UT SOUTHWESTERN MEDICAL CENTER

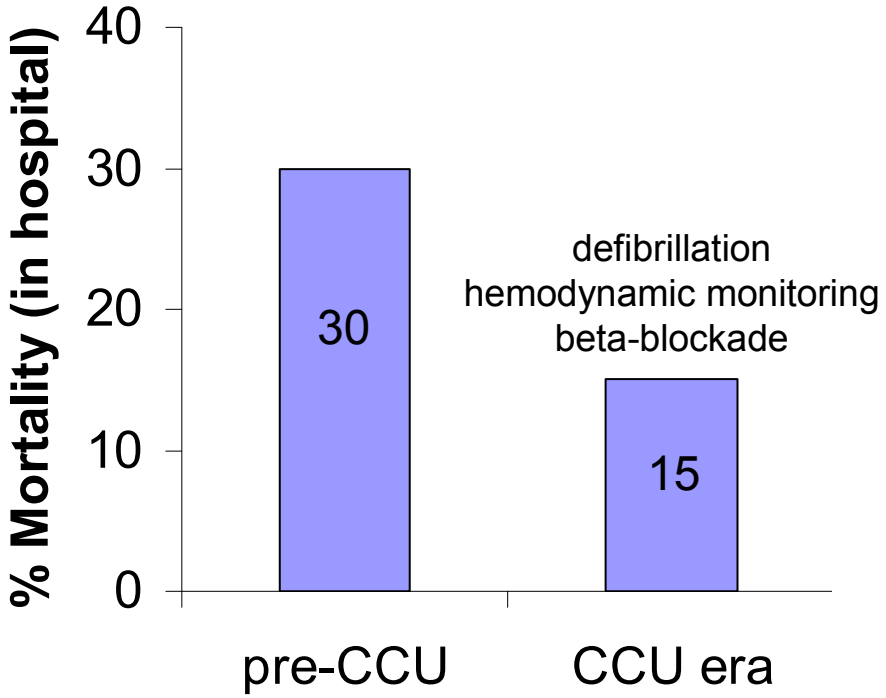
Heart Failure Progression: Targeting Hypertrophy

Joseph A. Hill, MD, PhD

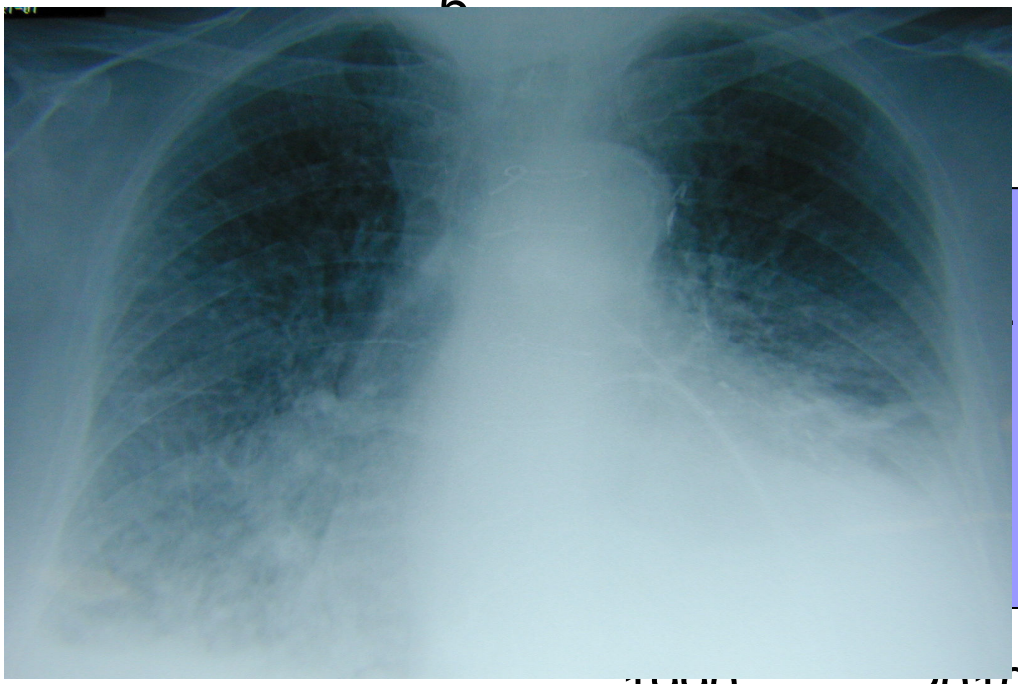
October 12, 2007

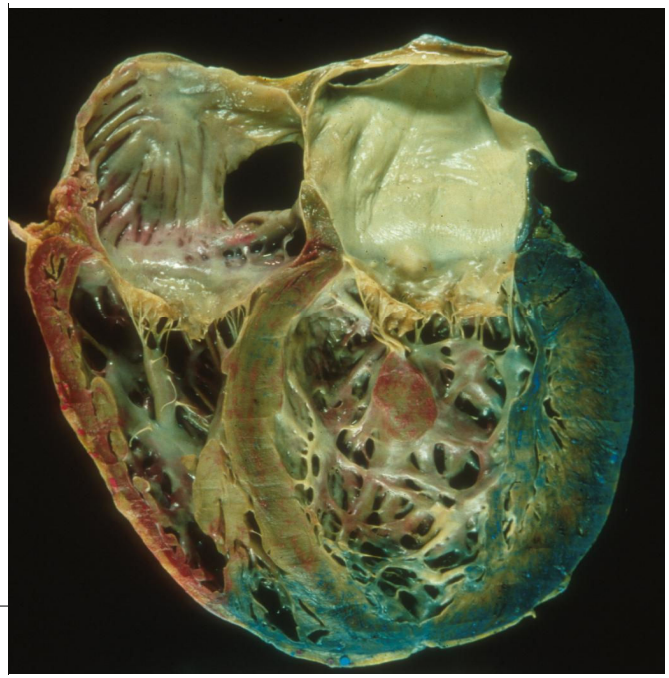
No disclosures

Acute Myocardial Infarction: Dramatic Clinical Advances



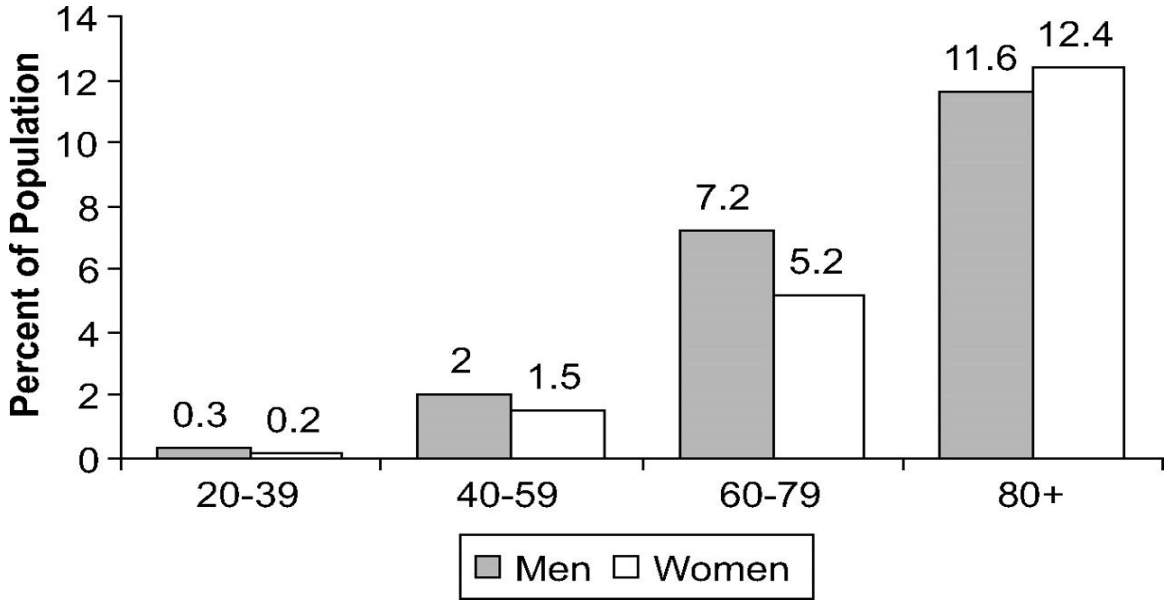
Transformed to a Chronic Disease: Heart Failure

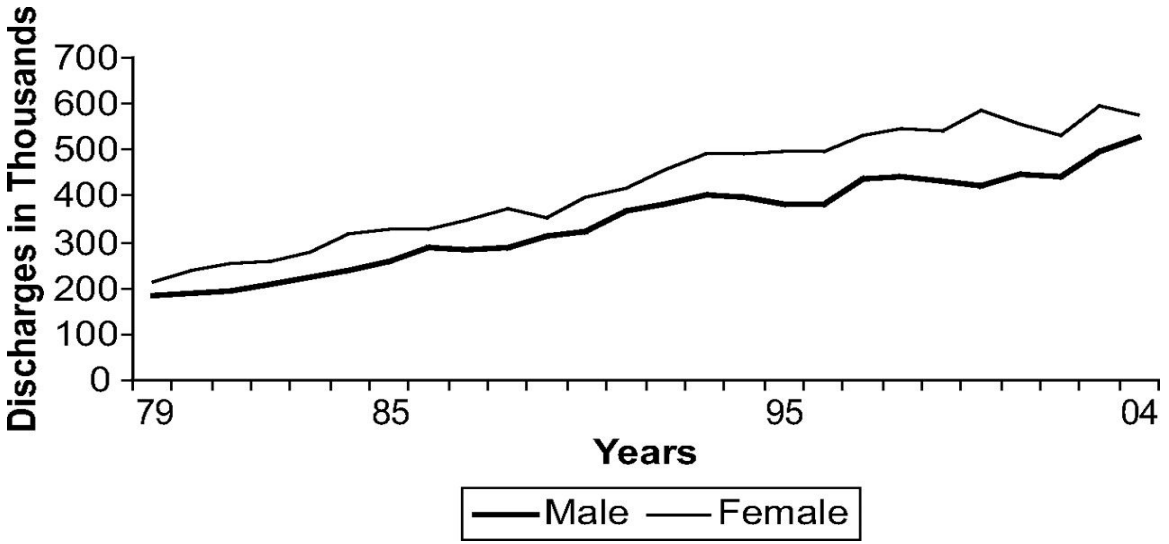




1990 2010 est

Epidemic of Heart Failure





AHA Heart Disease and Stroke Statistics, 2007

Chronic Heart Failure

Failed Therapies

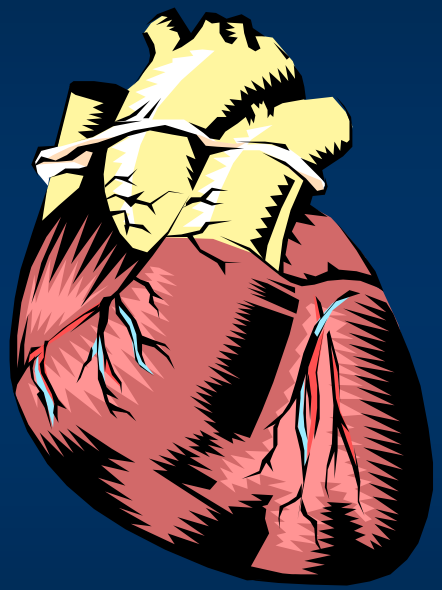
Beta-adrenergic agonists
Phosphodiesterase inhibitors
Ca^{2+} channel activators
Sarcomere Ca^{2+} sensitizers
Cytokine antagonists
…

Successful Therapies

1970	2007
Diuretics Digitalis glycosides	Diuretics Digitalis glycosides RAAS antagonists Beta-blockade

