PAH priorities for the next 10 years

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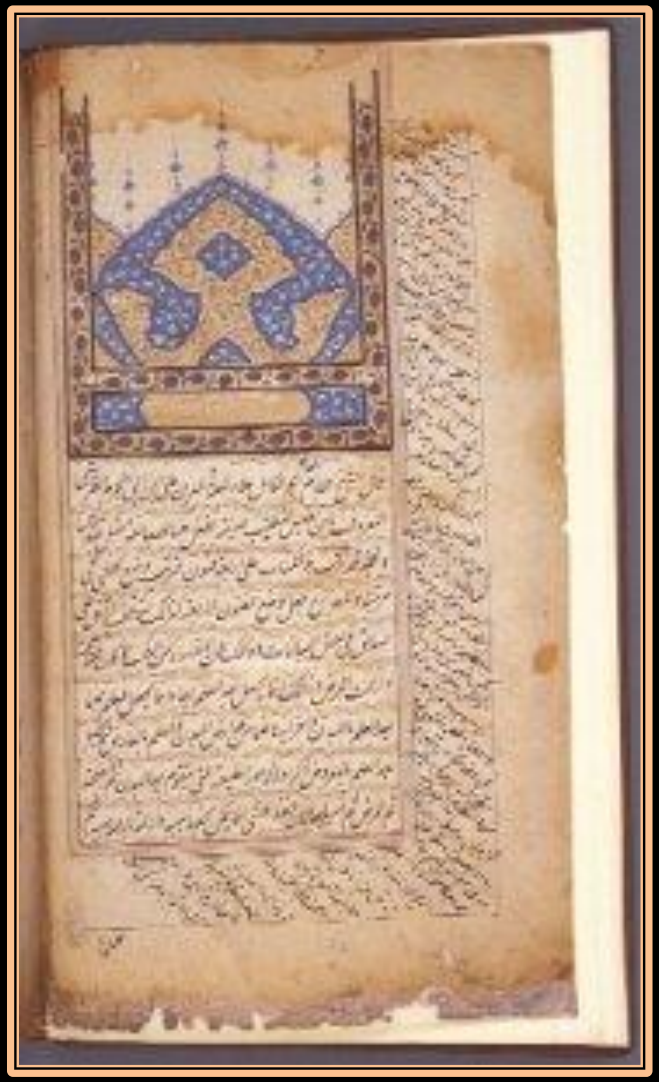
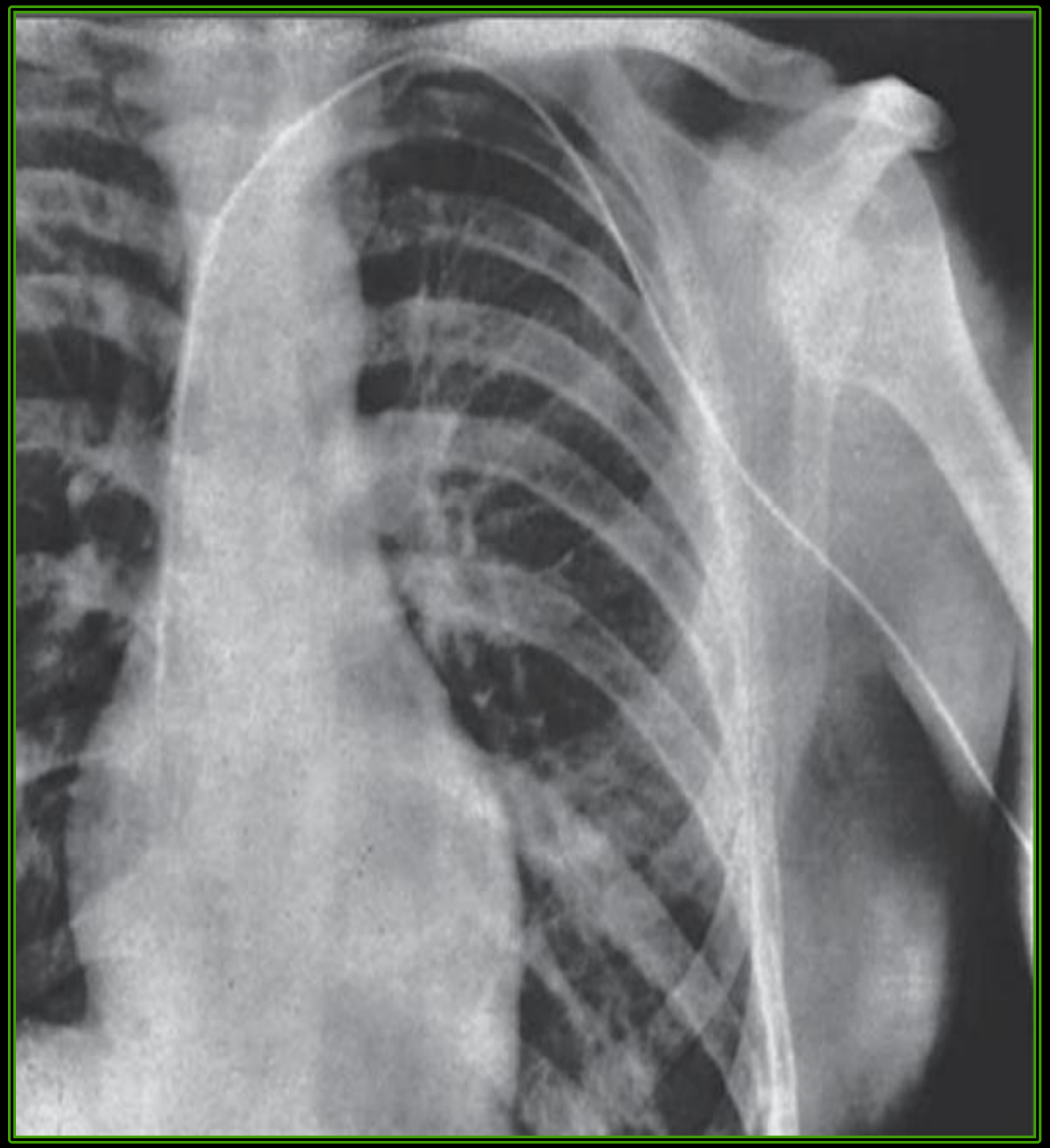
Ala-al-din abu Al-Hassan Ali ibn Abi-Hazm al-Qarshi al-Dimashqi (Ibn Nafis)

