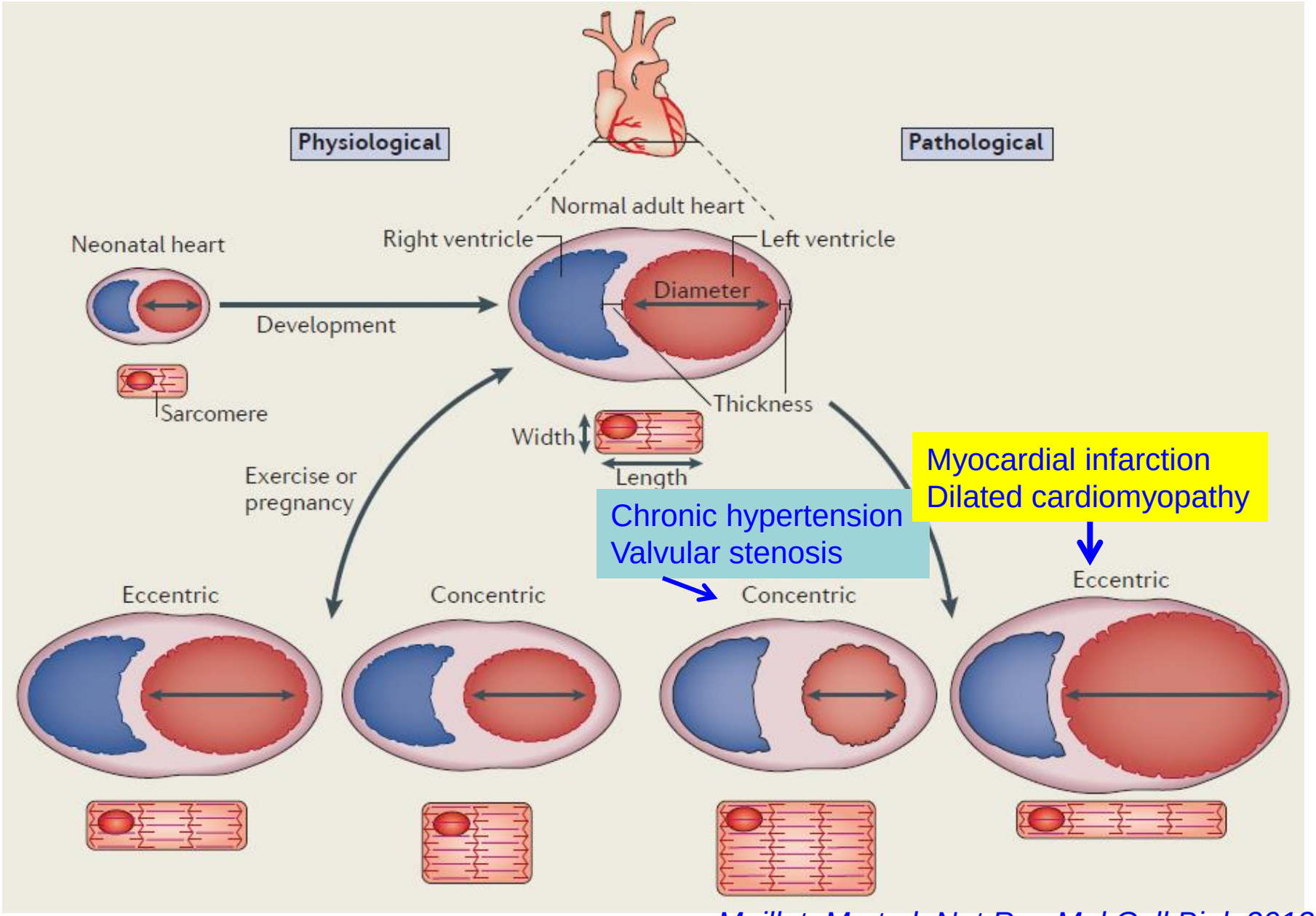
HDAC inhibitors in cardiac hypertrophy and fibrosis:

Class I, class IIa HDAC inhibitor (Valproic acid)

Class I, class IIa/b, class IV HDAC inhibitor (TSA)

HDAC1- and HDAC2-selective inhibitor (SK7041)

Physiological vs Pathological Hypertrophy



Maillet M et al. Nat Rev Mol Cell Biol, 2013

Inhibition of Histone Deacetylation Blocks Cardiac Hypertrophy Induced by Angiotensin II Infusion and Aortic Banding

Hae Jin Kee, PhD; Il Suk Sohn, MD, PhD; Kwang Il Nam, MD, PhD; Jong Eun Park, BS; Yong Ri Qian, MD; Zhan Yin, PhD; Youngkeun Ahn, MD, PhD; Myung Ho Jeong, MD, PhD; Yung-Jue Bang, MD, PhD; Nacksung Kim, PhD; Jong-Keun Kim, MD, PhD; Kyung Keun Kim, MD, PhD; Jonathan A. Epstein, MD; Hyun Kook, MD, PhD

Background—A number of distinct stress signaling pathways in myocardium cause cardiac hypertrophy and heart failure. Class II histone deacetylases (HDACs) antagonize several stress-induced pathways and hypertrophy. However, cardiac hypertrophy induced by transgenic overexpression of the homeodomain only protein, HOP, can be prevented by the nonspecific HDAC inhibitors trichostatin A and valproic acid, suggesting that alternate targets that oppose class II HDAC function might exist in myocardium. We tested the effects of several HDAC inhibitors, including a class I HDAC-selective inhibitor, SK-7041, on cardiac hypertrophy induced by angiotensin II (Ang II) treatment or aortic banding (AB).

Methods and Results—Cardiac hypertrophy was induced by chronic infusion of Ang II or by AB in mice or rats and evaluated by determining the ratio of heart weight to body weight or to tibia length, cross-sectional area, or echocardiogram. Cardiac hypertrophy induced by Ang II or AB for 2 weeks was significantly reduced by simultaneous administration of trichostatin A, valproic acid, or SK-7041. Echocardiogram revealed that exaggerated left ventricular systolic dimensions were relieved by HDAC inhibitors. HDAC inhibitors partially reversed preestablished cardiac hypertrophy and improved survival of AB mice. The expressions of atrial natriuretic factor, α-tubulin, β-myosin heavy chain, and interstitial fibrosis were reduced by HDAC inhibition.

Conclusions—These results suggest that the predominant effect of HDAC inhibition, mainly mediated by class I HDACs, is to prevent cardiac hypertrophy in response to a broad range of agonist and stretch stimuli. (***Circulation*. 2006;113: 51-59.**)