Devices!
Implantable defibrillators
Resynchronization therapy

Cardiac Responses to Stress

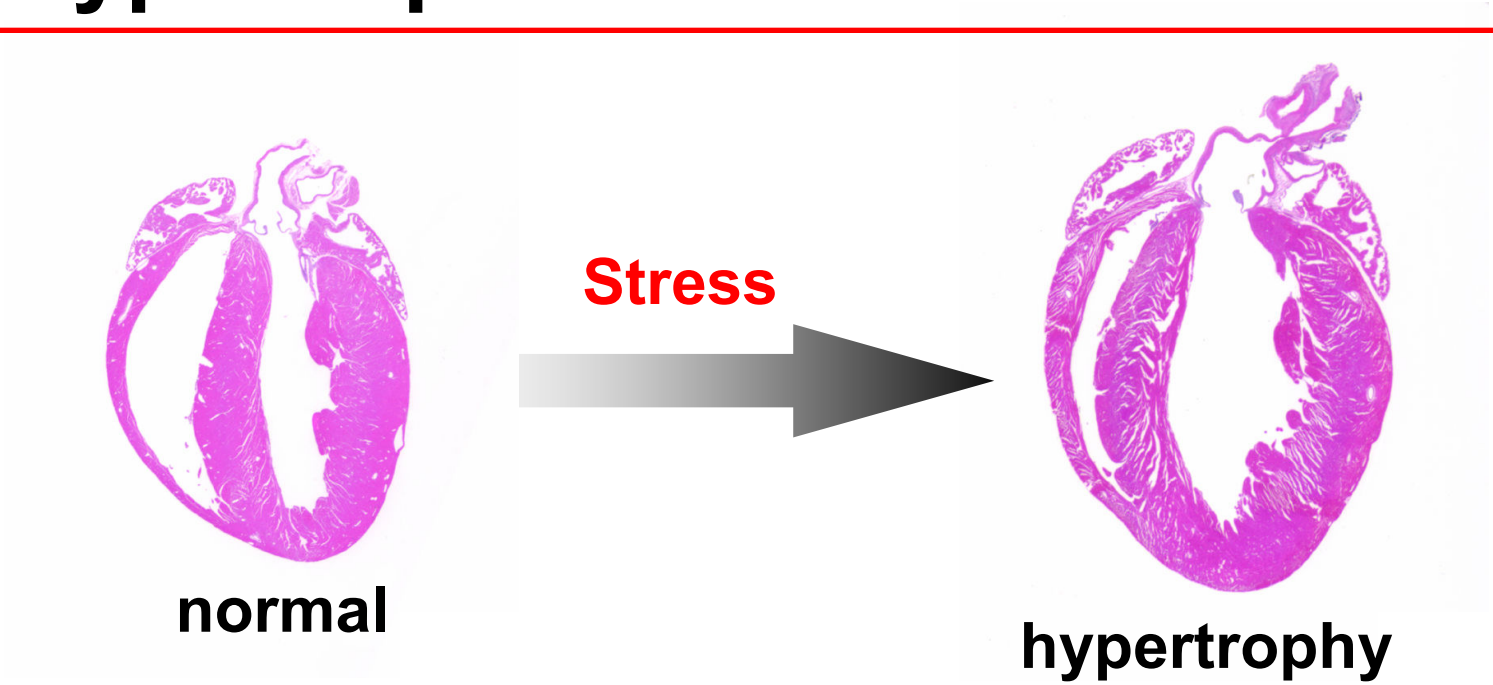


↑ heart rate

↑ stroke volume

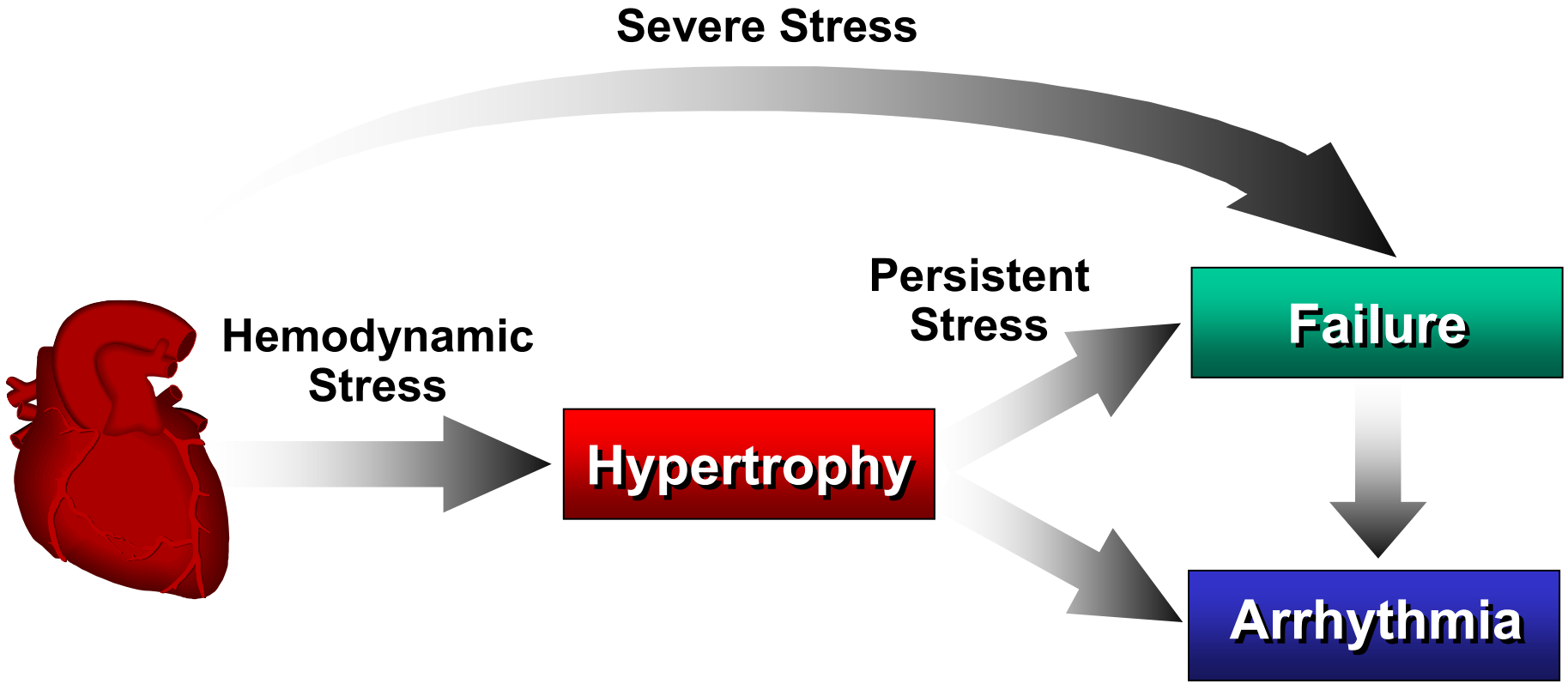
hypertrophy

Hypertrophic Growth of the Heart



…encompasses many molecular and cellular responses:

↑protein synthesis
re-activation of "fetal" genes
sarcomere recruitment and assembly
action potential prolongation
fibrosis


Severe Stress
Hemodynamic Stress
Persistent Stress
Hypertrophy
Failure
Arrhythmia