1213-1288

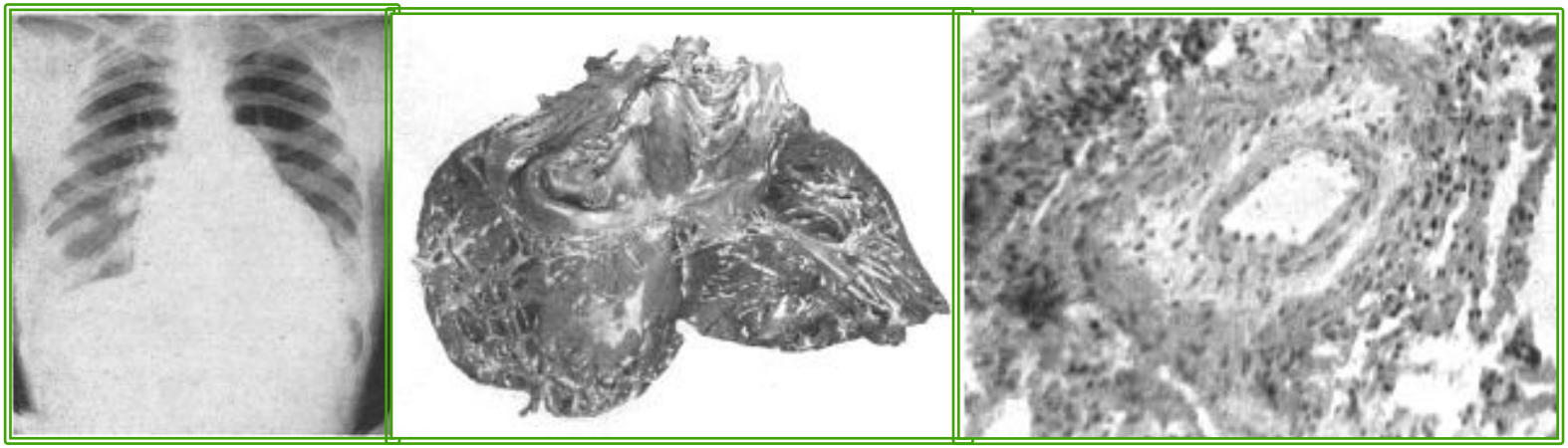


"…The blood from the right chamber must flow through the vena arteriosa (pulmonary artery) to the lungs, spread through its substances, be mingled with air, pass through the arteria venosa (pulmonary vein) to reach the left chambers of the heart and there

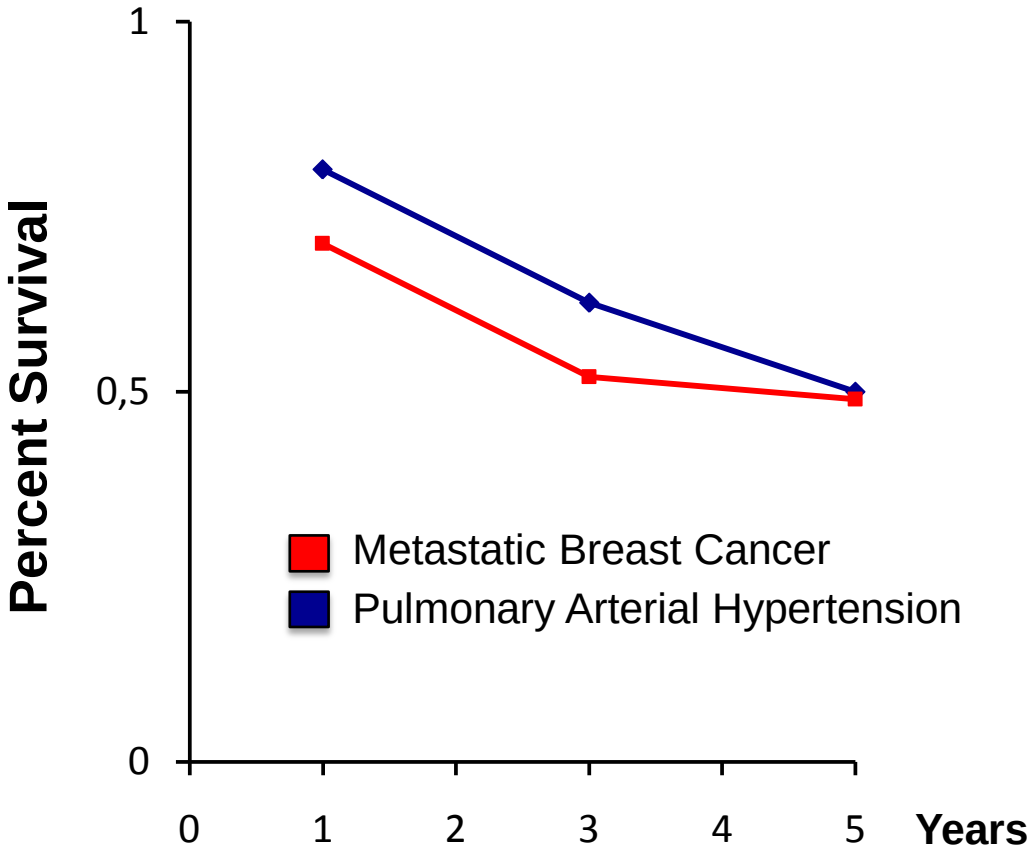


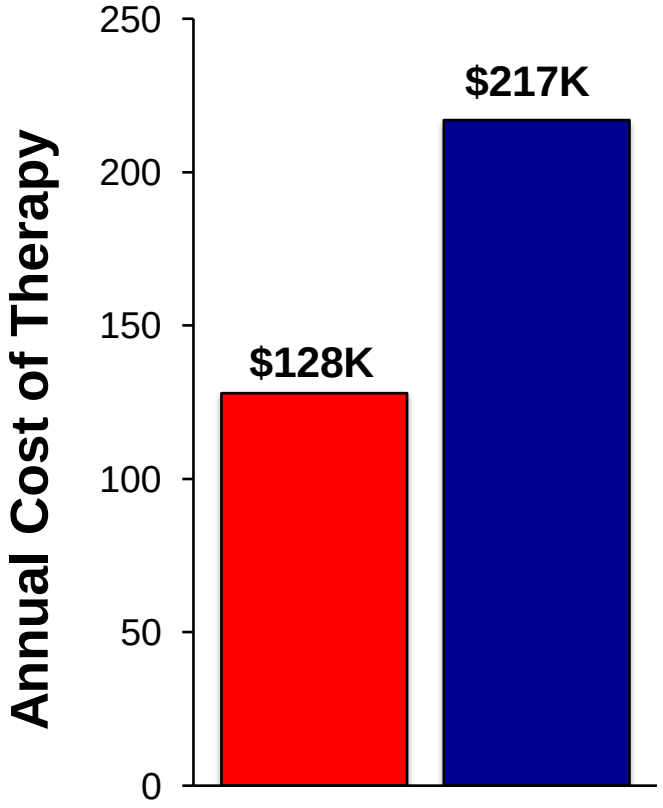
Forssmann W. Die sondierung des rechten herzens. *Klinische Wochenschrift*. 1929;8:2085-2087

PA pressure mmHg	Arterial pressure mmHg	Right Atrial pressure mmHg	Cardiac Output L/min	Heart Rate b/min
73/41, mean 53	135/91, mean 76	12	2.16	93



Dresdale et al, Am J Med, 1951





Michelakis ED; CircRes; 2014

Challenge the current dogma for the pathogenesis of PAH:

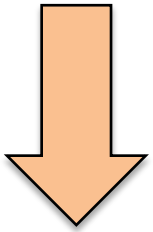
A non-proliferative disease?