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

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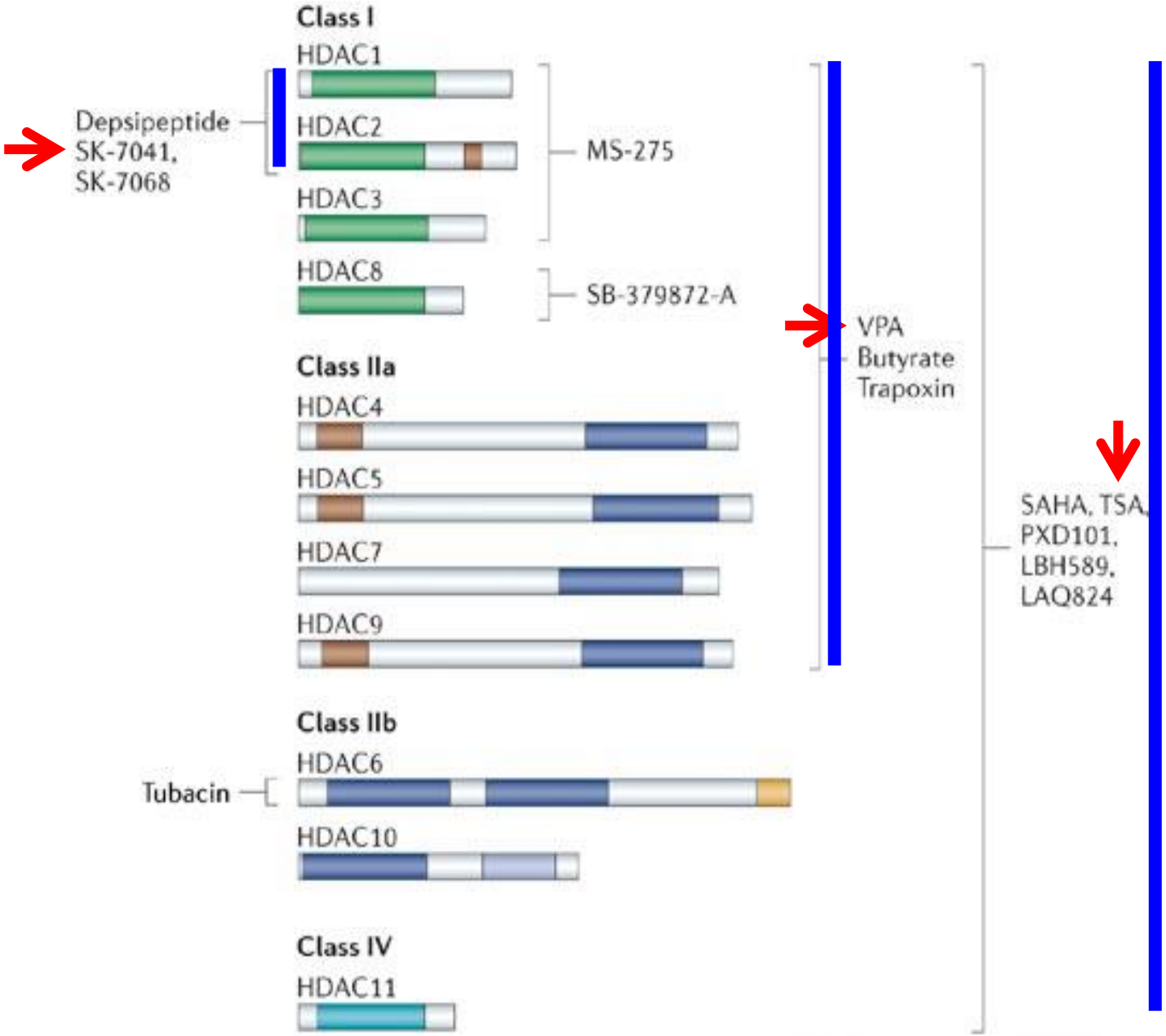
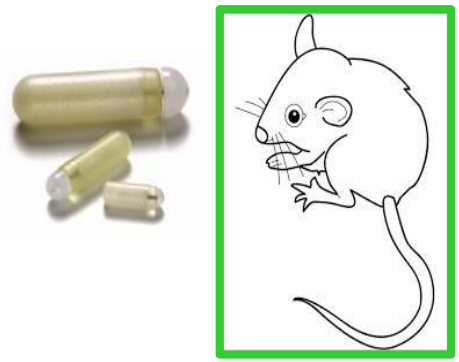
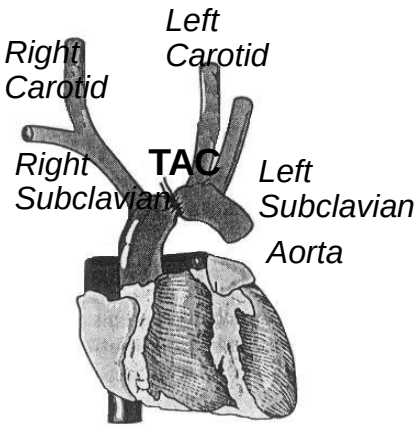
HDAC inhibitors



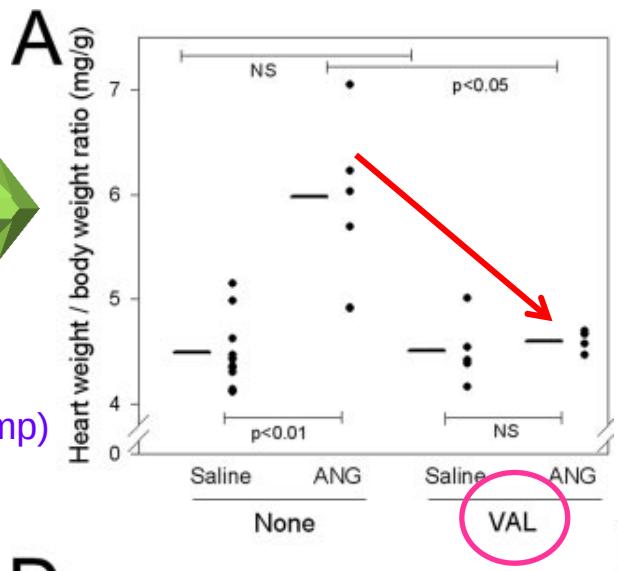
Inhibition of histone deacetylation blocks cardiac hypertrophy induced by angiotensin II Infusion and aortic banding (*Kee et al., Circulation, 2006;113:51-59, IF : 17.047*)

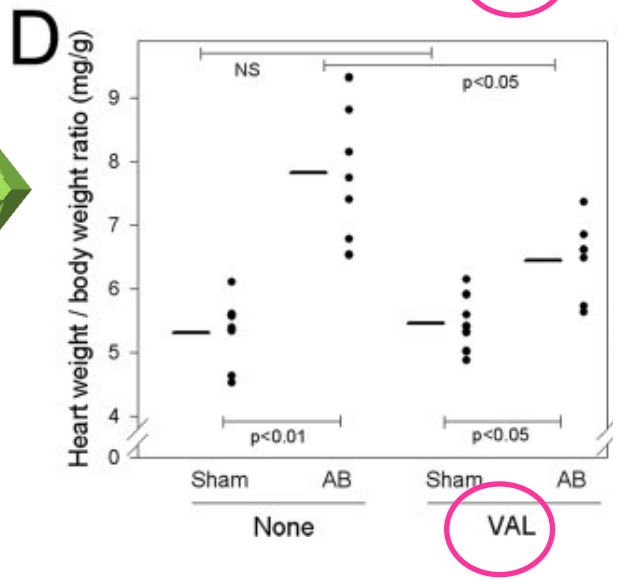


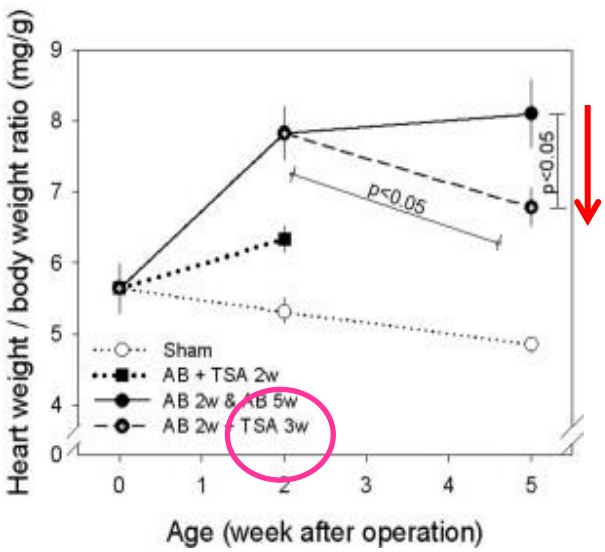
Angiotensin II (osmotic minipump)