Cardiac Hypertrophy

Adaptive

Normalized wall stress

↓ Myocardial O_2 demand

Maladaptive

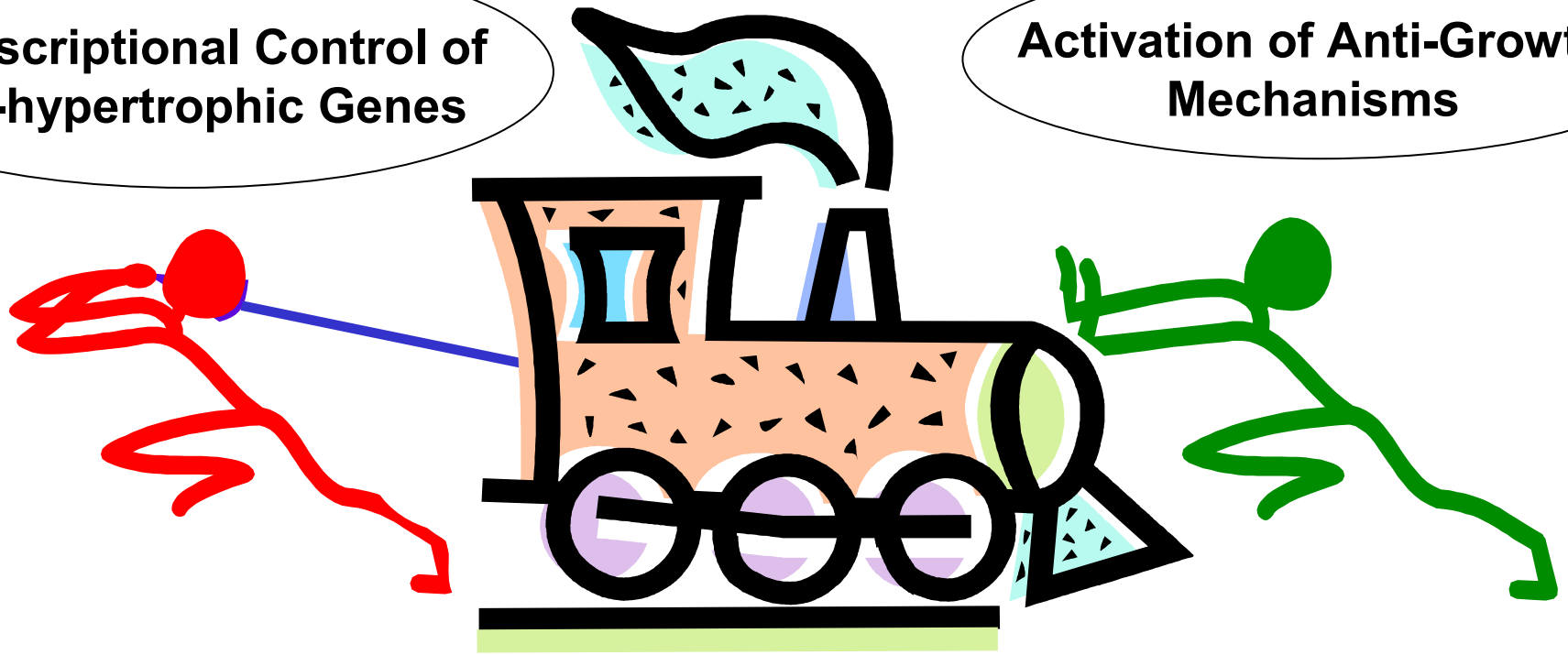
↑ Risk of heart failure

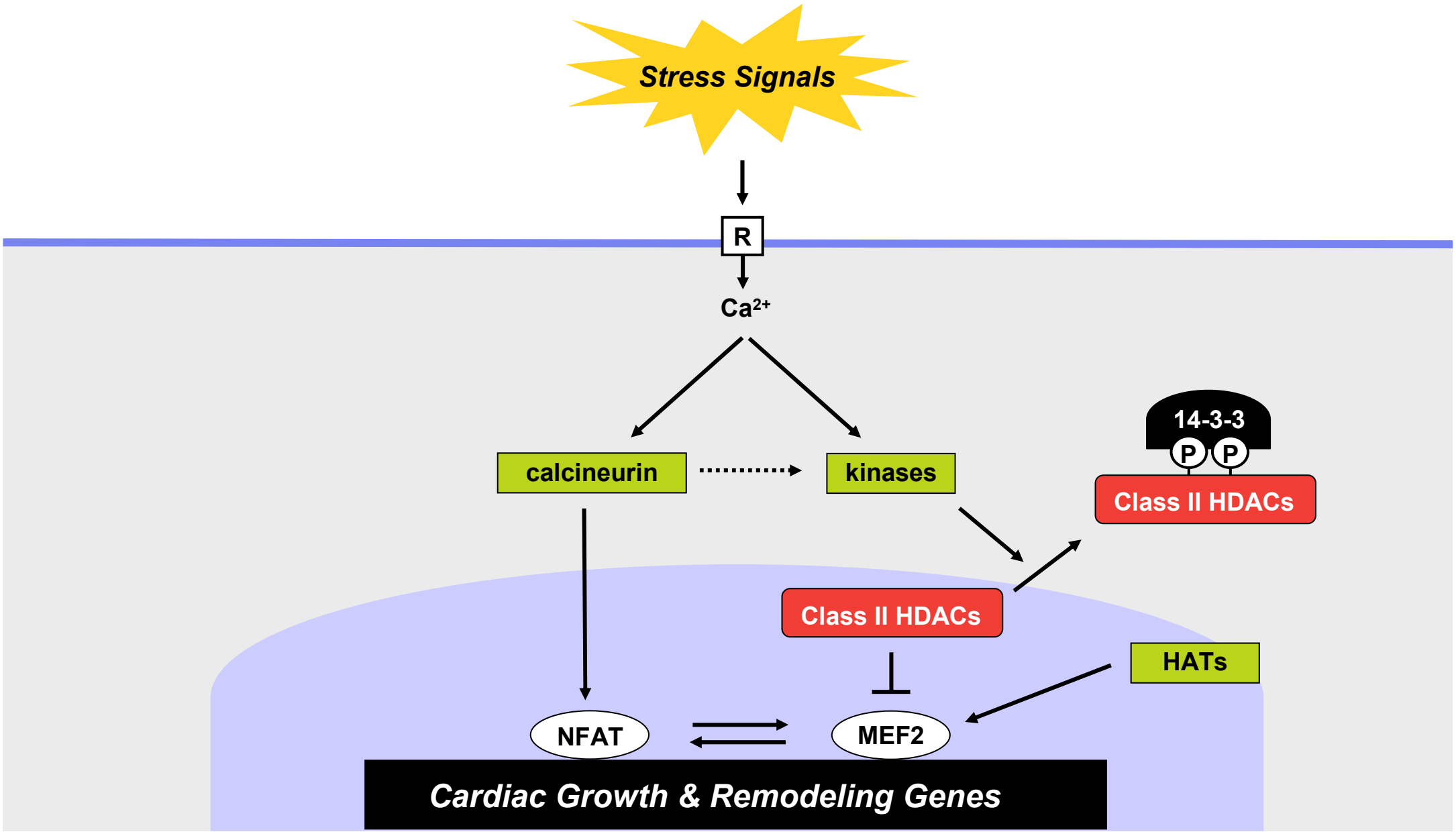
↑ Risk of arrhythmia

Slowing Disease Progression

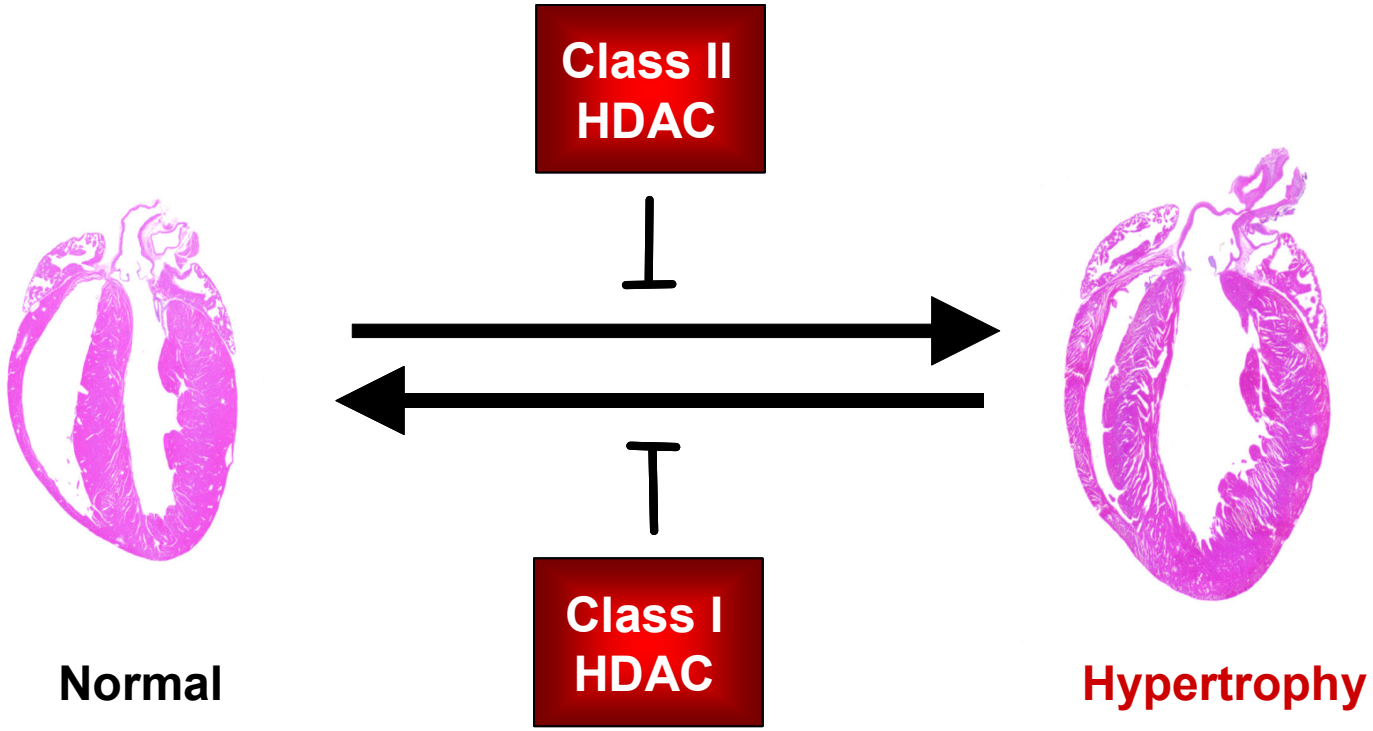
Transcriptional Control of Pro-hypertrophic Genes