Study the Right Ventricle:

What causes the transition from compensation to de-compensation?

Challenge the WHO classification:

Precision Medicine in PAH



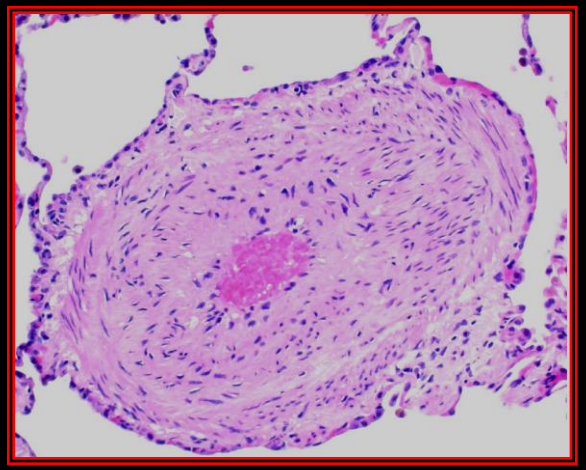
Completely different therapies

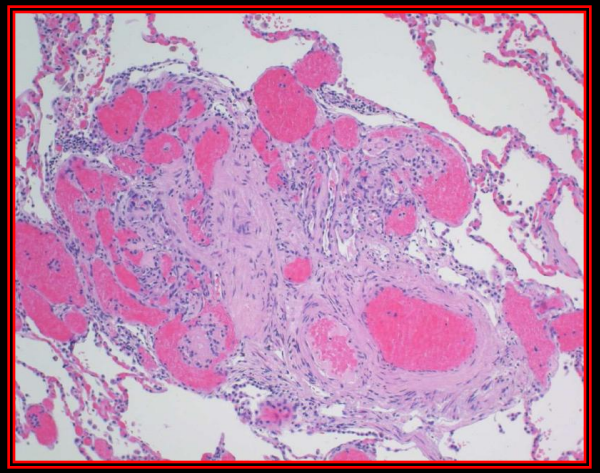
Completely different biomarkers

Completely different disease classification

Completely different way of doing clinical trials