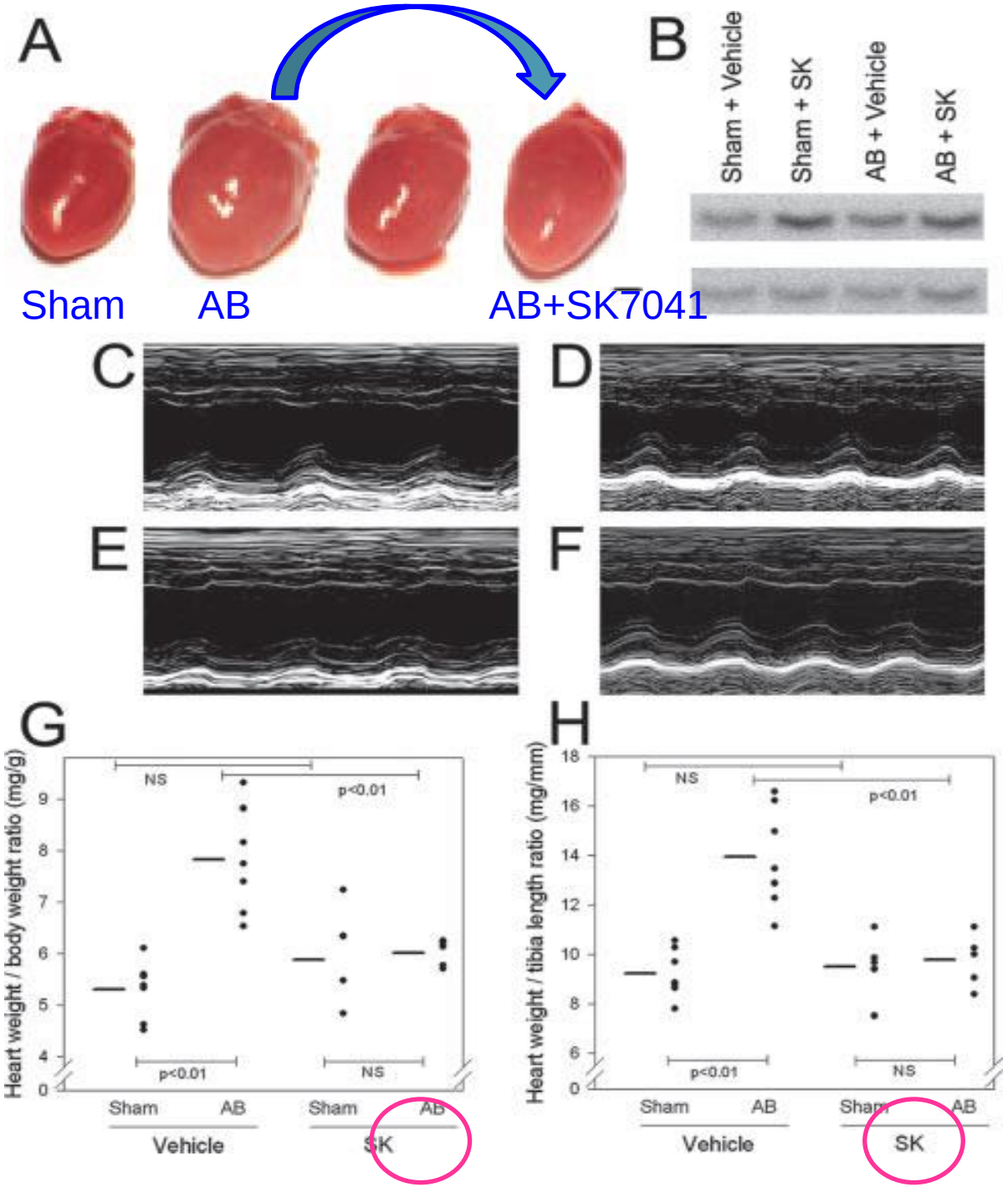
Aortic banding



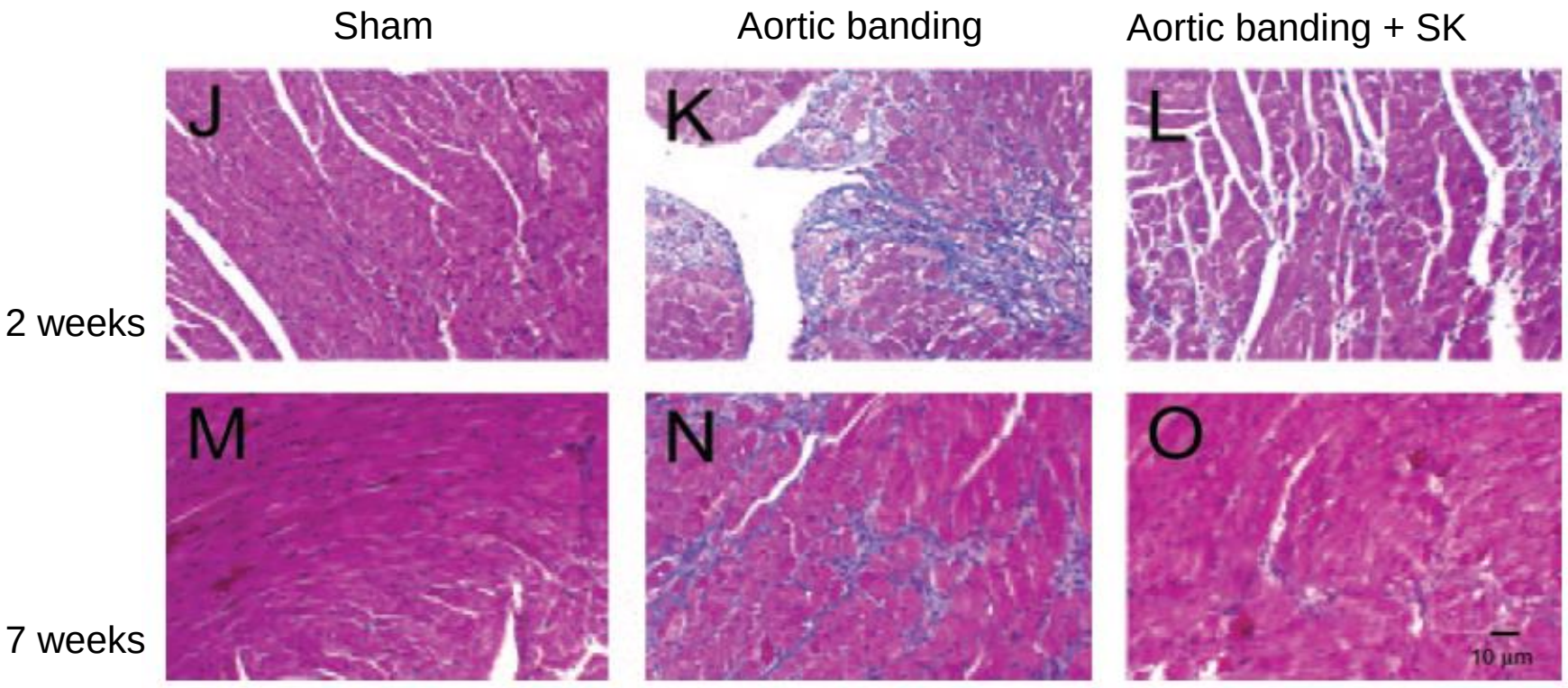




Prevention of cardiac hypertrophy by **SK-7041,** a class I HDAC-selective inhibitor