Activation of Anti-Growth Mechanisms

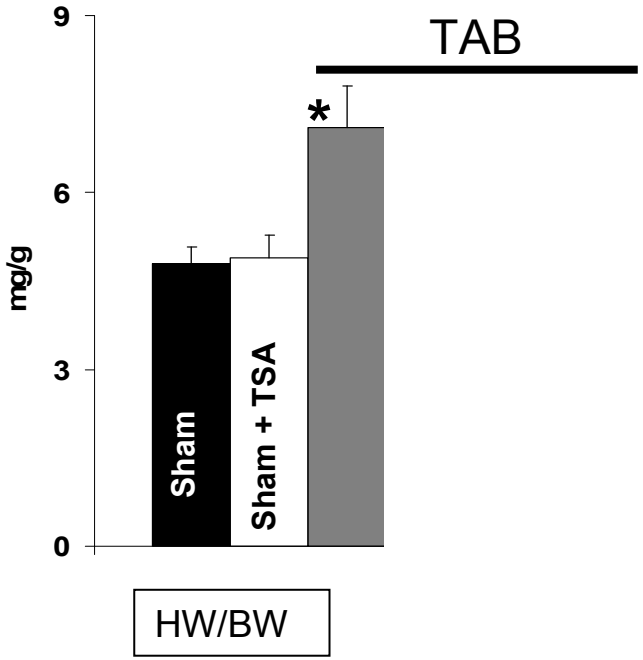


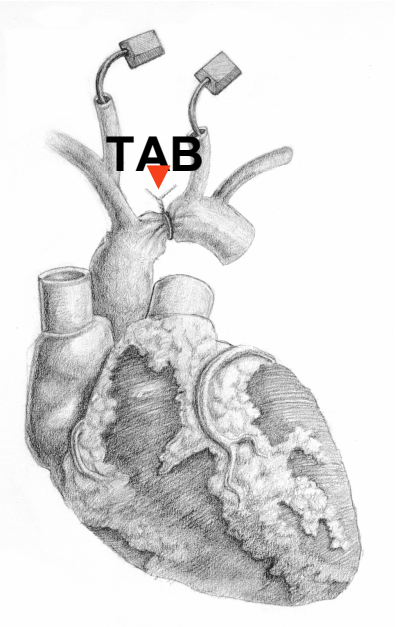


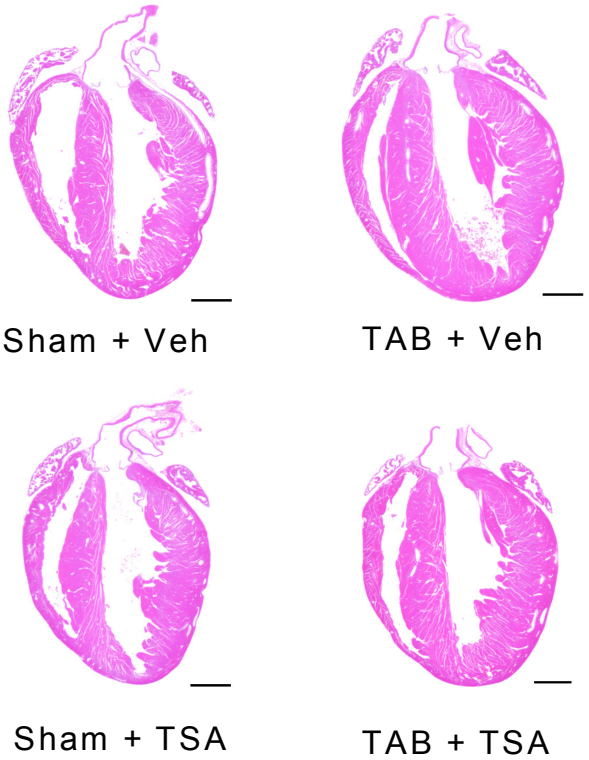
Eric Olson et al


Class II
HDAC
Class I
HDAC
Normal
Hypertrophy

TSA blunts pressure-overload hypertrophy

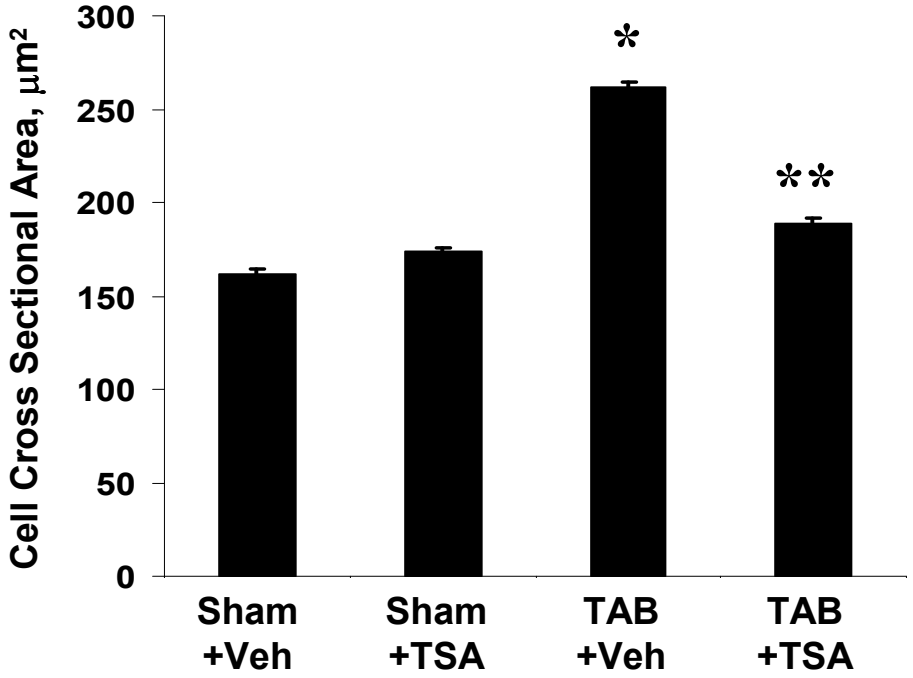


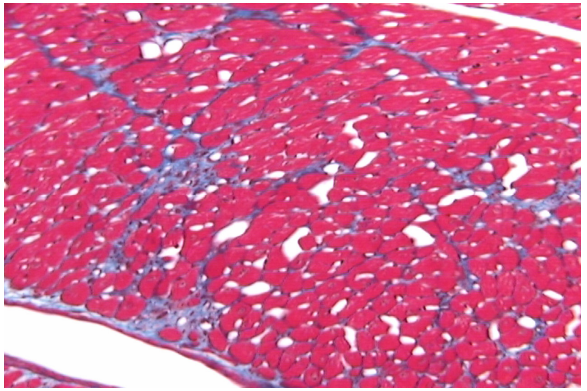




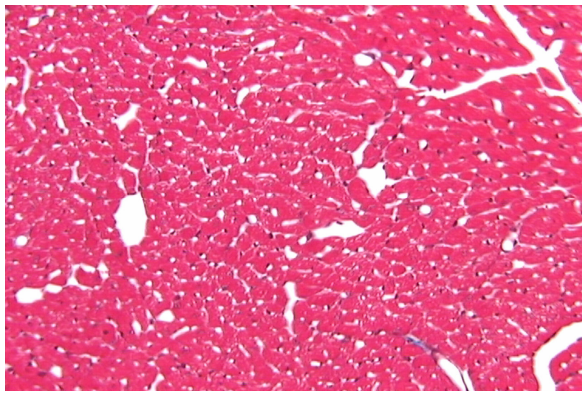
Kong et al., *Circulation* 2006

TSA blunts cardiomyocyte growth and fibrotic change





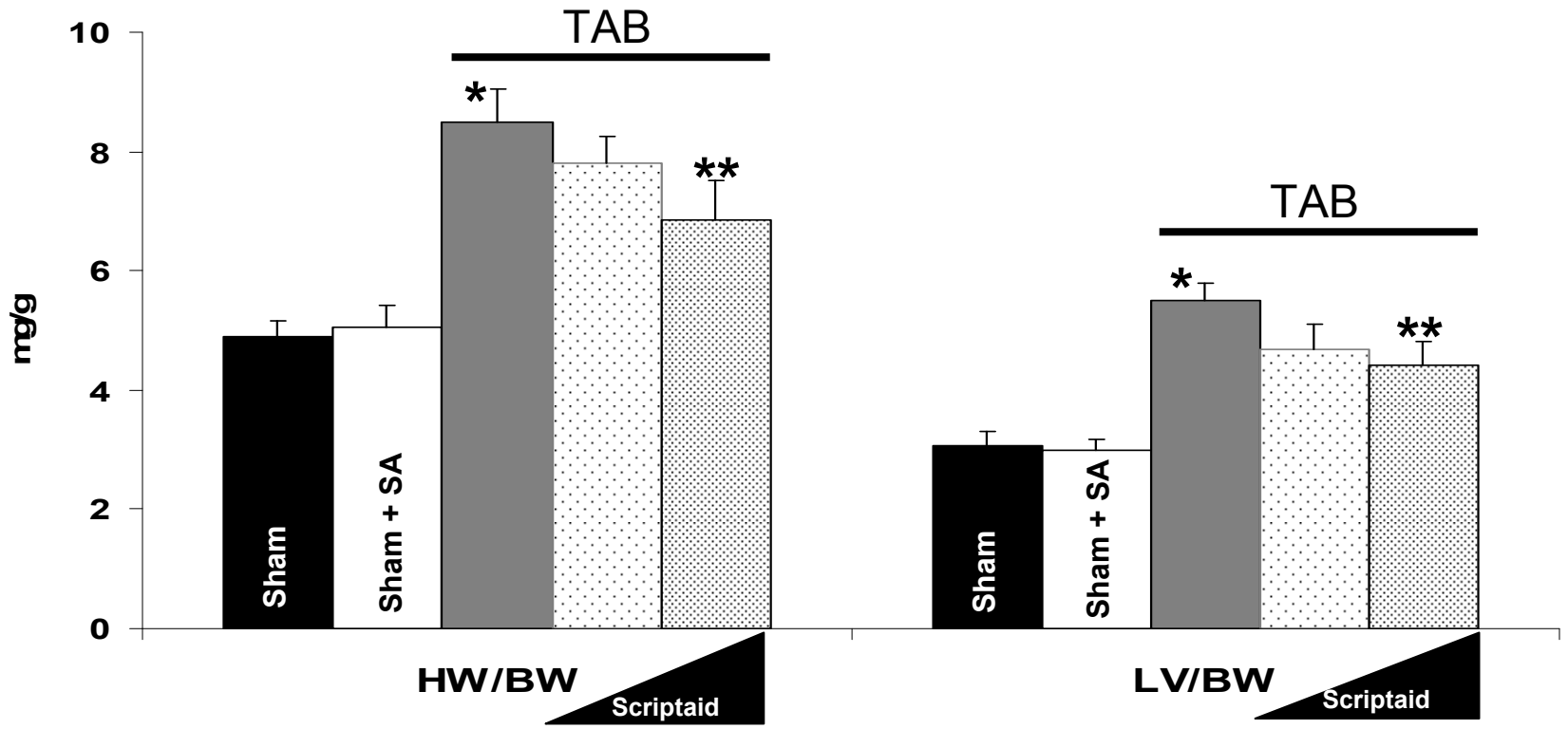
TAB+Veh



TAB+TSA

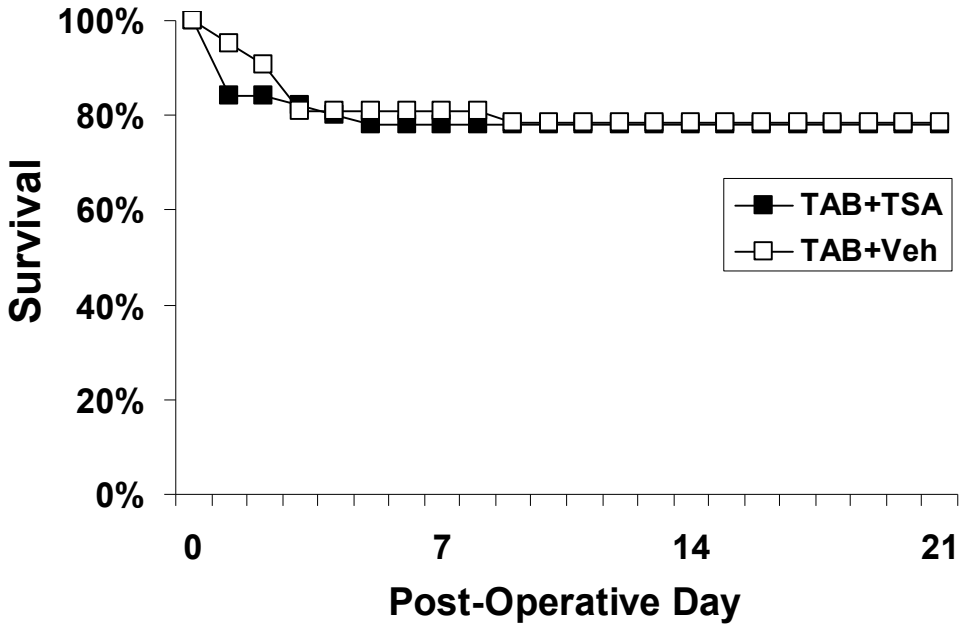
Kong et al., *Circulation* 2006

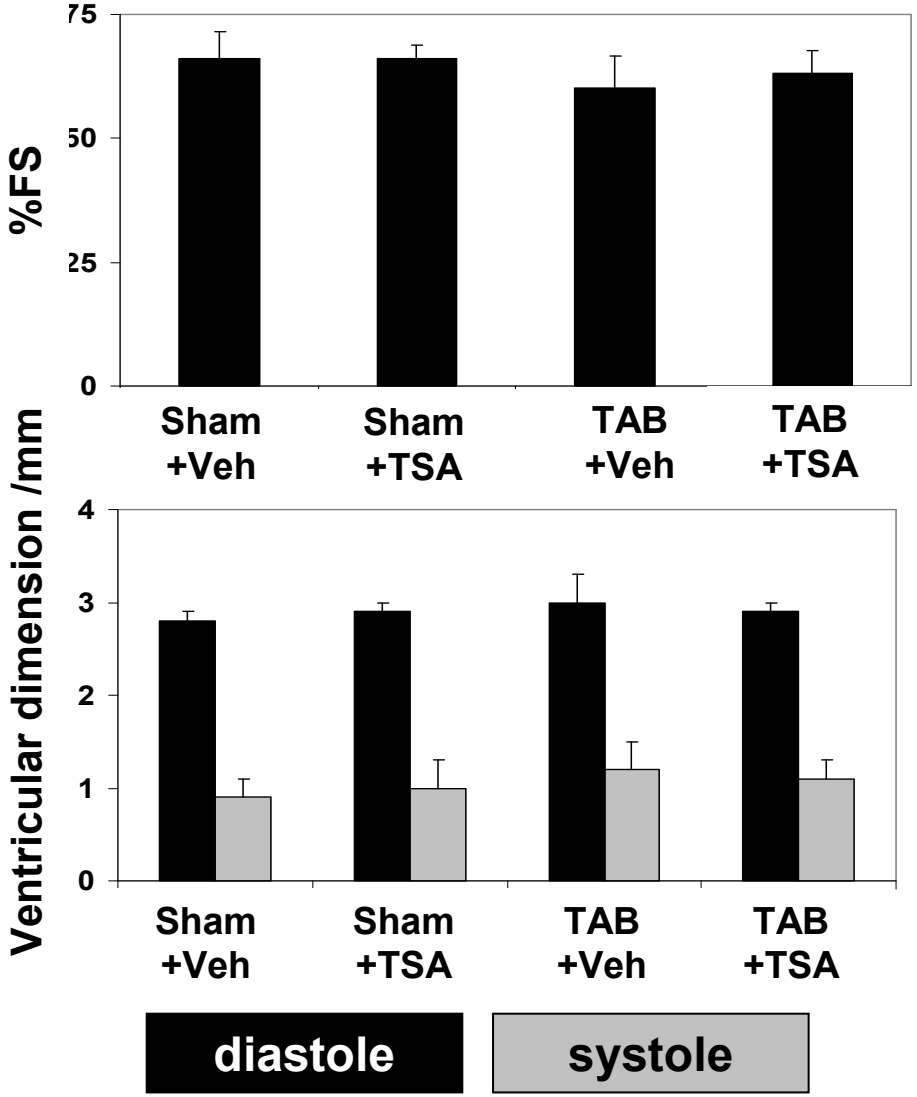
Scriptaid blunts hypertrophy



Kong et al., *Circulation* 2006

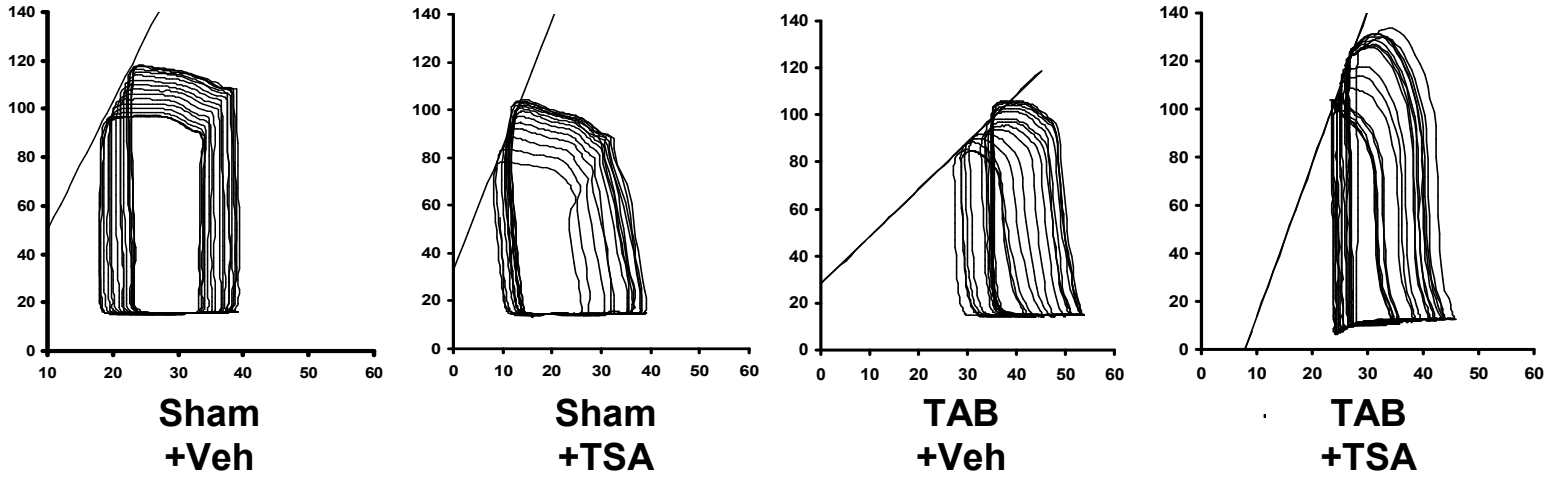
TSA-blunted hypertrophy: Similar survival and preserved LV size and performance