53 year old patient, clinically stable after 18 years on Flolan, WHO class I



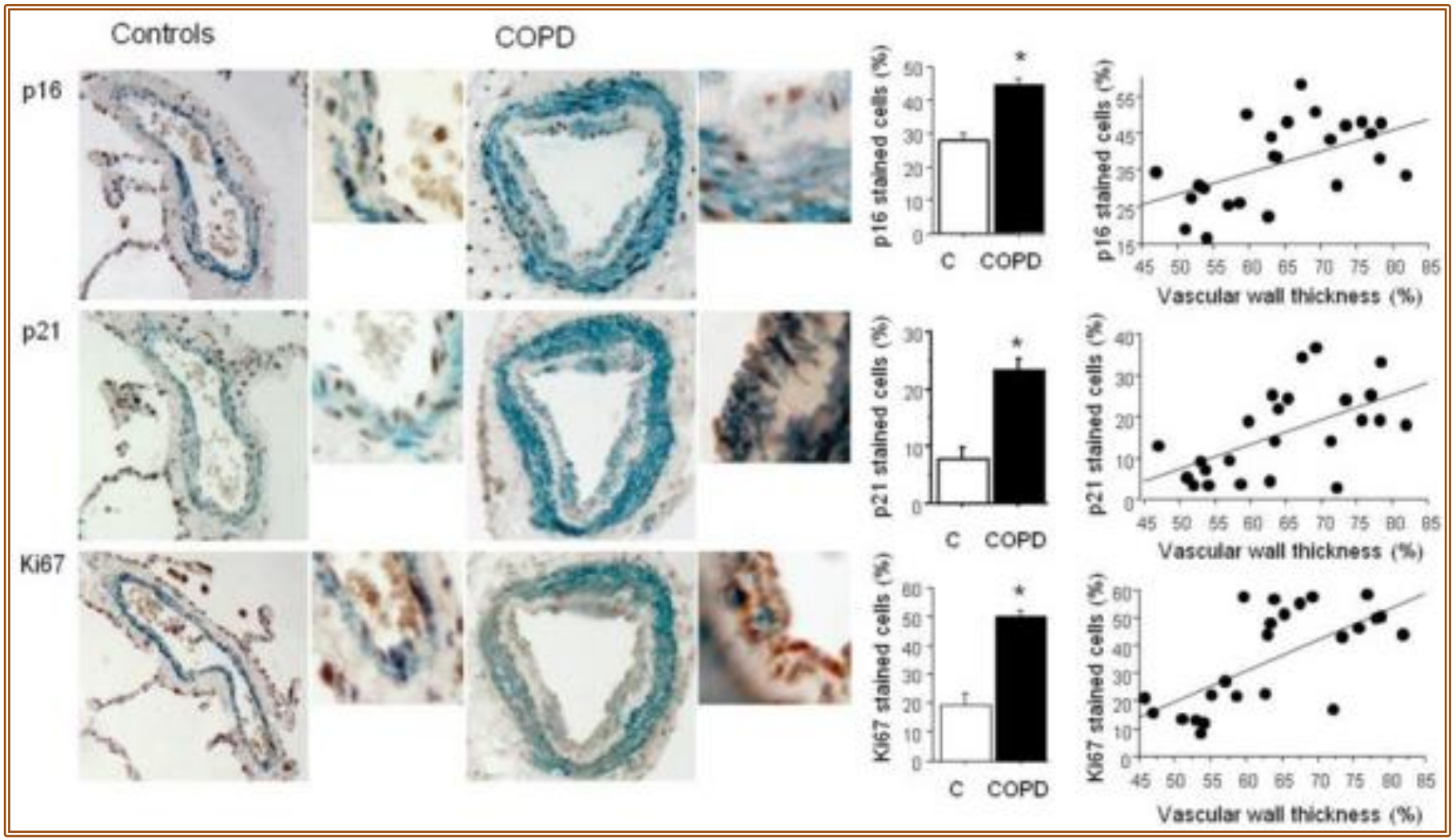


A failed RV from a patient with decompensated PAH

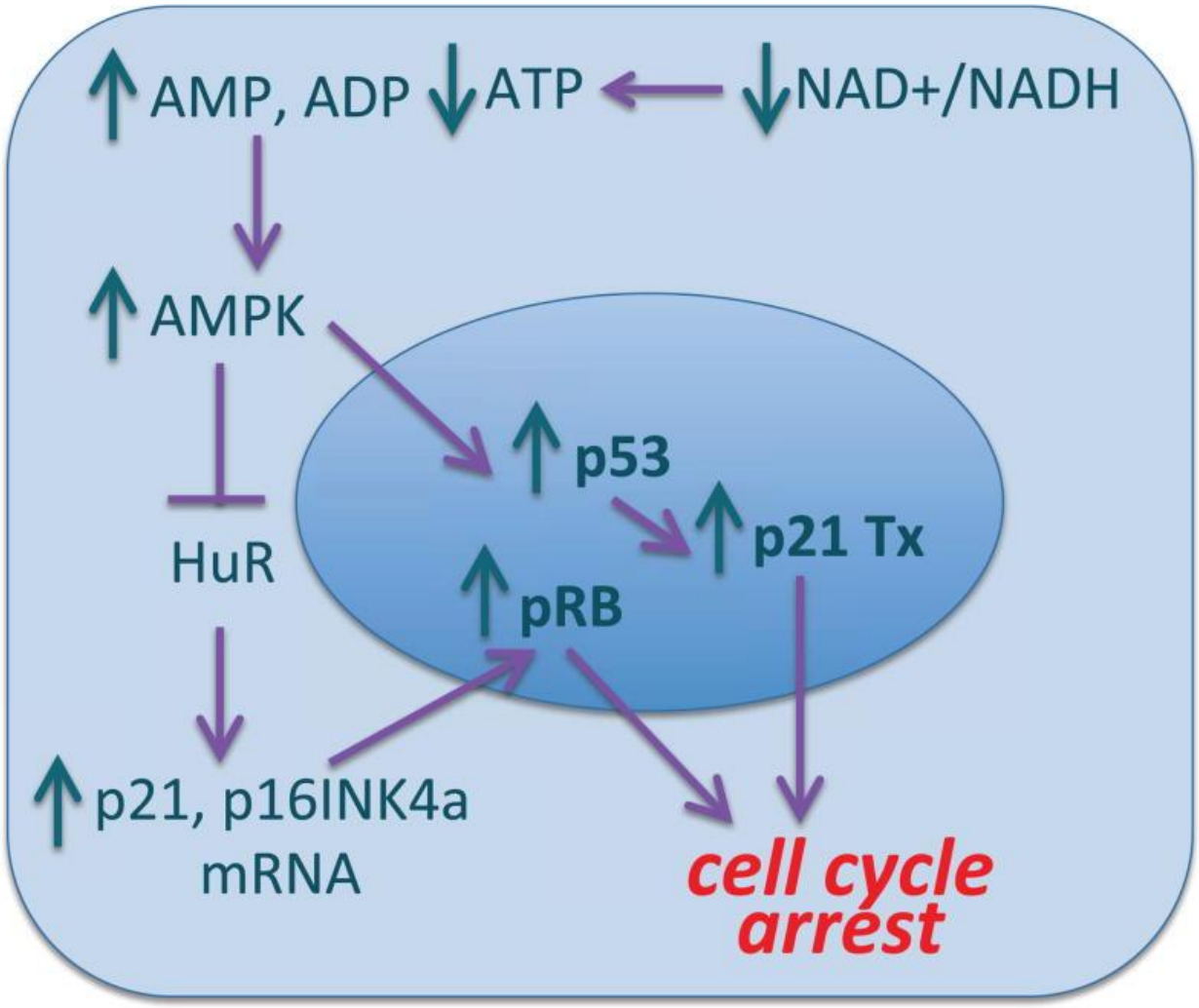
S. Rich, et al, Chest 2010

H Noureddine et al; ***Pulmonary artery smooth muscle cell senescence is a pathogenic mechanism for pulmonary hypertension in chronic lung disease***

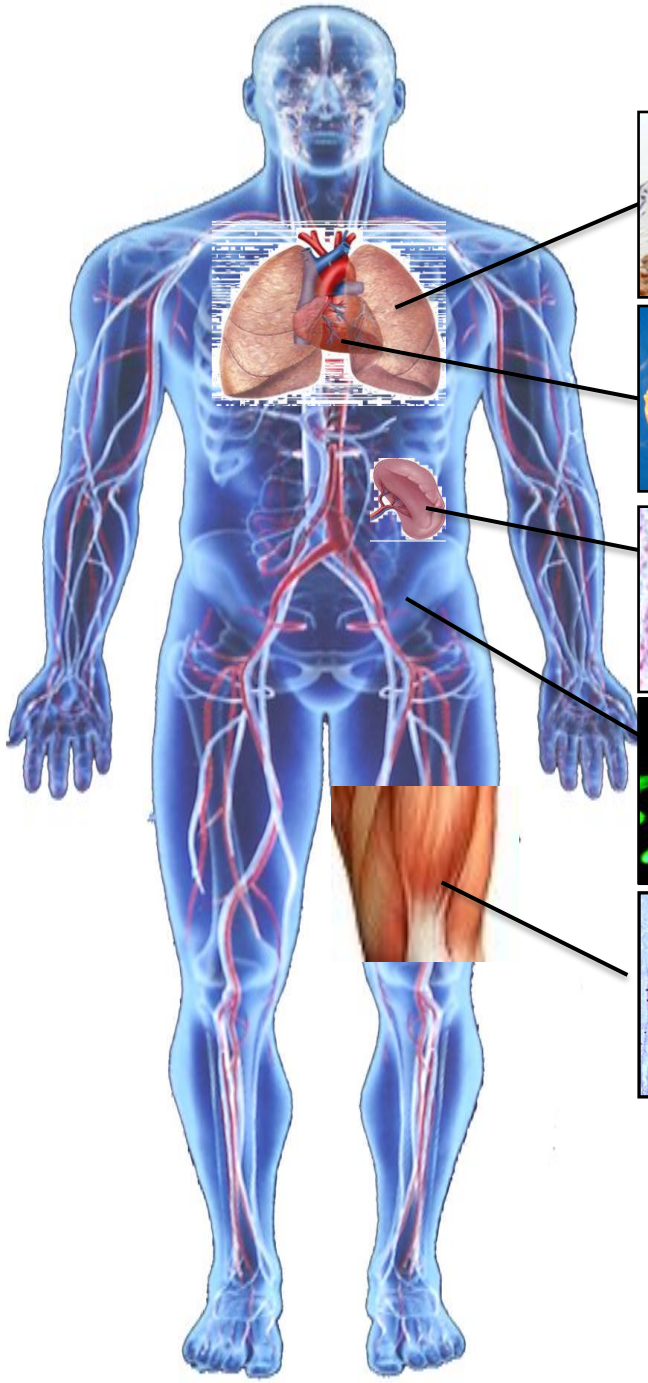
Circ Res. 2011 Aug; 109(5): 543–553.