Reduction of cardiac fibrosis induced by SK7041



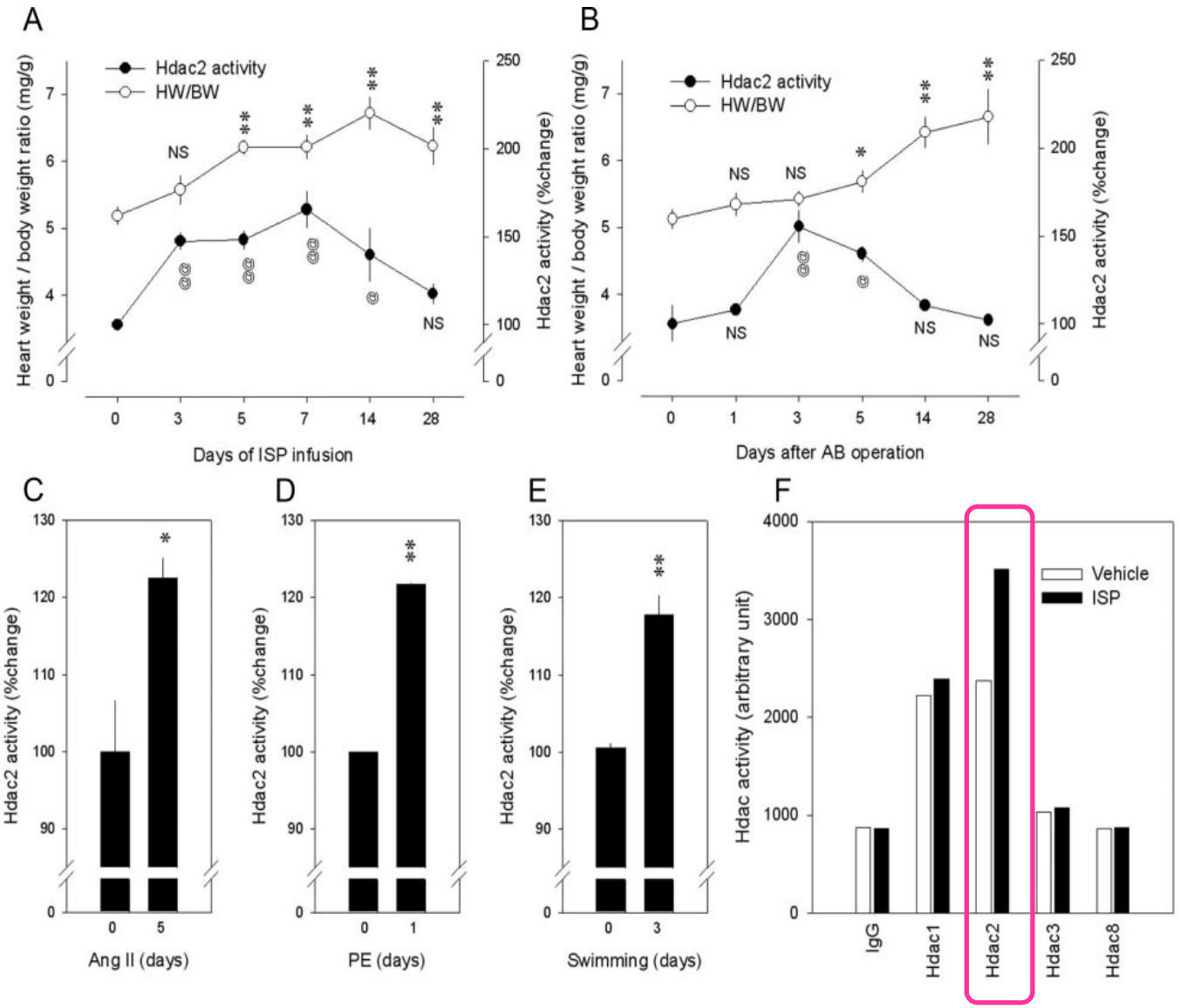
Summary

HDAC inhibitors can prevent or treat cardiac hypertrophy and fibrosis.

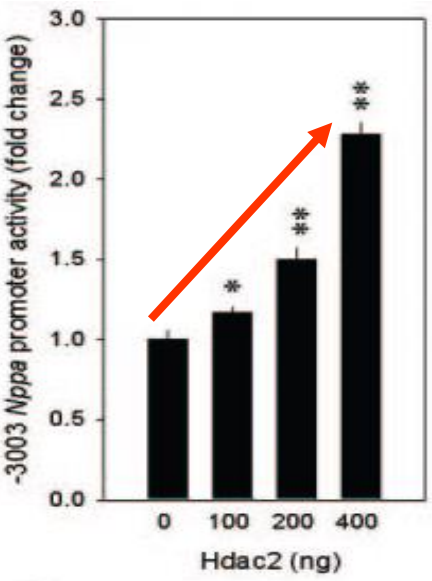
Activation of histone deacetylase 2 by inducible heat shock protein 70 in cardiac hypertrophy

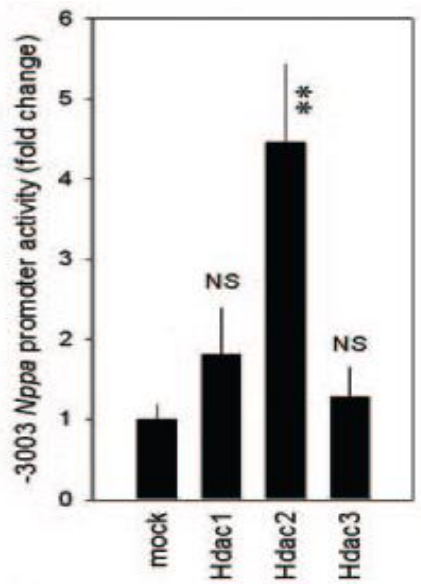
(*Kee et al., Circulation Research, 2008;103:1259-1269, IF : 11.551*)

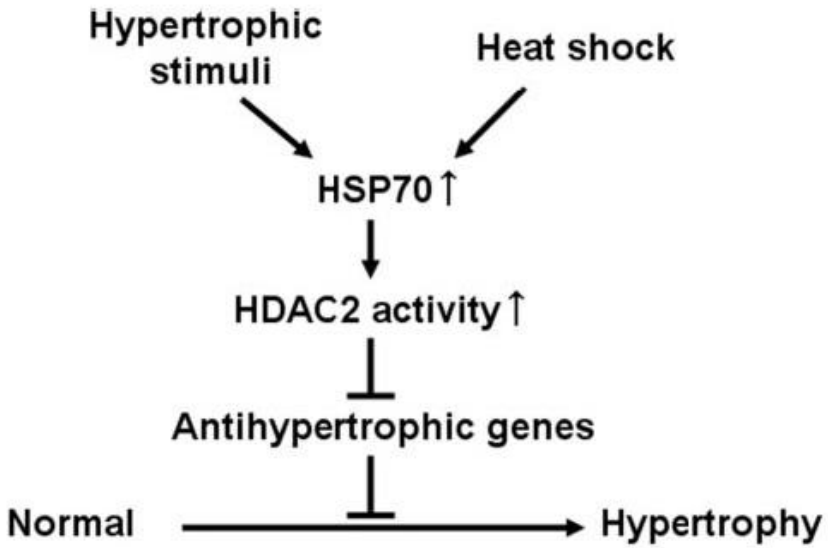
HDAC2 is activated in the mouse hypertrophy model



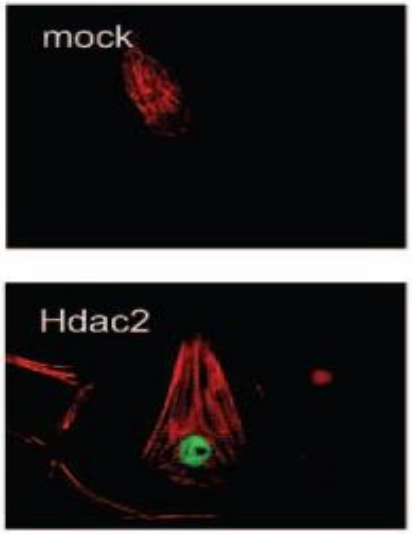
HDAC2 acts as a prohypertrophic mediator





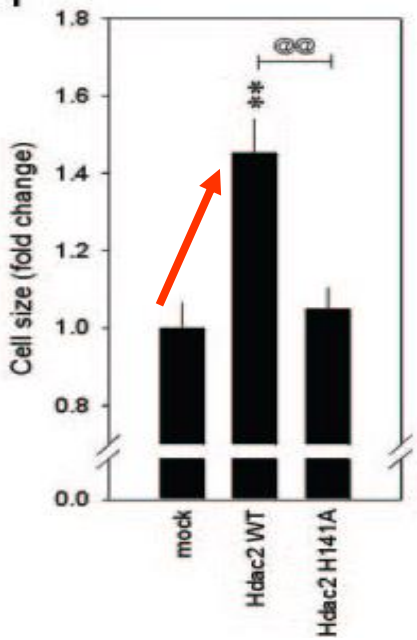


G



cardiomyocyte

H



Nppa = ANP (atrial natriuretic peptide)

Part 3

HDAC inhibitors in hypertension:

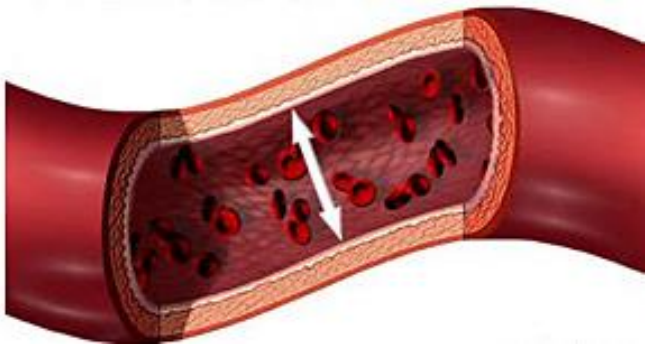
HDAC6-selective inhibitor (Tubastatin A)