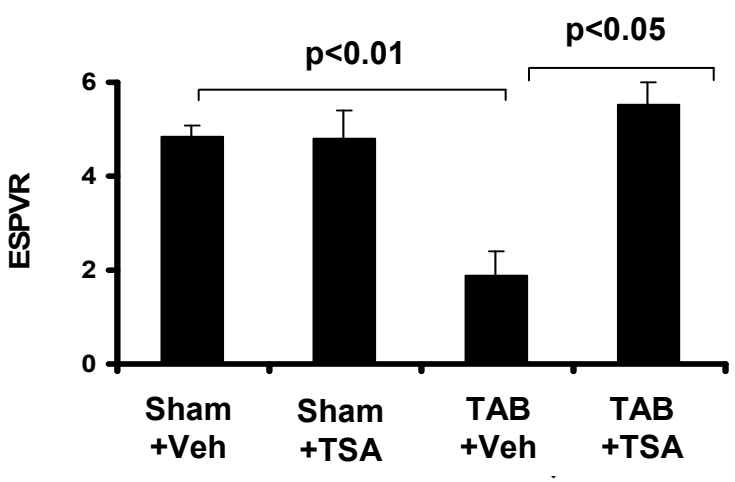


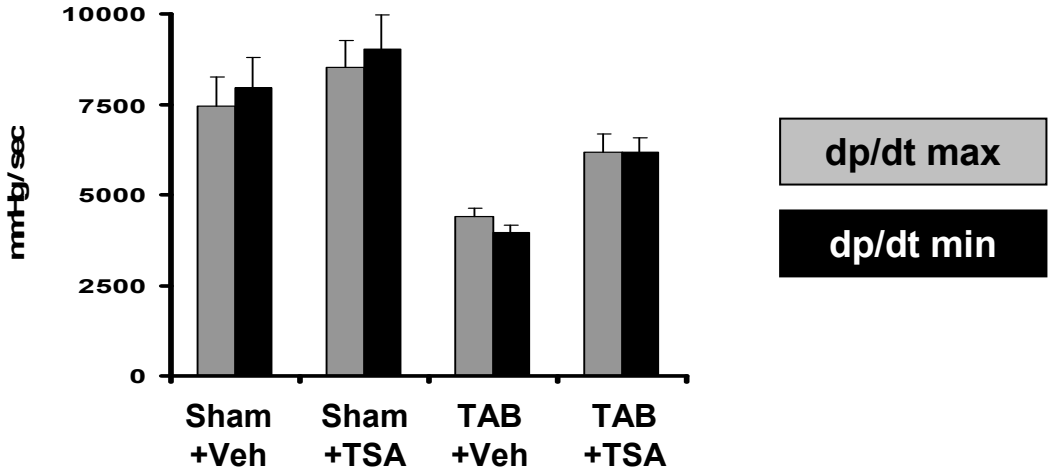


Kong et al., *Circulation* 2006

Preservation of systolic function

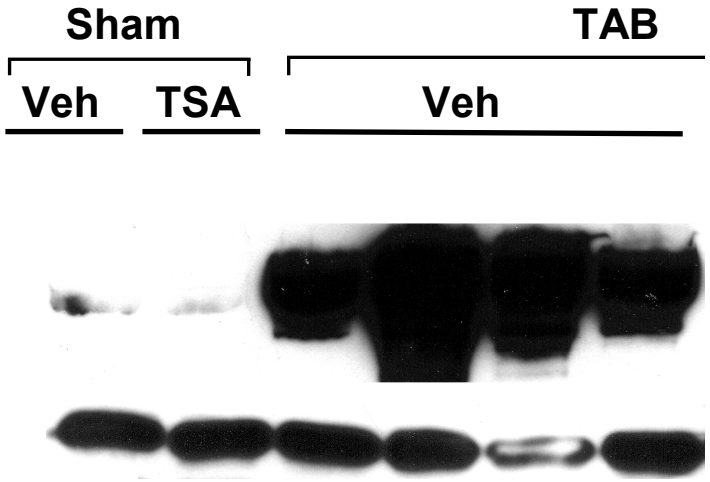






Kong et al., *Circulation* 2006

TSA blunts hypertrophy-associated MHC isoform switch

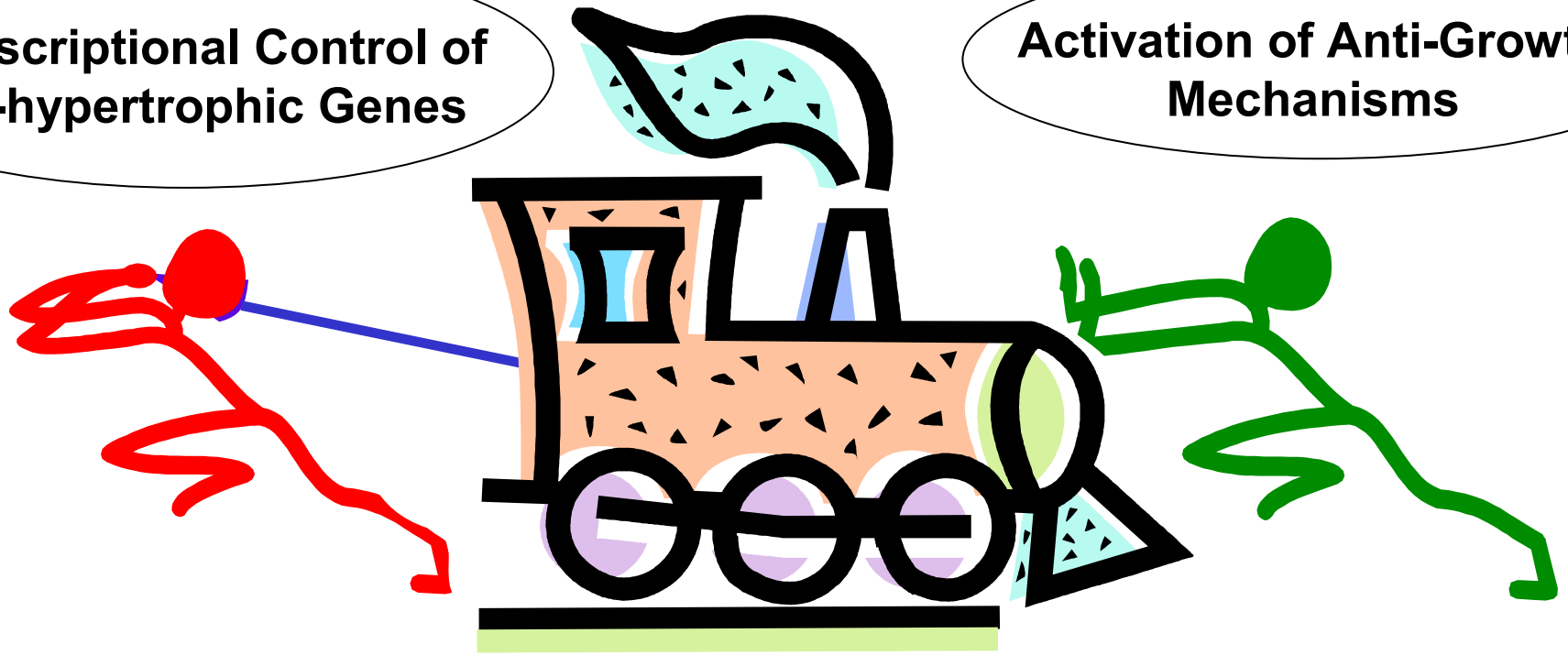


Kong et al., *Circulation* 2006

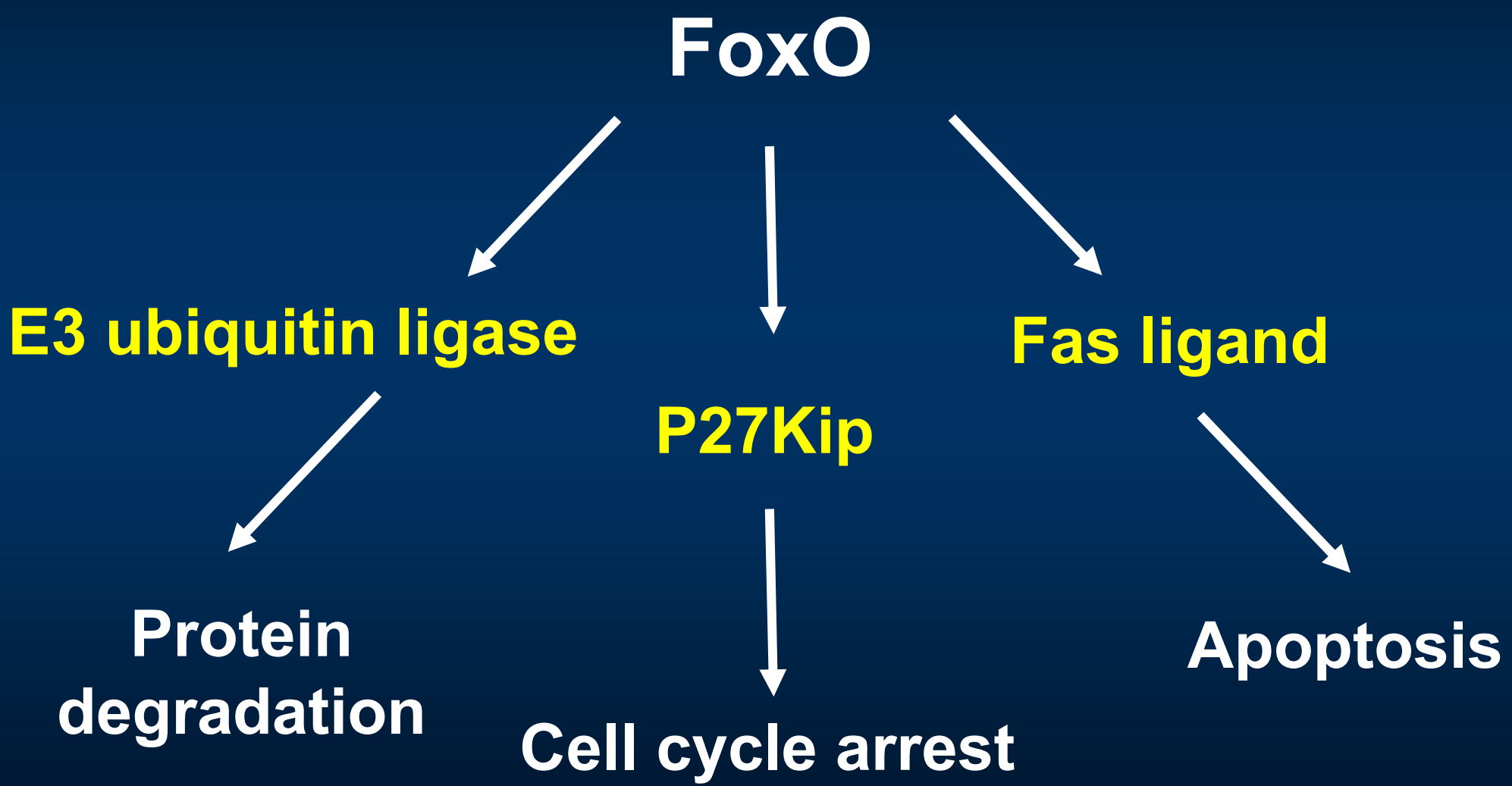
Slowing Disease Progression

Transcriptional Control of Pro-hypertrophic Genes

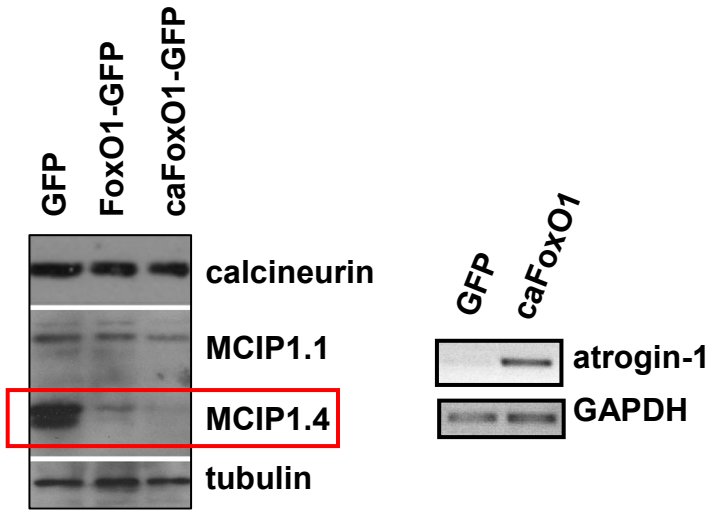
Activation of Anti-Growth Mechanisms

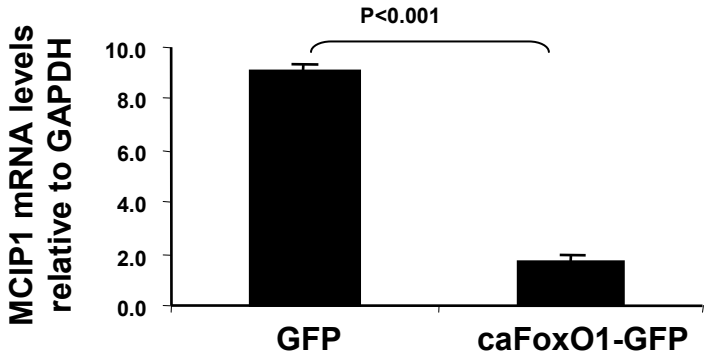