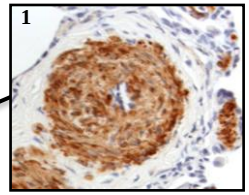


Metabolism and Senescence

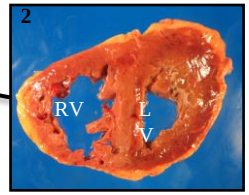


resistance to cell death

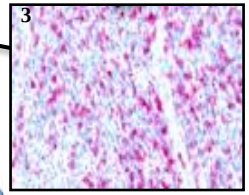




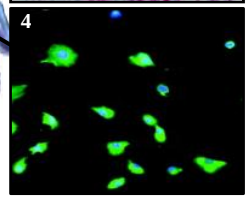
Remodeled Distal PA



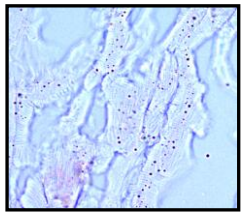
Dilated RV



Activated T-cells



? Endothelial Progenitor Cells

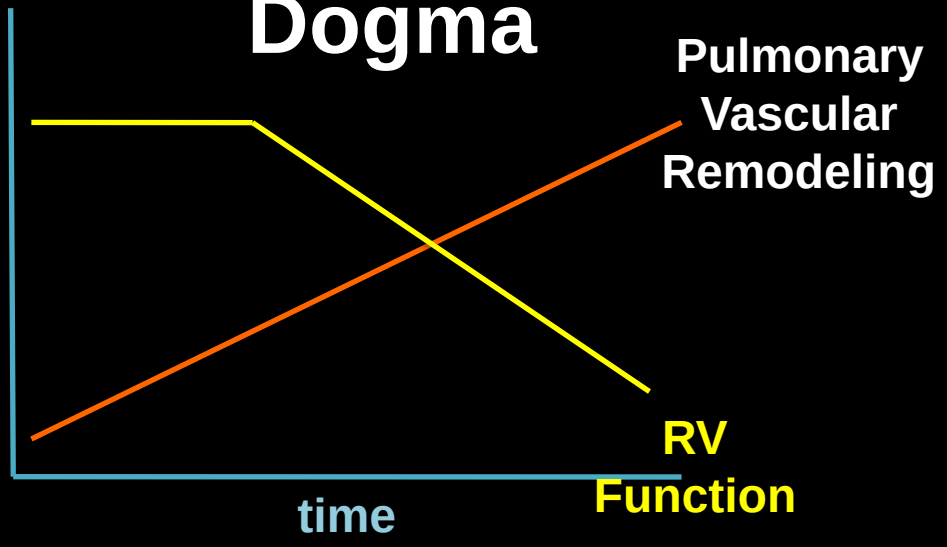


Insulin resistance

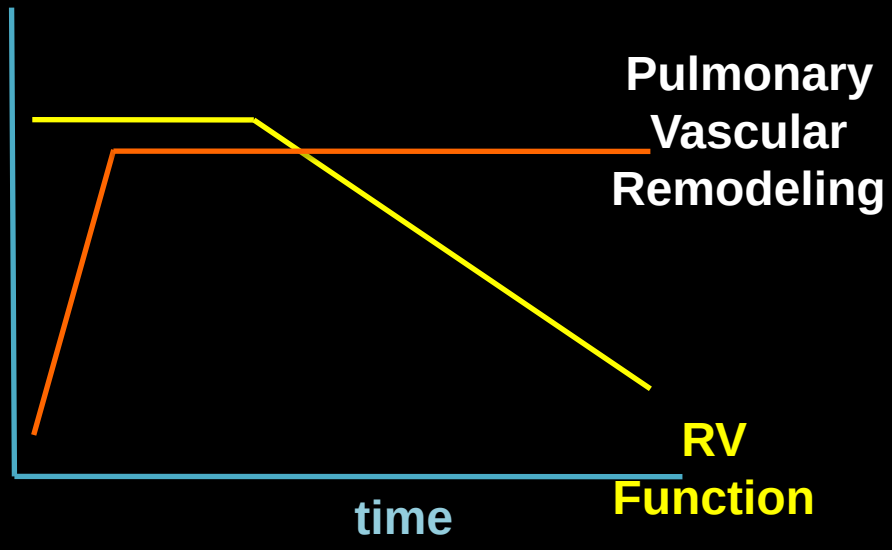
↓ GO/GLY

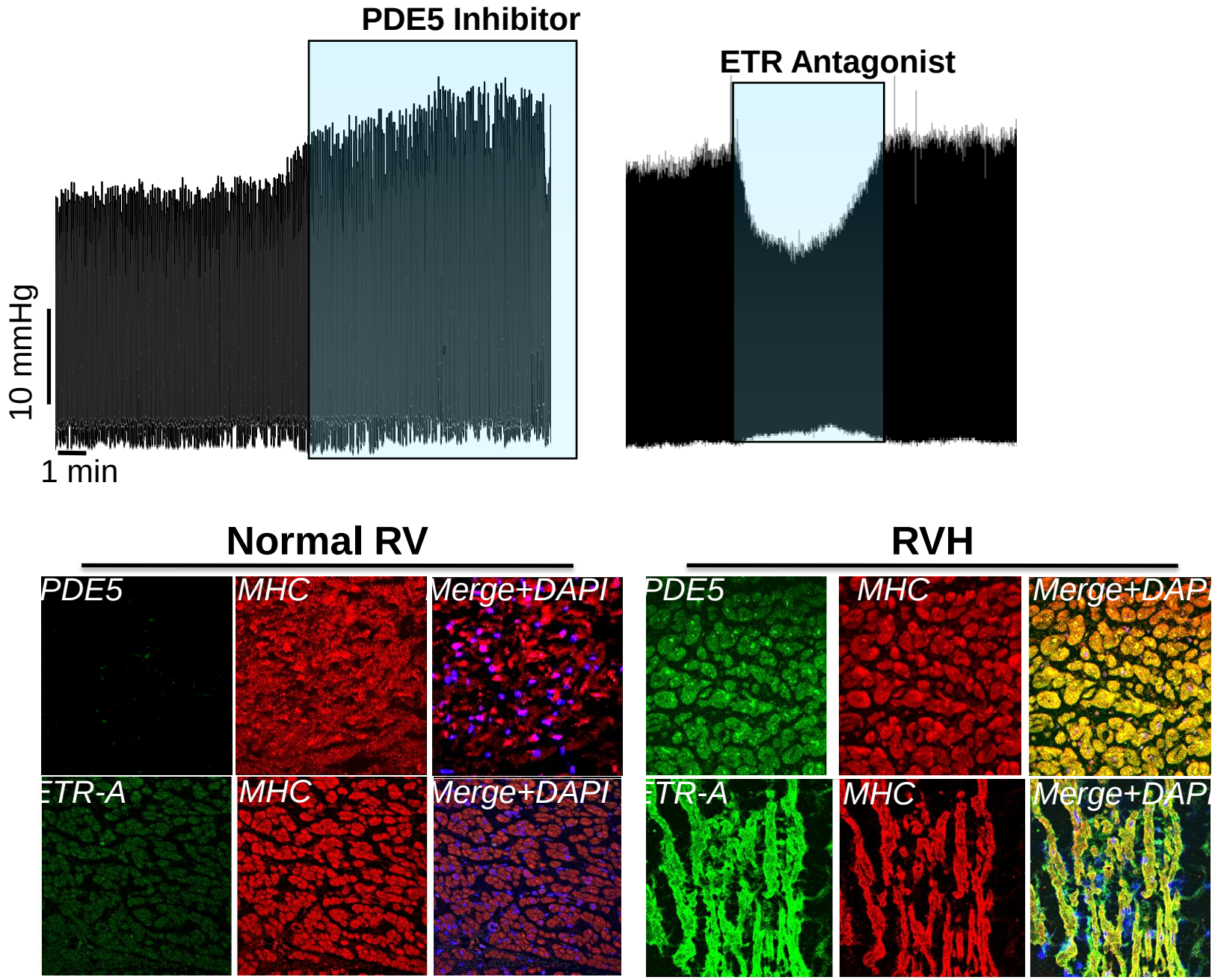
Sutendra and Michelakis
Cell Metabolism 2014