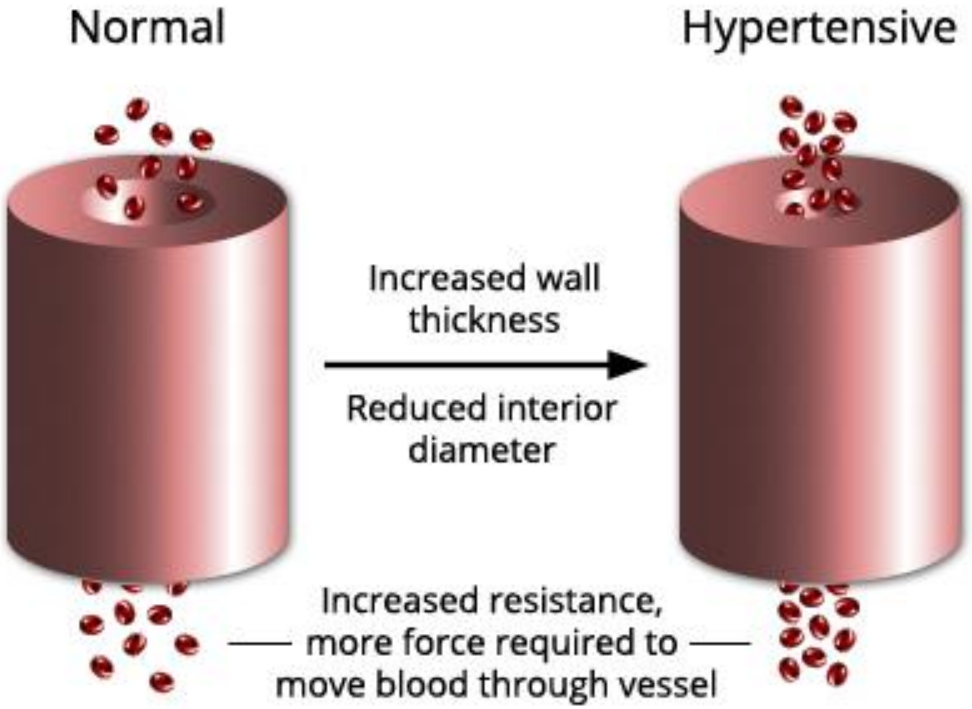
Class IIa/b HDAC inhibitor (MC1568)

HDAC4/5 selective inhibitor (LMK235)

Hypertension

1. **Hypertension is also known as high blood pressure.**
2. **Blood pressure (arterial) is the pressure exerted by circulating blood on the walls of blood vessels.**
3. **If left untreated, hypertension can lead to atherosclerosis and heart failure.**





J Mol Cell Cardiol. 2011 July ; 51(1): 41–50. doi:10.1016/j.yjmcc.2011.04.005.

Cardiac HDAC6 Catalytic Activity is Induced in Response to Chronic Hypertension

Douglas D. Lemon[1], **Todd R. Horn**[1], **Maria A. Cavasin**[1], **Mark Y. Jeong**[1], **Kurt W. Haubold**[1], **Carlin S. Long**[1], **David C. Irwin**[2], **Sylvia A. McCune**[3], **Eunhee Chung**[4], **Leslie A. Leinwand**[4], and **Timothy A. McKinsey**[1,#]

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Abstract

Small molecule histone deacetylase (HDAC) inhibitors block adverse cardiac remodeling in animal models of heart failure. The efficacious compounds target class I, class IIb and, to a lesser extent, class IIa HDACs. It is hypothesized that a selective inhibitor of a specific HDAC class (or an isoform within that class) will provide a favorable therapeutic window for the treatment of heart failure, although the optimal selectivity profile for such a compound remains unknown. Genetic studies have suggested that class I HDACs promote pathological cardiac remodeling, while class IIa HDACs are protective. In contrast, nothing is known about the function or

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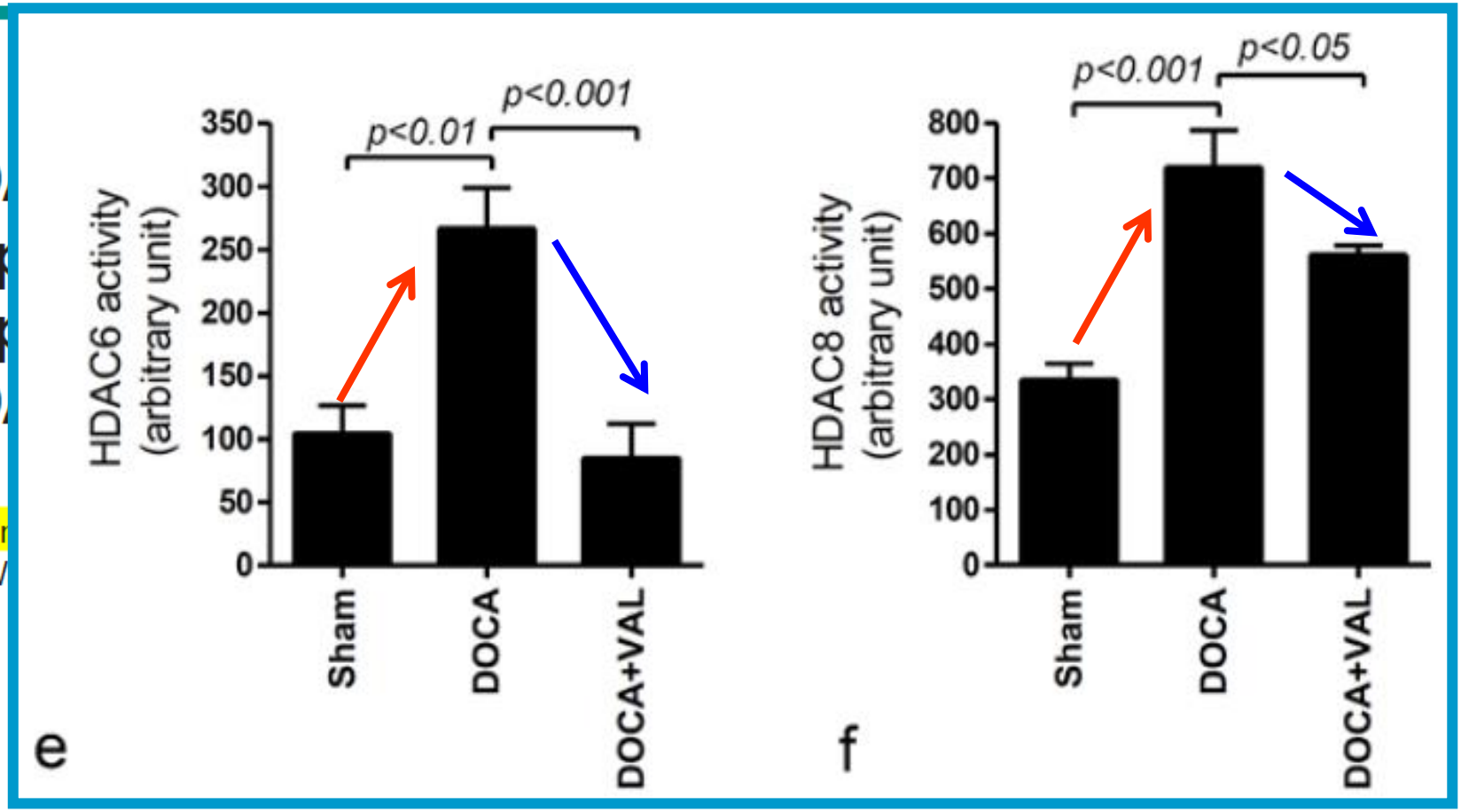
1423-0143/13/0375-0229$38.00/0

Original Paper

HDA
Hyp
Hyp
HDA

Hae Ji
Soo W



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HDAC6 ?