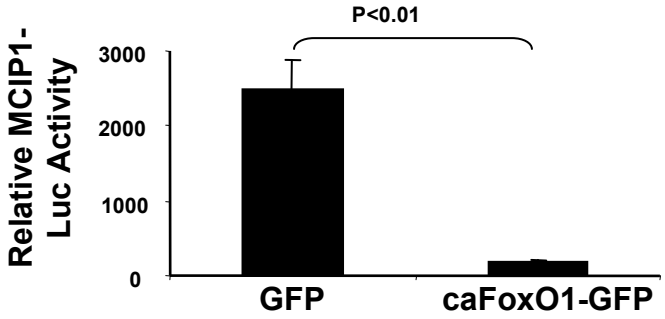
Downstream Targets



FoxO antagonizes calcineurin

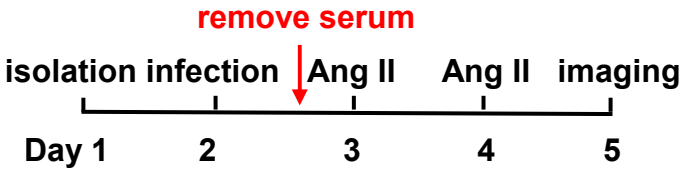


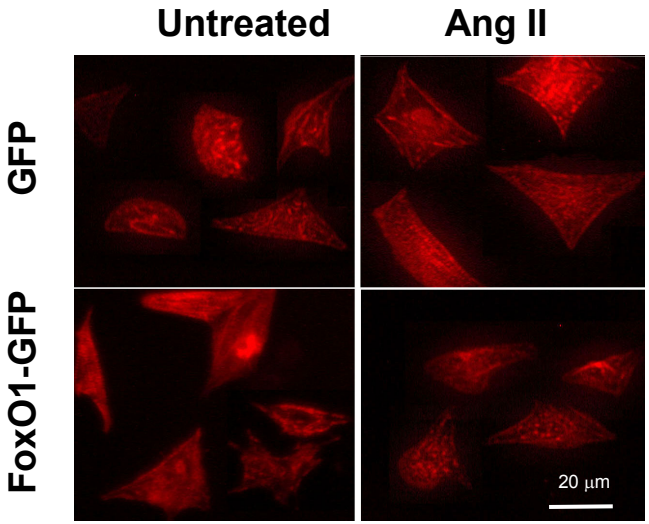


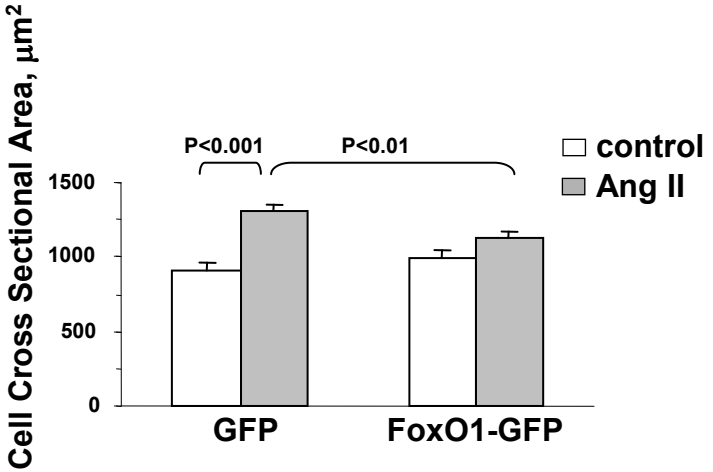


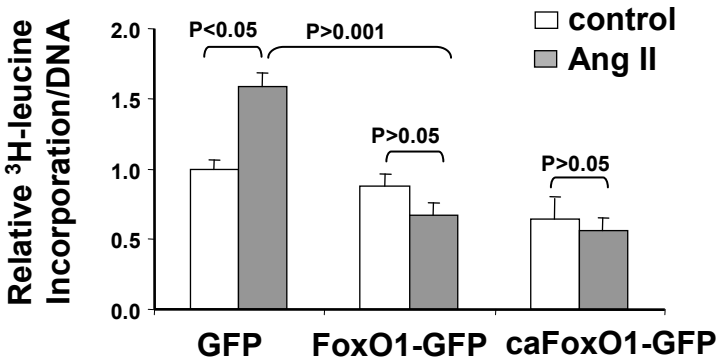
Ni et al., *Circulation* 2006.

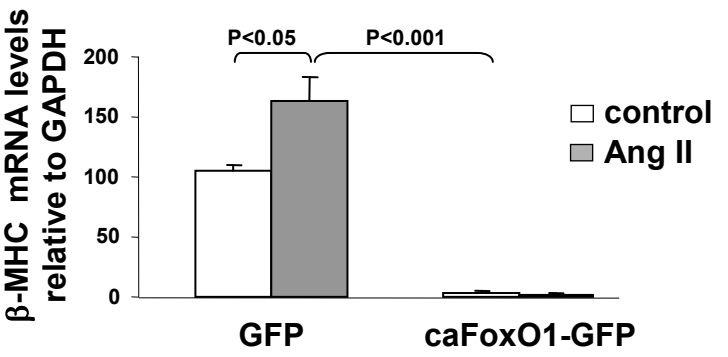
FoxO blocks hypertrophy



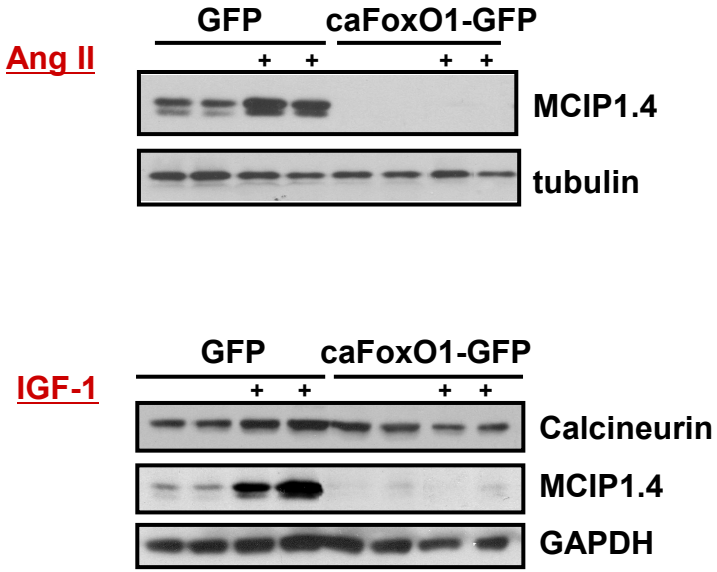






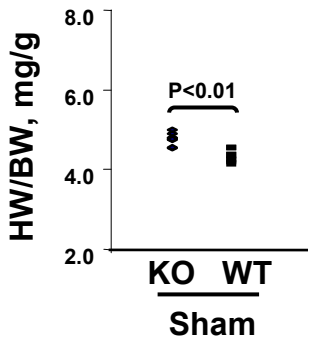


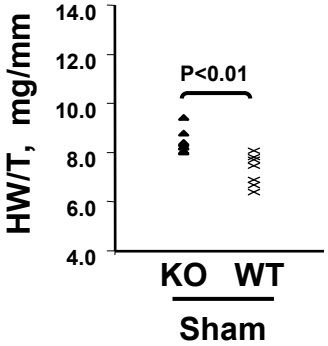
FoxO blocks agonist-induced activation of calcineurin

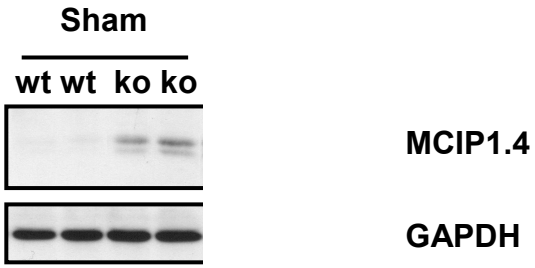


Ni et al., *Circulation* 2006.