Current Dogma

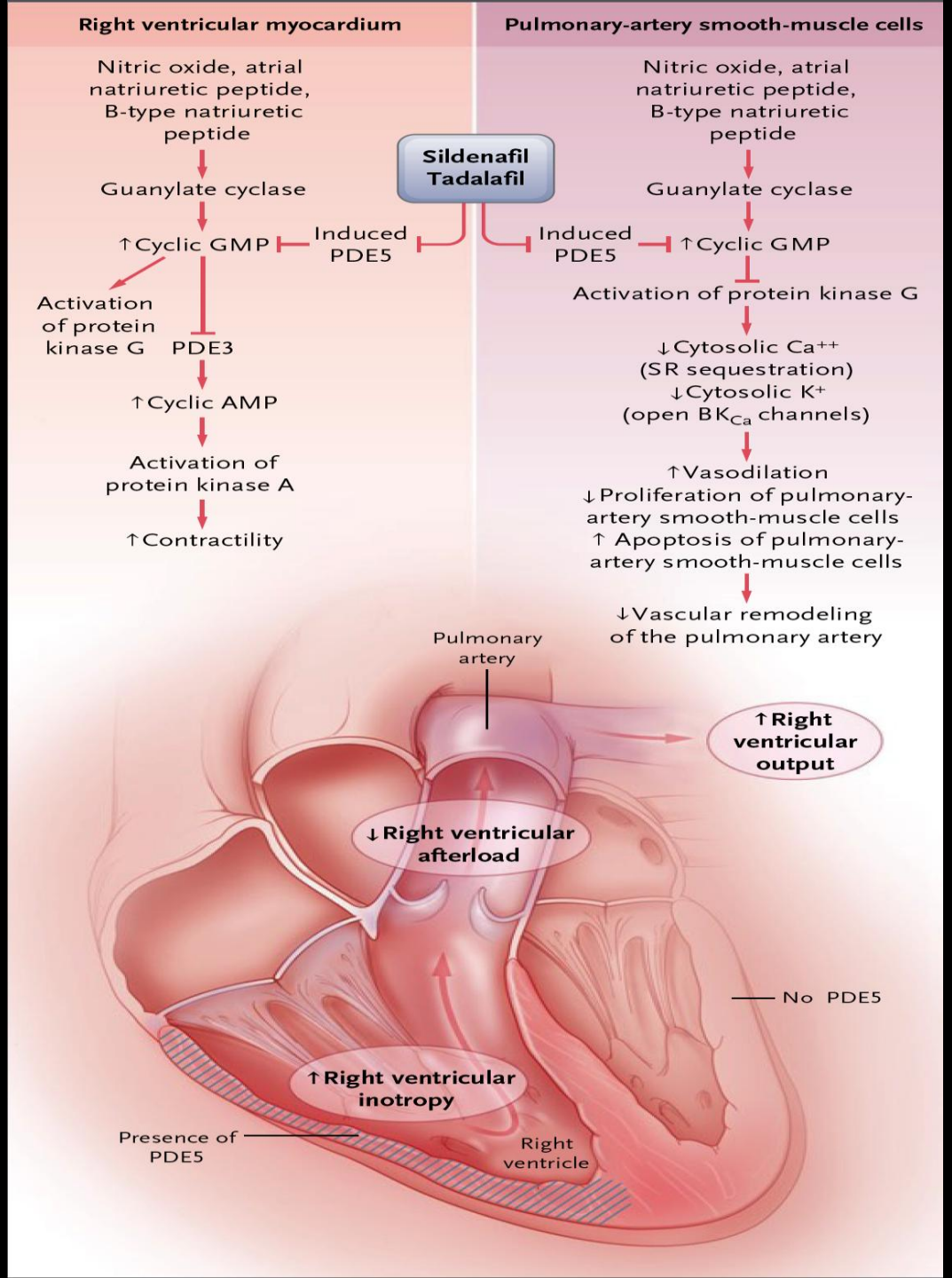


Alternate Theory





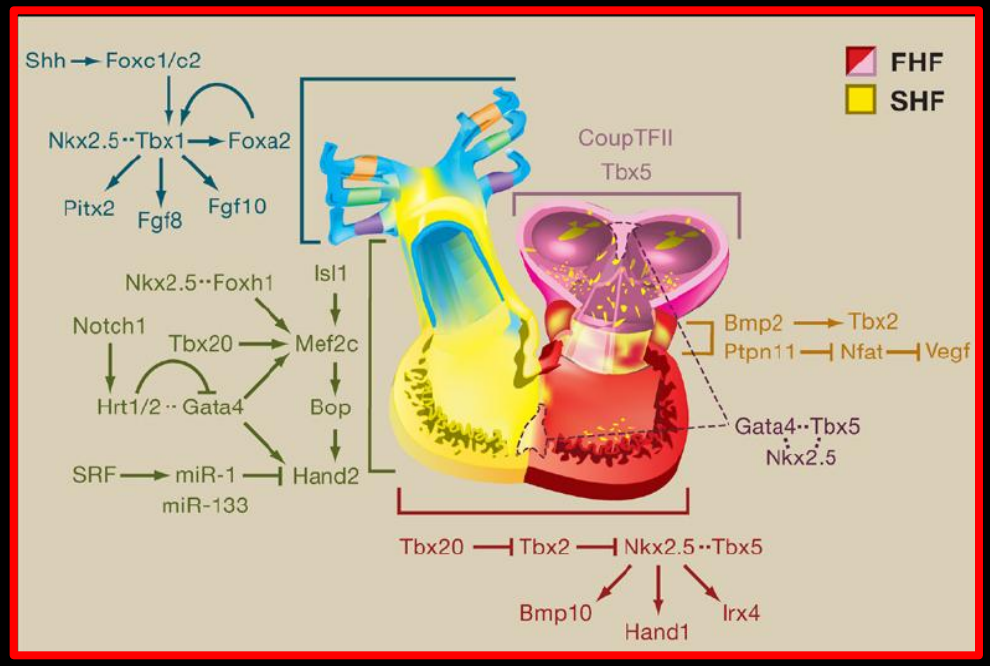
Sutendra and Michelakis, Science Translational Medicine, 2013