Tubastatin A suppresses renal fibrosis via regulation of epigenetic histone modification and Smad3-dependent fibrotic genes

Sin Young Choi [a,1], Yuhee Ryu [a,1], Hae Jin Kee [a,*], Soo-Na Cho [a], Gwi Ran Kim [a], Jae Yeong Cho [a], Hyung-Seok Kim [b], In-Kyeom Kim [c], Myung Ho Jeong [a,**]

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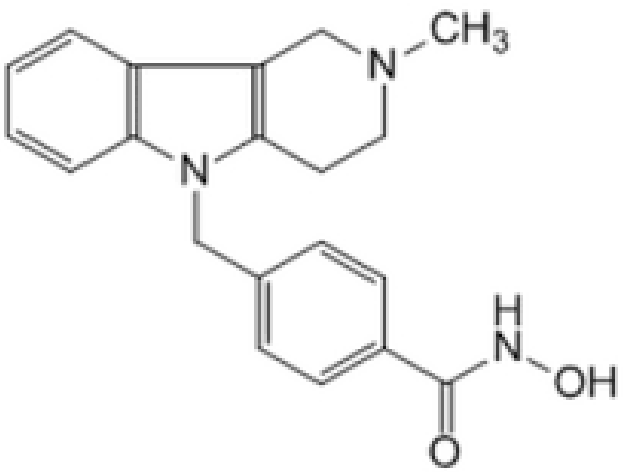
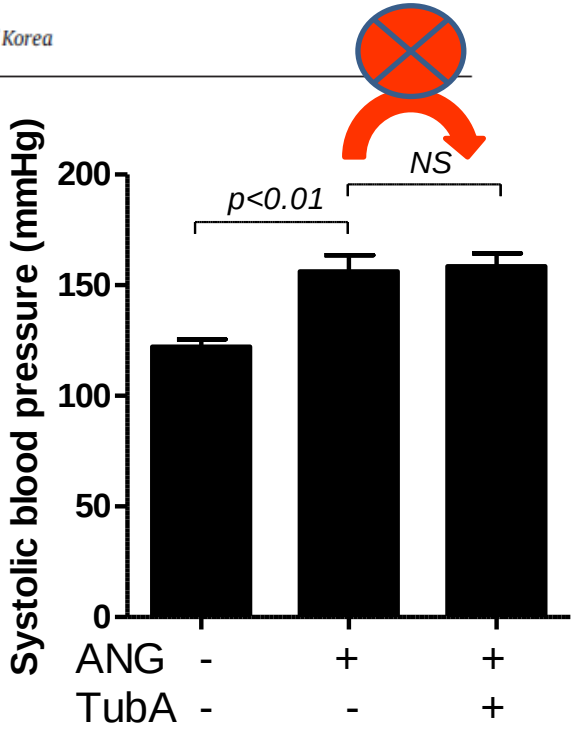
[b] Department of Anatomy, Chonnam National University Medical School, Gwangju 501-757, Republic of Korea
[c] Department of Pharmacology, Cardiovascular Research Institute, Kyungpook National University School of Medicine, Daegu, Republic of Korea



Tubastatin A (HDAC6 selective inhibitor)



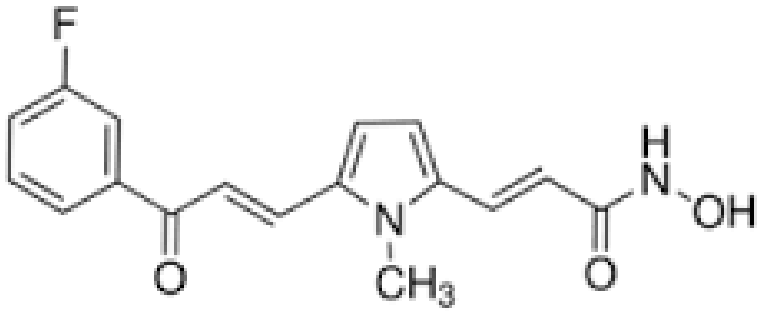
Original Article (Journal of Hypertension, 2016)

Histone deacetylase and GATA-binding factor 6 regulate arterial remodeling in angiotensin II-induced hypertension

Gwi Ran Kim[a,*], Soo-Na Cho[a,*], Hyung-Seok Kim[b,*], Seon Young Yu[b], Sin Young Choi[a], Yuhee Ryu[a], Ming Quan Lin[a], Li Jin[a,c], Hae Jin Kee[a], and Myung Ho Jeong[a]

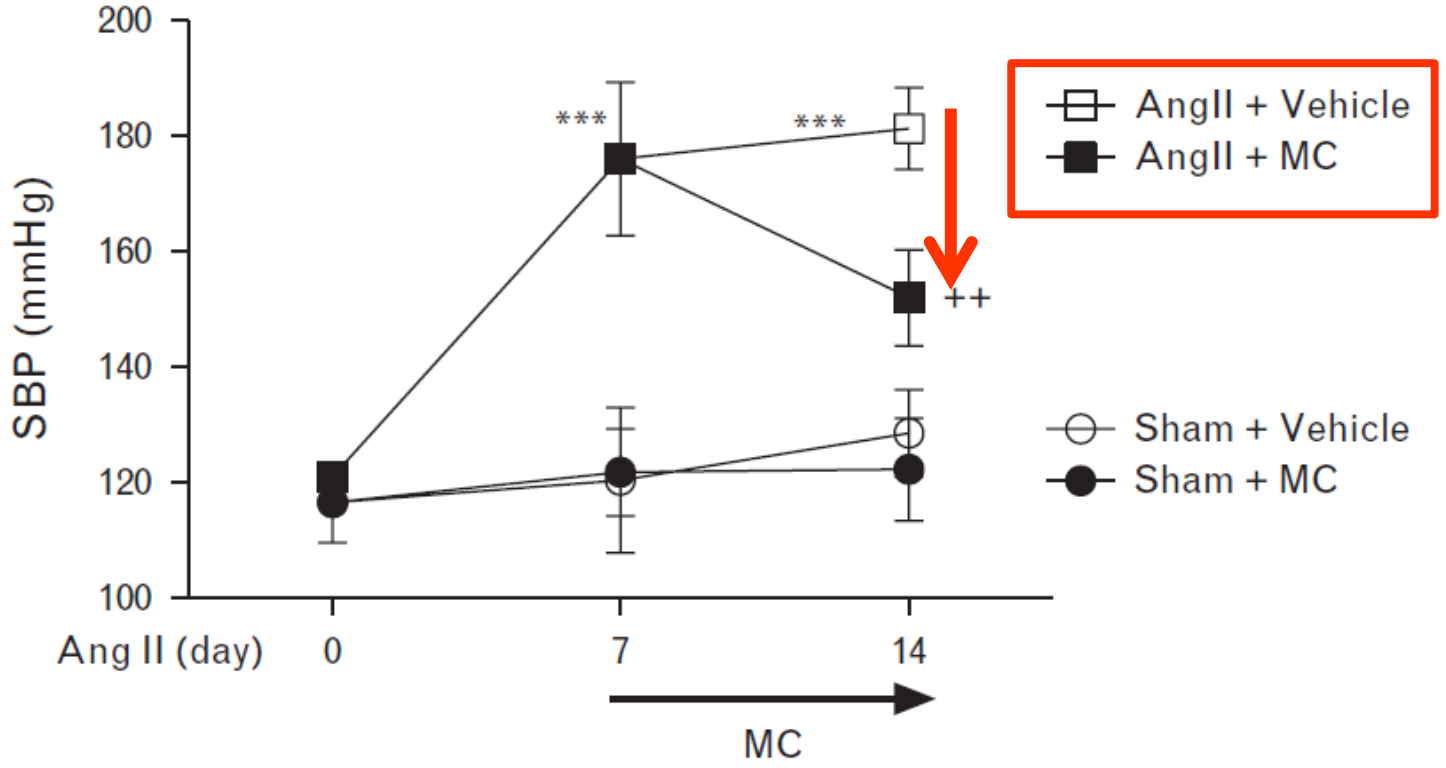
Objective: Histone deacetylase (HDAC) inhibitors have been reported to improve essential and secondary hypertension. However, the specific HDAC that might serve as a therapeutic target and the associated upstream and downstream molecules involved in regulating hypertension remain unknown. Our study was aimed at investigating whether a selective inhibitor of class II HDAC

GATA-binding factor 6; GFP, green fluorescent protein; HDAC, histone deacetylase; IHC, immunohistochemistry; phospho-HDAC4, phosphorylated HDAC4; phospho-PKD1, phosphorylated PKD1; PKD1, protein kinase D1; siRNA, small interfering RNA; SMA, smooth muscle α-actin; VSMC, vascular smooth muscle cell