FoxO3-null mice are hypertrophic

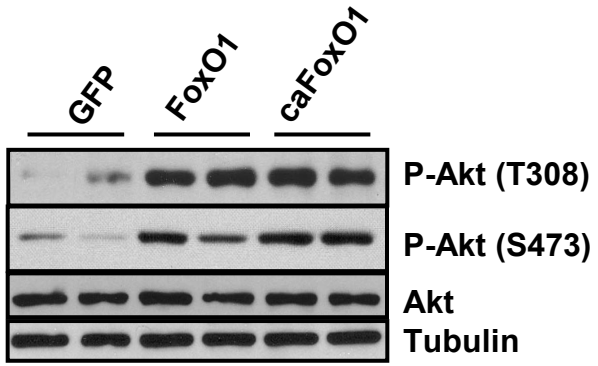


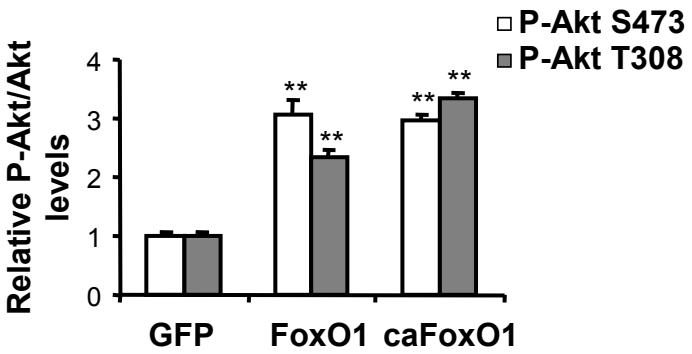


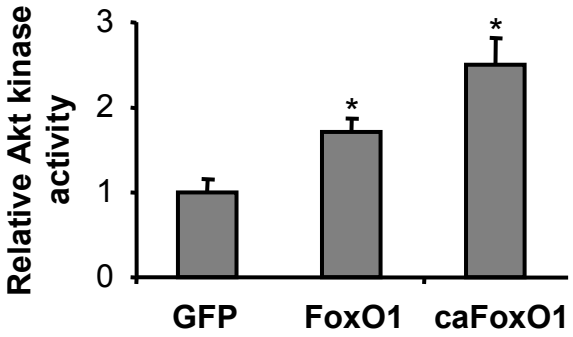


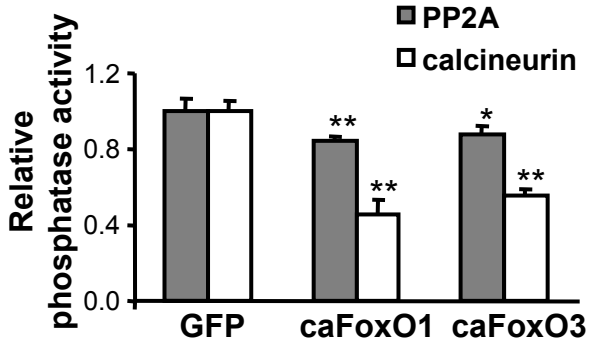
Ni et al., *Circulation* 2006.

FoxO triggers Akt, an upstream repressor



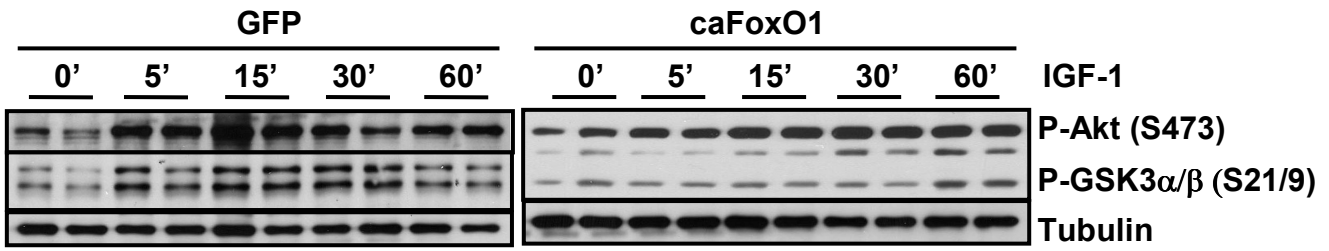


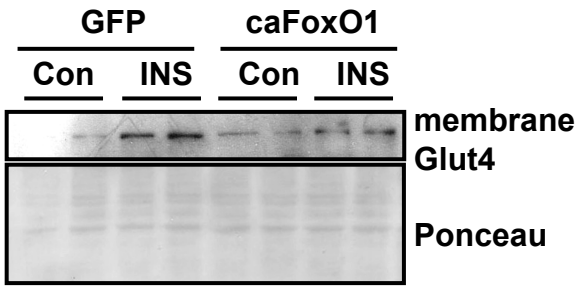


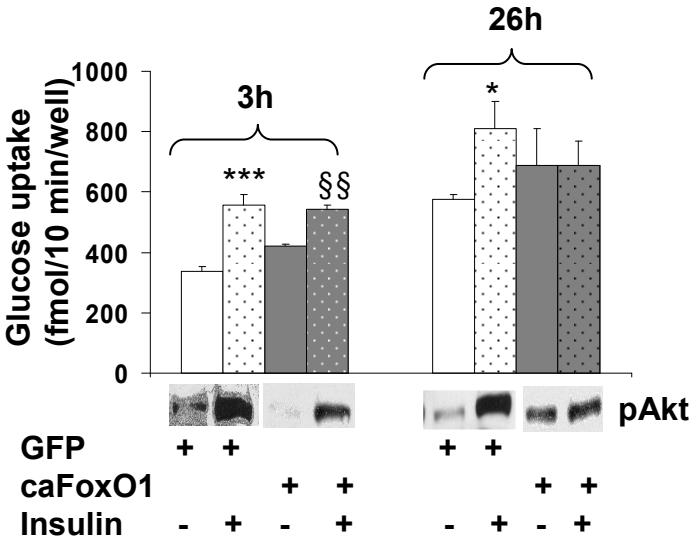


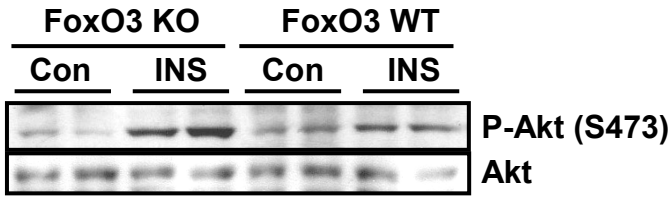
Ni et al., *PNAS* 2007, In Press.

Foxo activation induces insulin resistance



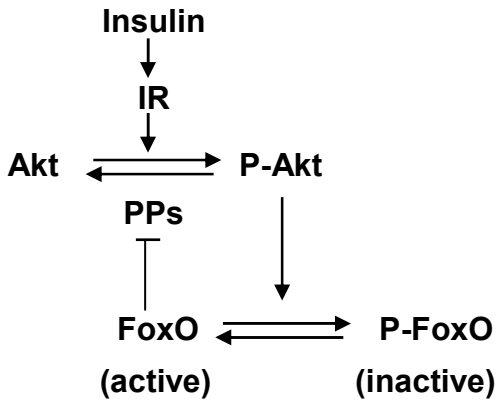






Ni et al., *PNAS* 2007, In Press.

A novel mechanism of insulin resistance in heart



Ni et al., *PNAS* 2007, In Press.

Conclusion

- Hypertrophic growth of the myocardium is a novel target for therapeutic intervention in heart failure.
- Strategies to block pro-growth pathways and/or activate anti-growth mechanisms warrant further evaluation.

Acknowledgments

Hill Lab

Andy Blag
Jeff Berry
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Yongli Kong
Vien Le
Xiang Luo
Andriy Nemchenko
Oktay Rifki
Sam Tandan
Paul Tannous
Hongxin Zhu

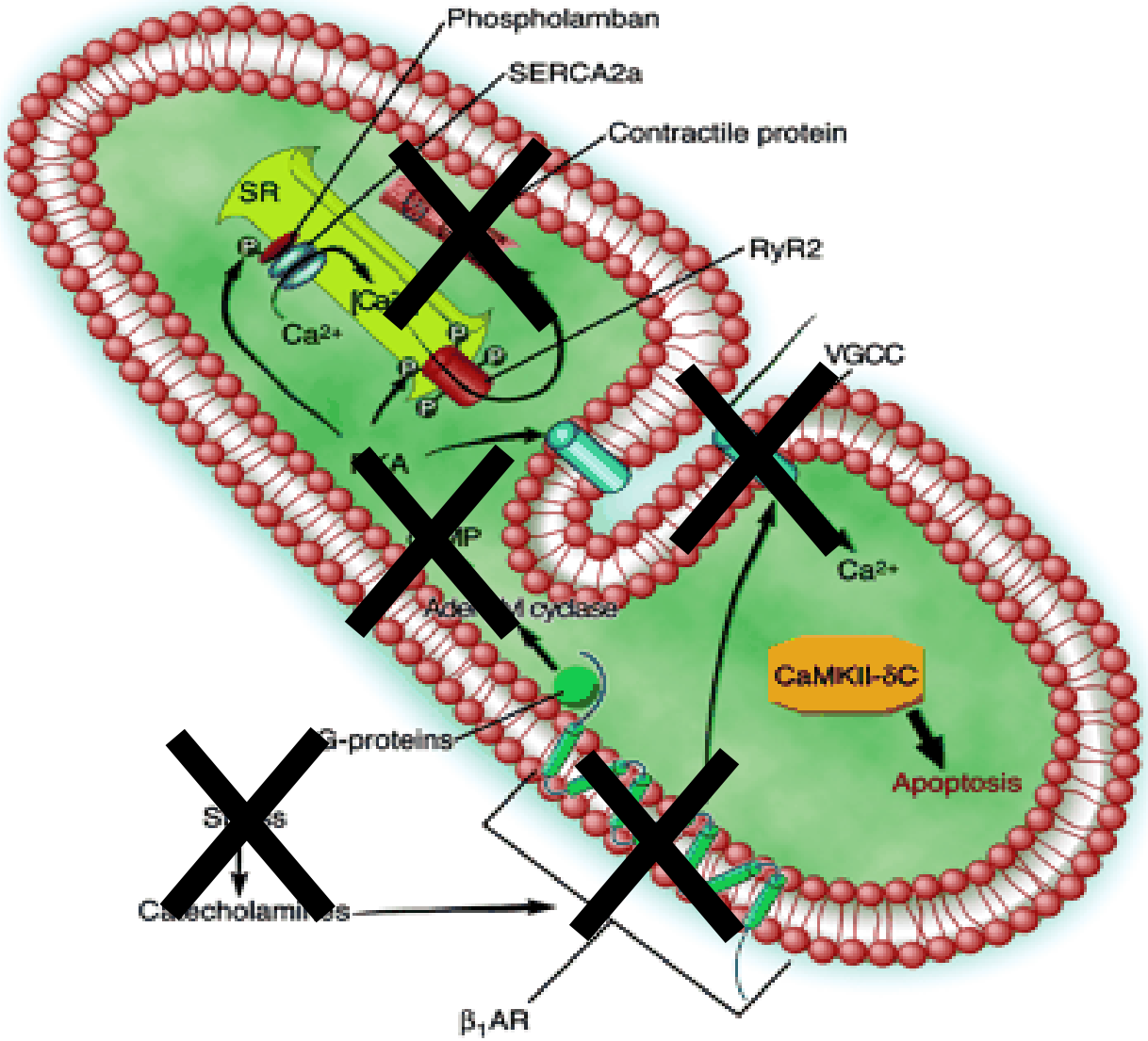
…gone but not forgotten

Kambeez Berenji
Jun Cheng
Minjie Jiang
Bill Kutschke
Greg Lu
Yan Ni
Bridgid Nolan
Ken Richardson
Yanggan Wang
Zhengyi Wang

Collaborators

Beverly Rothermel, PhD
Eric Olson, PhD
Rhonda Bassel-Duby, PhD
Beth Levine, MD
James Richardson, DVM, PhD

Targets of Heart Failure Therapy



Conclusion

HDAC inhibition is a promising strategy to target pathological remodeling of the stressed ventricle.