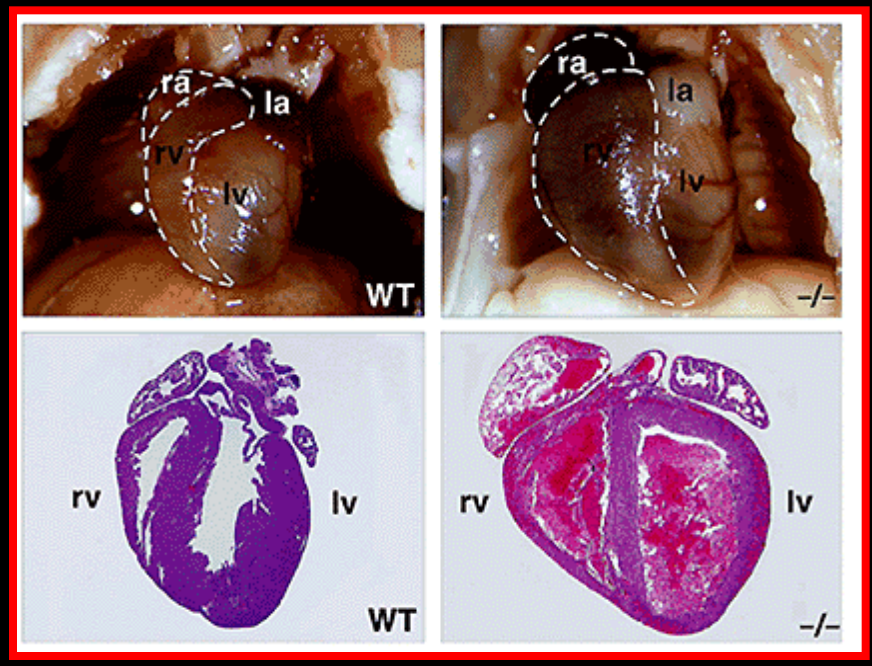
Archer and Michelakis
NEJM, Nov 7, 2009

Myocyte enhancer factor 2 (Mef2)

- Mef2c is critical for RV development
- Mef2a$^{-/-}$ associated with RV dilatation/failure