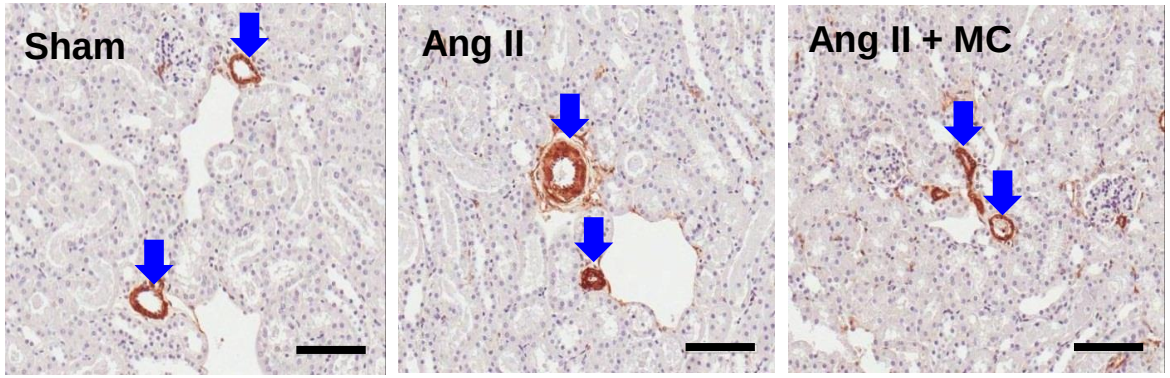


MC1568 (class II HDAC inhibitor)

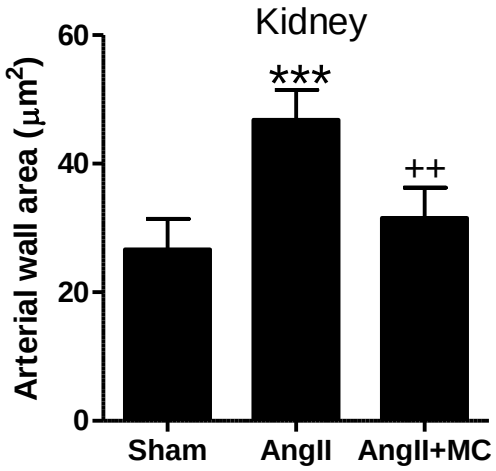
MC1568 reduces high blood pressure in Ang II-induced hypertensive mice

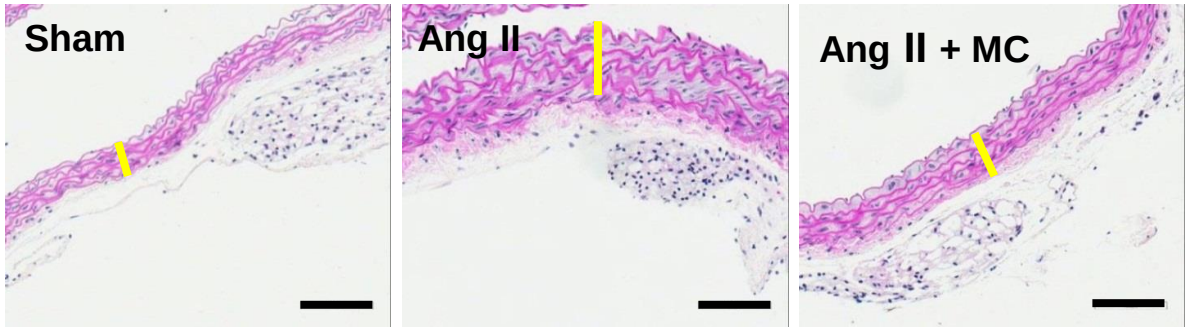


MC1568 attenuates the thickening of kidney arterial wall and thoracic wall in Ang II-infused mice

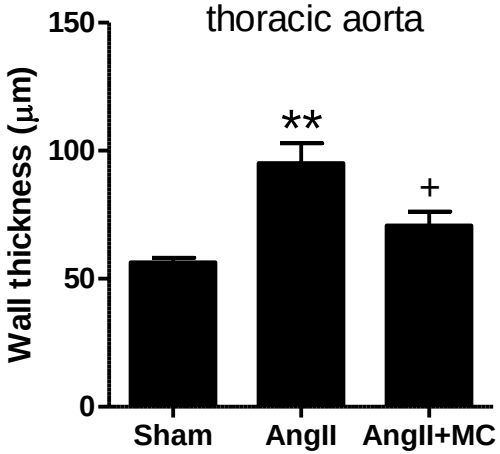


IHC: SMA (kidney)





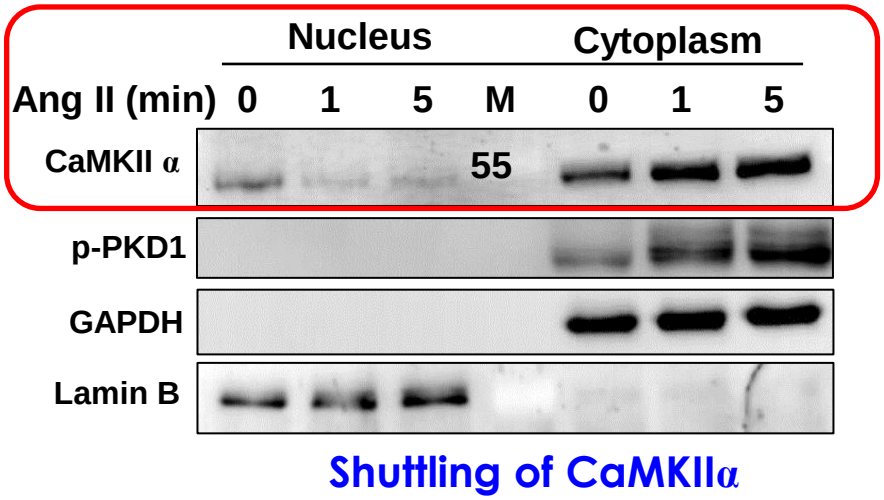
H&E (aorta)



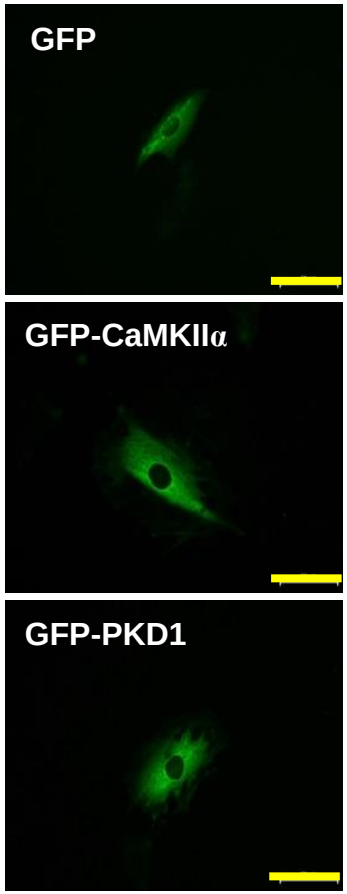
SMA : α smooth muscle actin

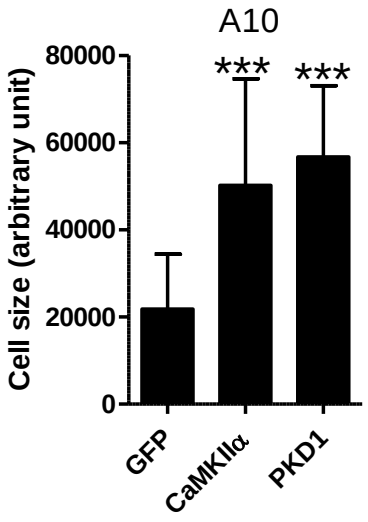
CaMKIIα and PKD1, kinases acting upstream of HDAC4, increases the vascular cell size and number