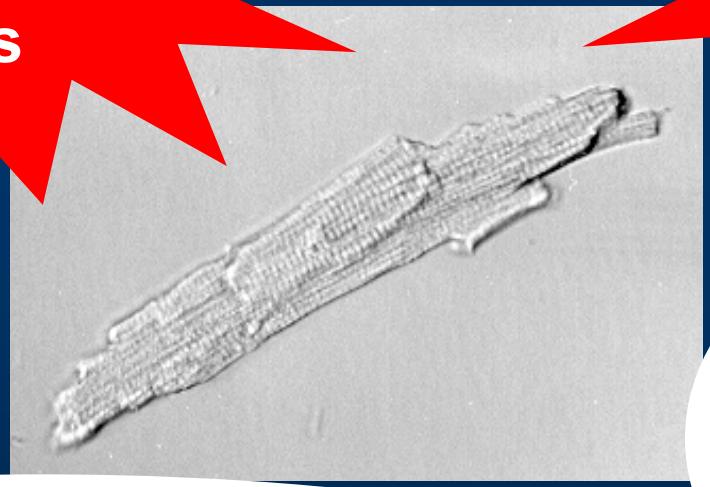
Conclusion

Foxo transcription factors inhibit cardiomyocyte hypertrophy due, at least in part, to their suppression of calcineurin signaling.

Disease-Associated Cardiomyocyte Stress

Biomechanical stress

Pressure
Stretch



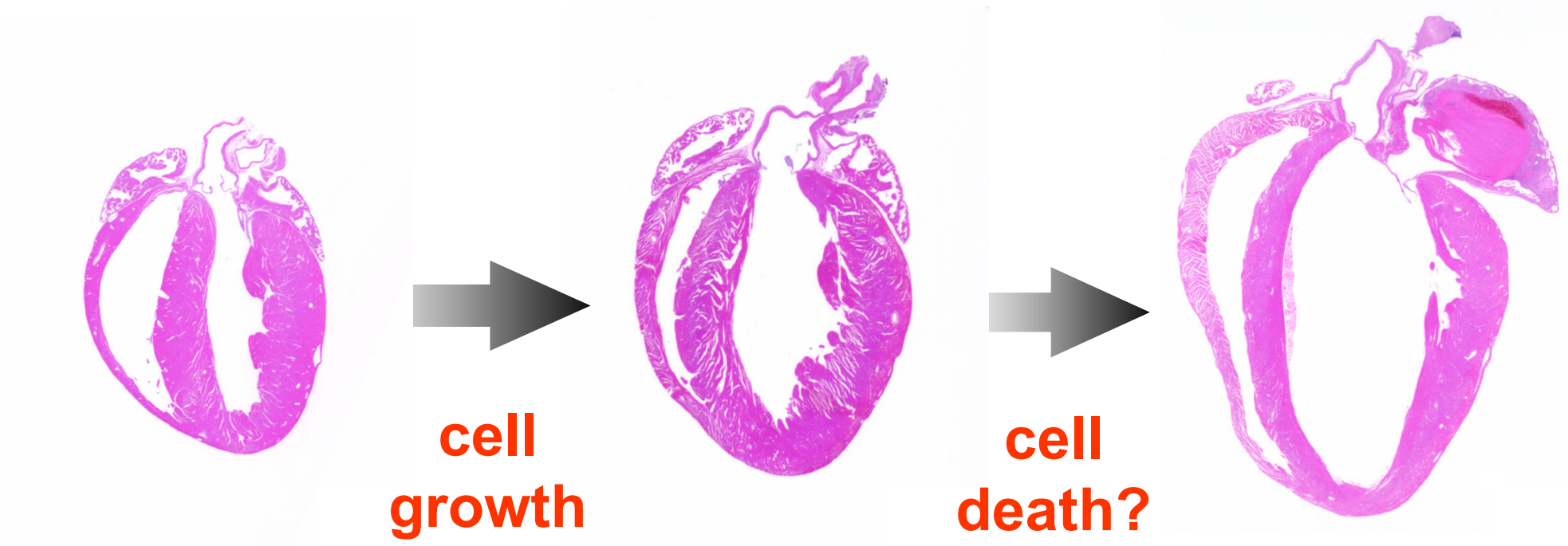
Neurohumoral stress

RAAS
Adrenergic hormones
Cytokines
Vasoactive peptides
Growth factors

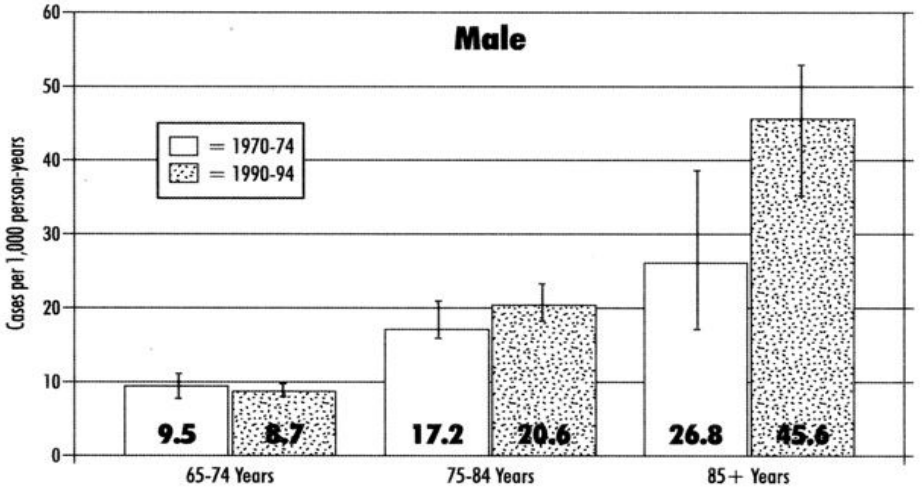
Altered gene expression
Transcript processing
Post-translational mechanisms

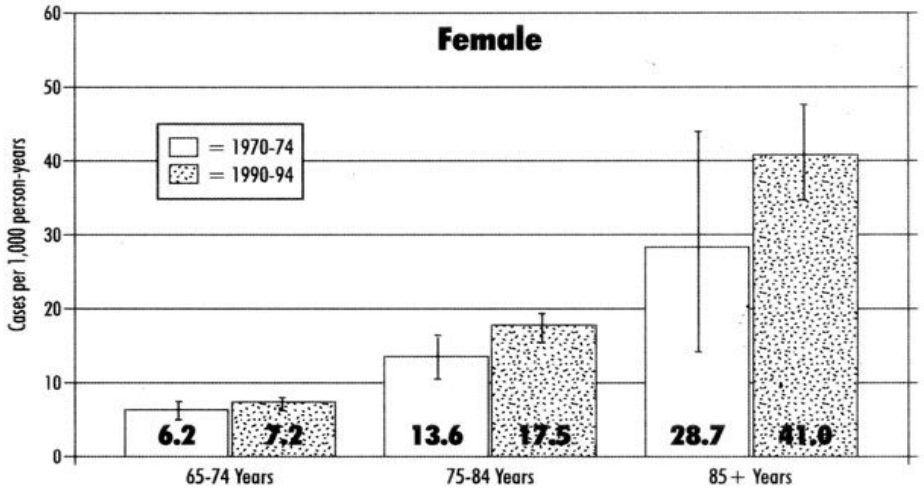
"Never, ever, think outside the box."

Heart Failure Progression



Heart Failure Epidemic: Incidence per 1000 person-years

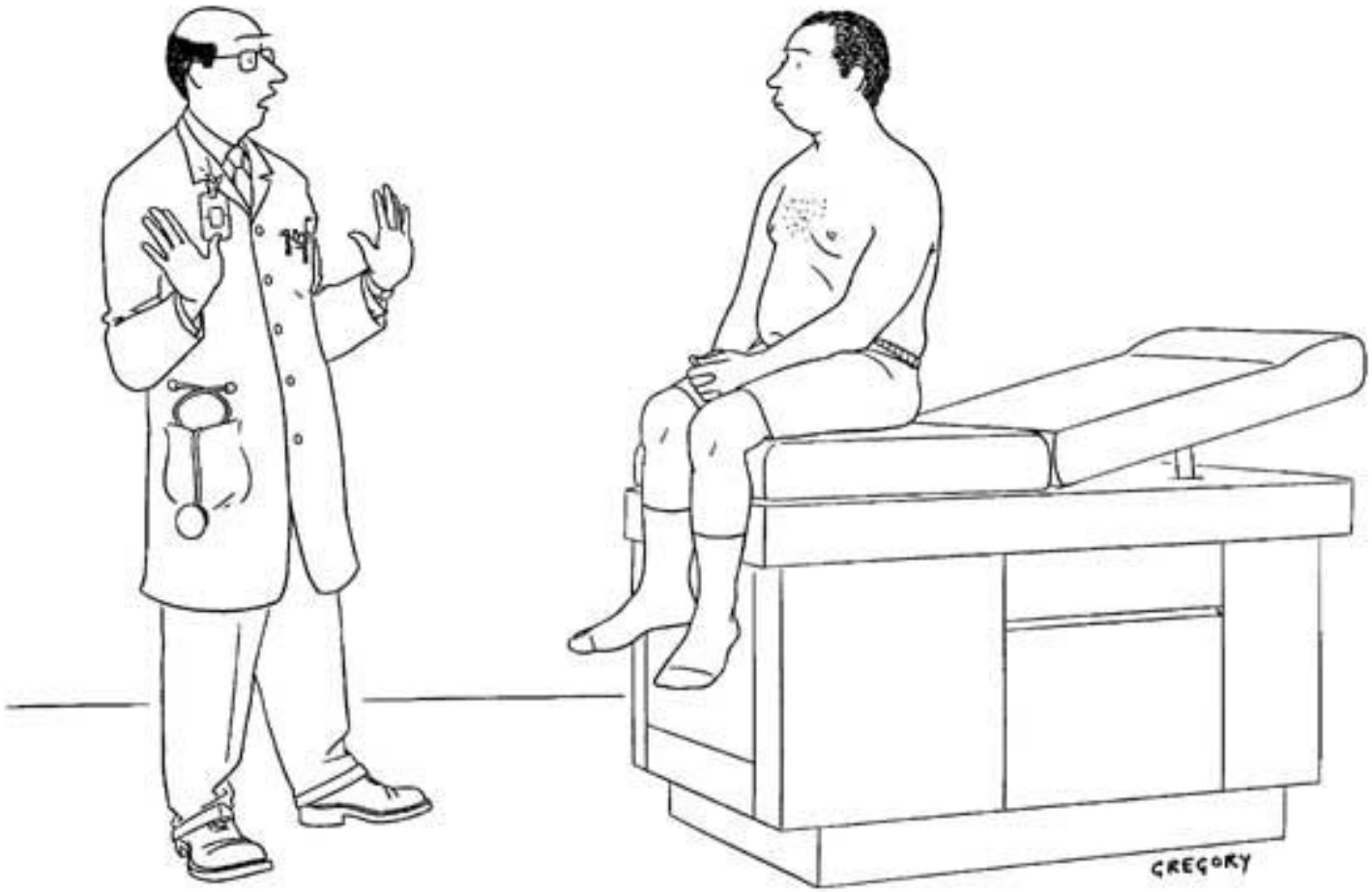




Barker, et al. *Circulation* 2006

Potential New Strategies to Treat Heart Failure

- Blocking pro-growth (hypertrophic) pathways
  - HDAC inhibitors
- **Activating anti-growth (atrophic) pathways**
  - **Foxo**
- Targeting programmed cell death
  - Autophagy



"Whoa—way too much information."