CaMKII : Ca^{2+}/calmodulin-dependent protein kinase II
PKD1 : protein kinase D1

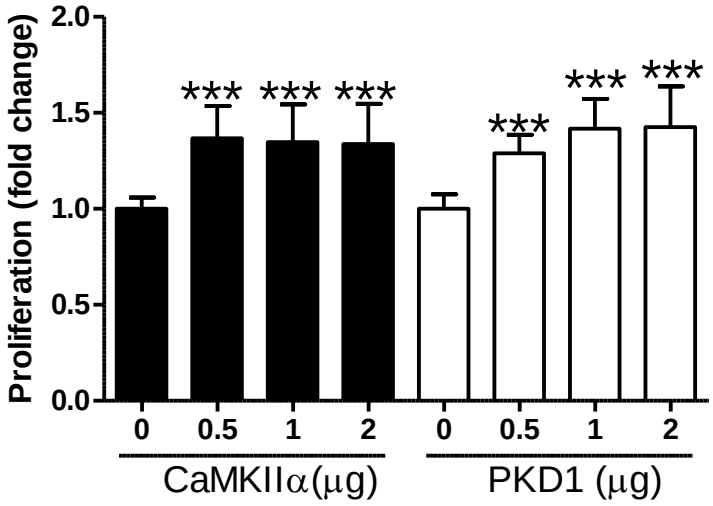


Shuttling of CaMKIIα



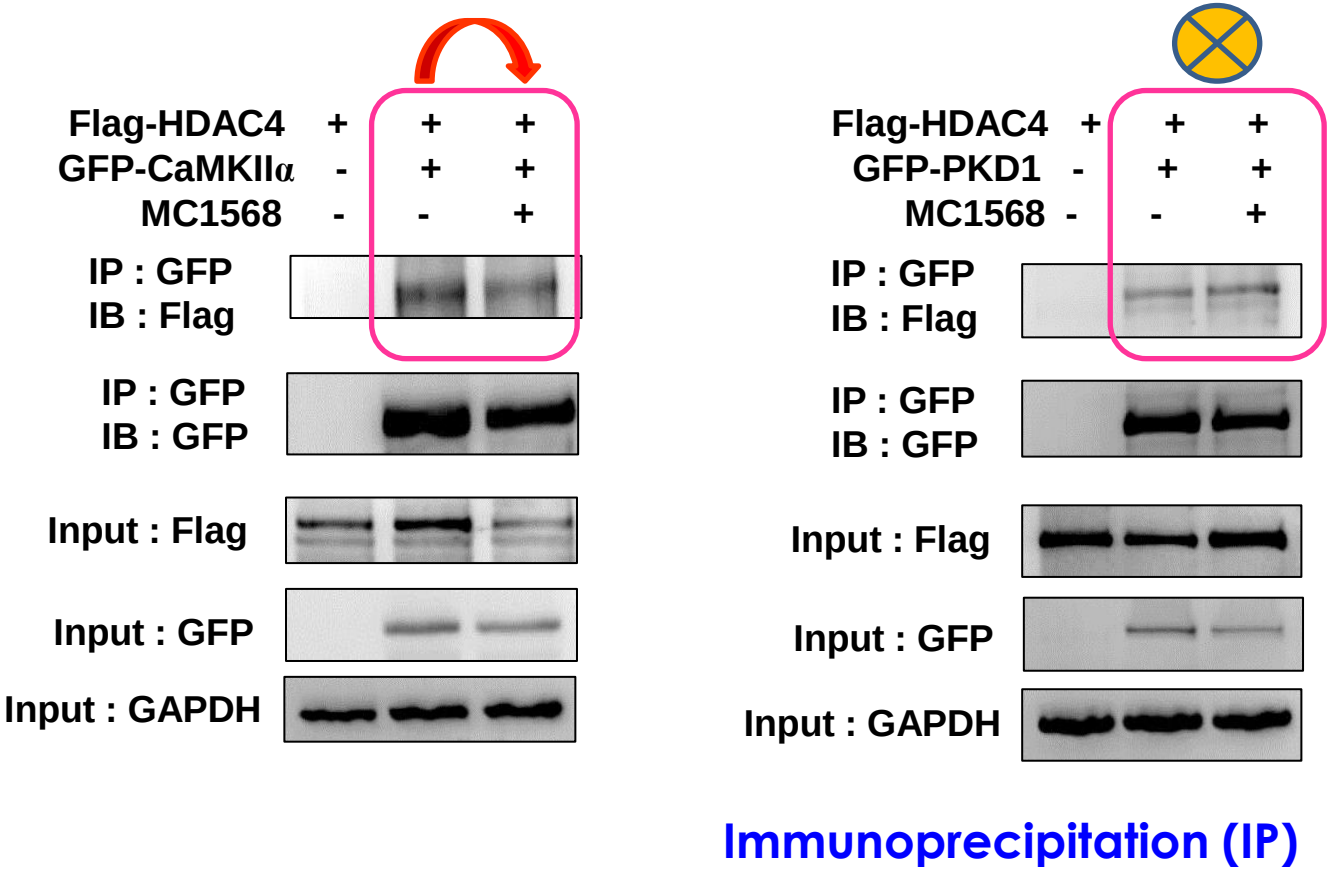


VSMC hypertrophy (cell size)



VSMC hyperplasia (cell number)

MC1568 weakens the association between HDAC4 and CaMKIIα



Immunoprecipitation (IP)

CaMKII : calcium $^{2+}$/calmodulin-dependent protein kinase II
PKD1 : protein kinase D1

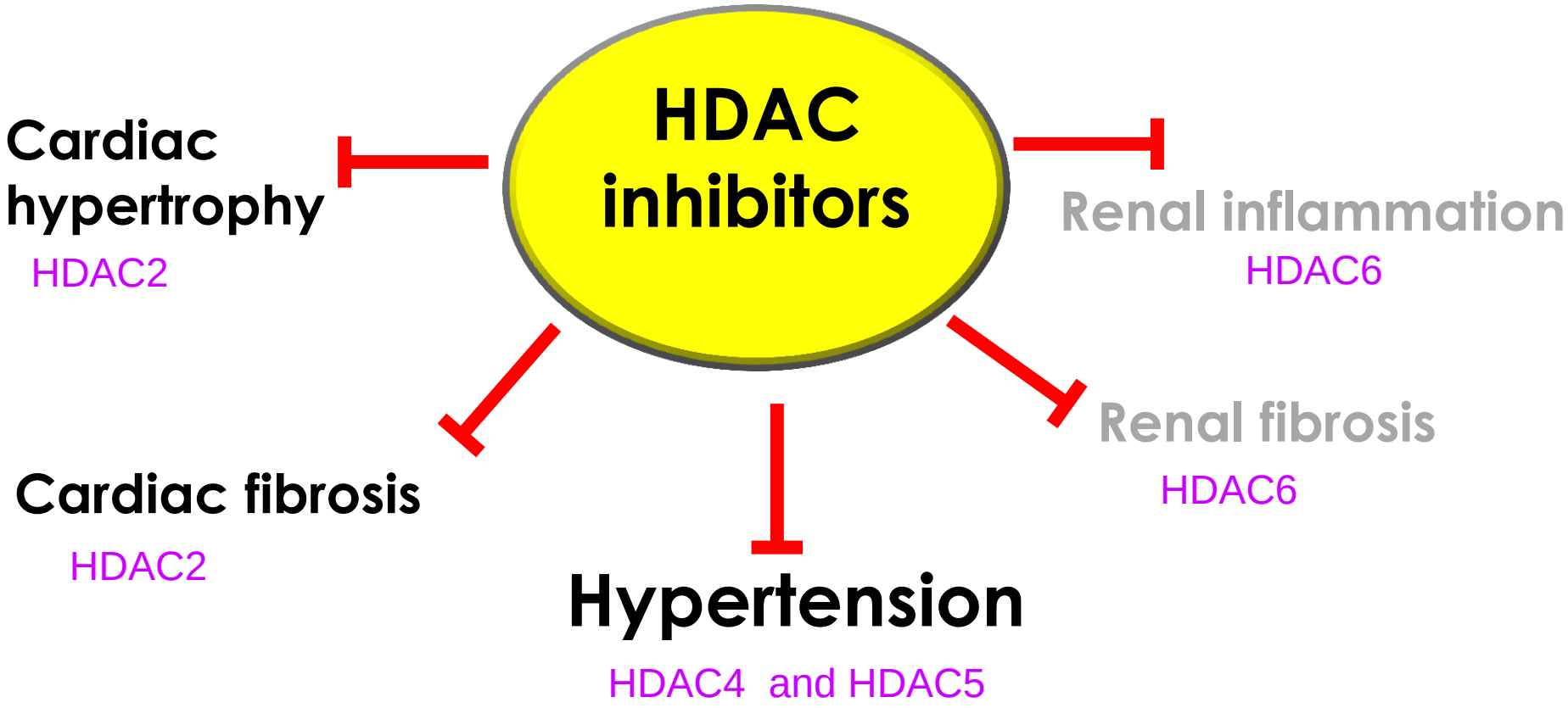
COLLABORATION

✓ **LMK235 (HDAC4/5 inhibitor)**

Prof. Dr. Thomas Kurz
(Heinrich Heine University, Germany)

Prof. Dr. Finn Hansen
(Leipzig University, Germany)

Final Summary :
Novel therapeutics of HDAC inhibitors in cardiovascular disease



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Bin Liu, MD. PhD (China)
Tianyi Li, MD. PhD (China)
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