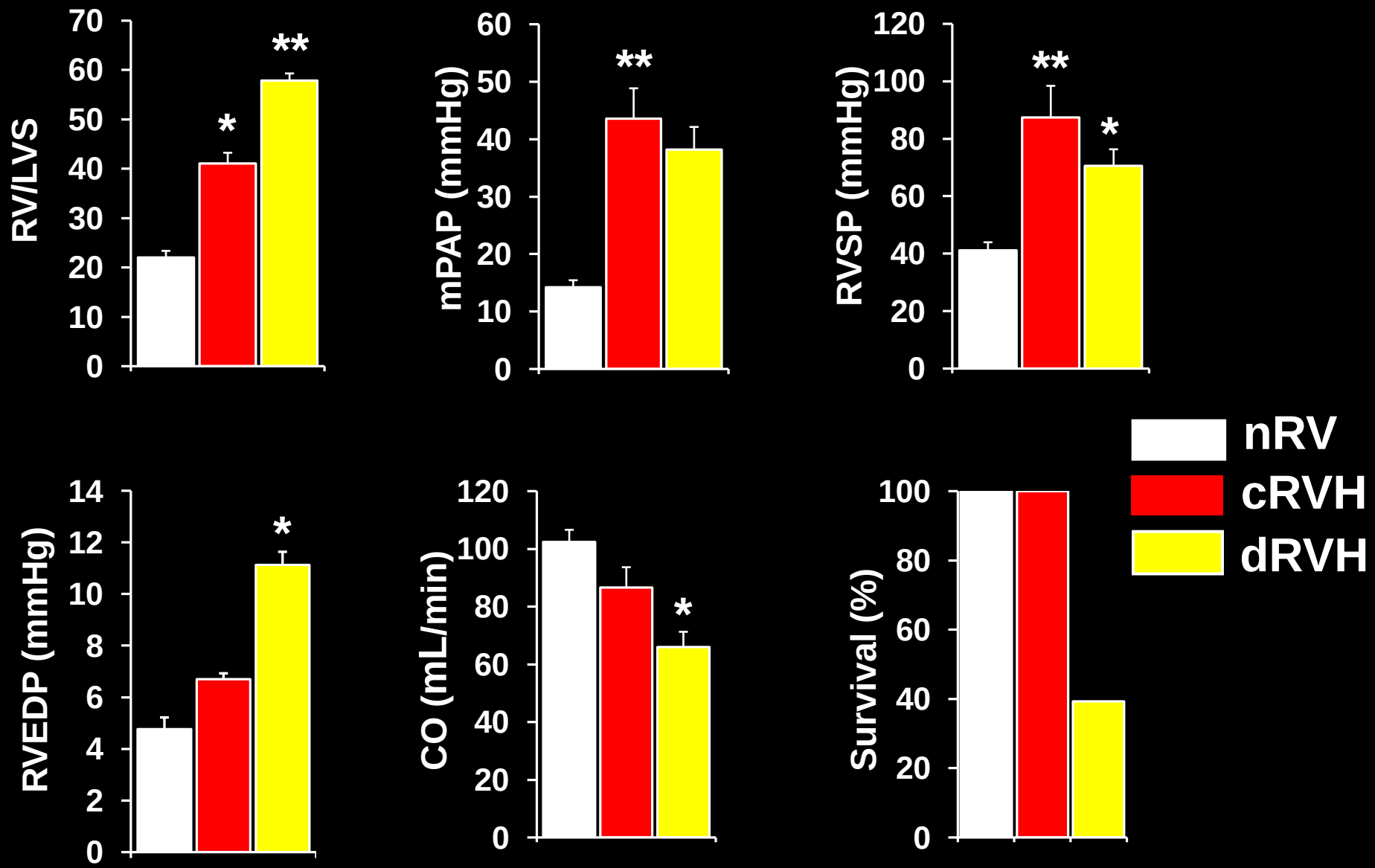
Srivastava et al, Cell. 2006



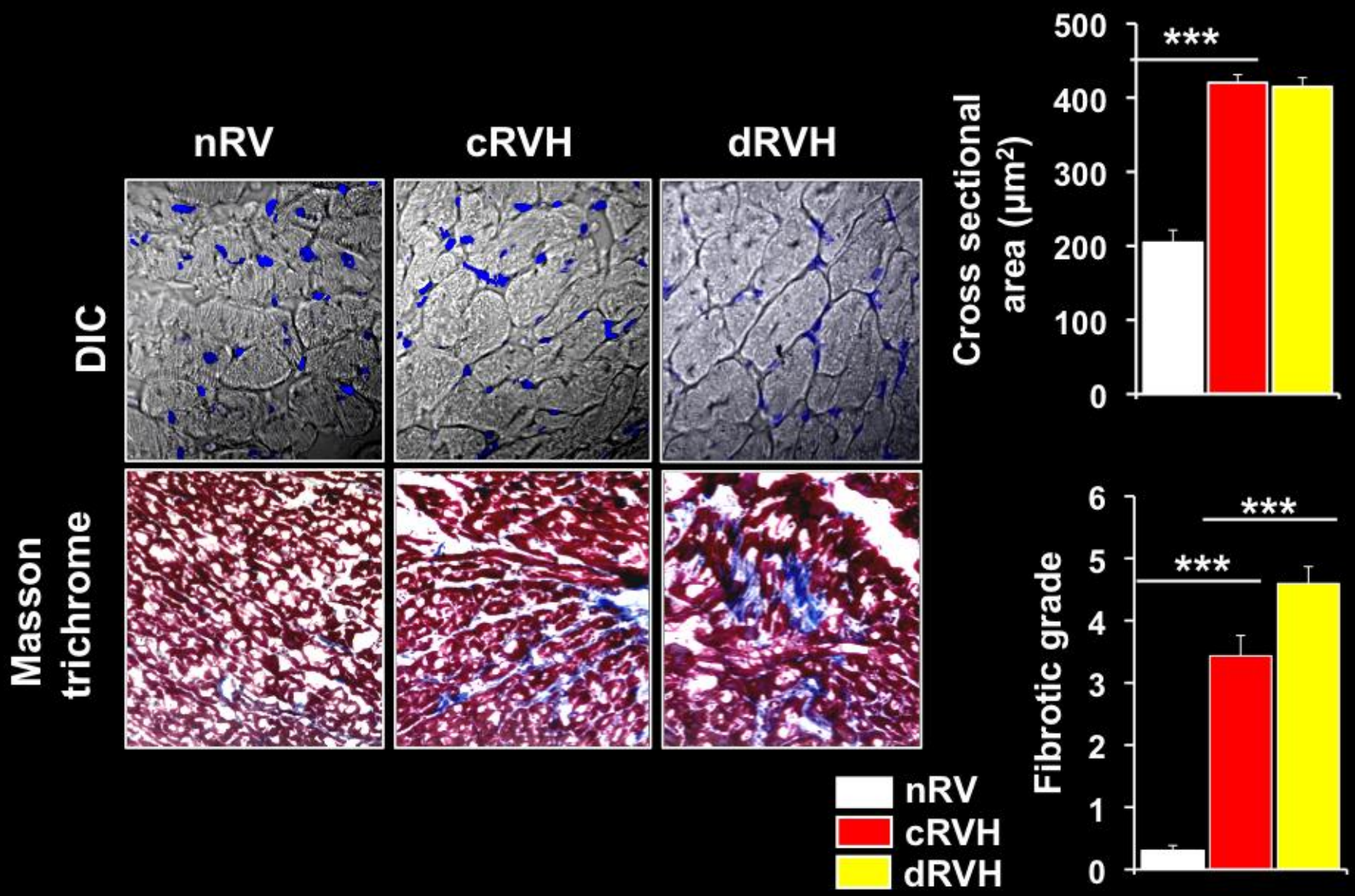
Naya et al, Nature Medicine. 2002

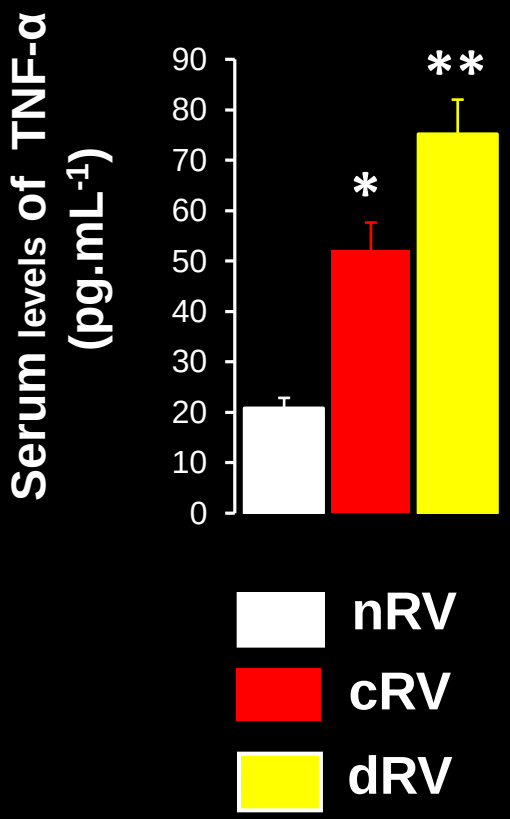
- Mef2 regulates many metabolic genes, cardiac MHC, angiogenesis.
- Mef2 regulates the transcription of several miRNAs

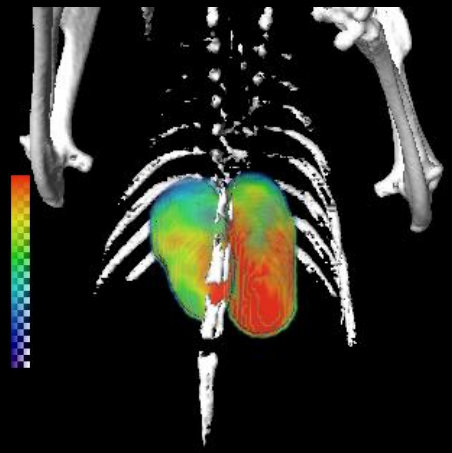
A rat model of the natural history of RV failure

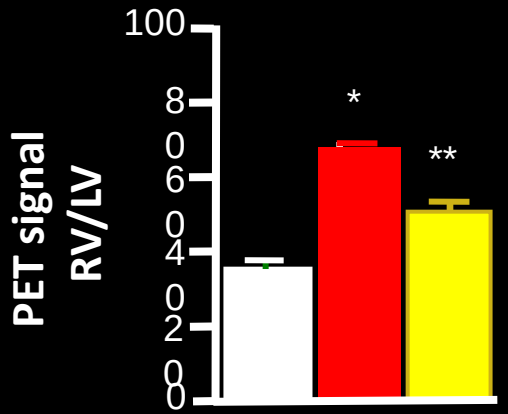


A rat model of the natural history of RV failure

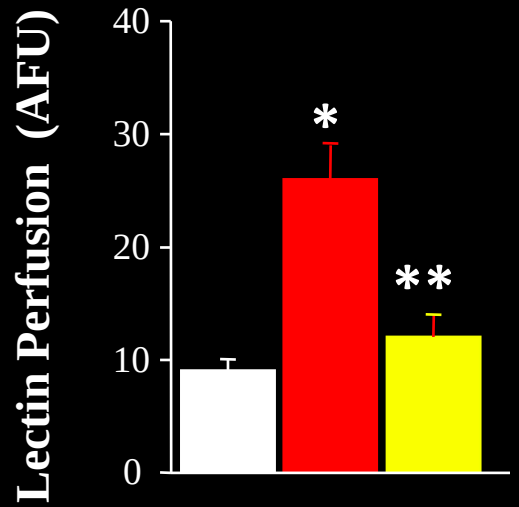




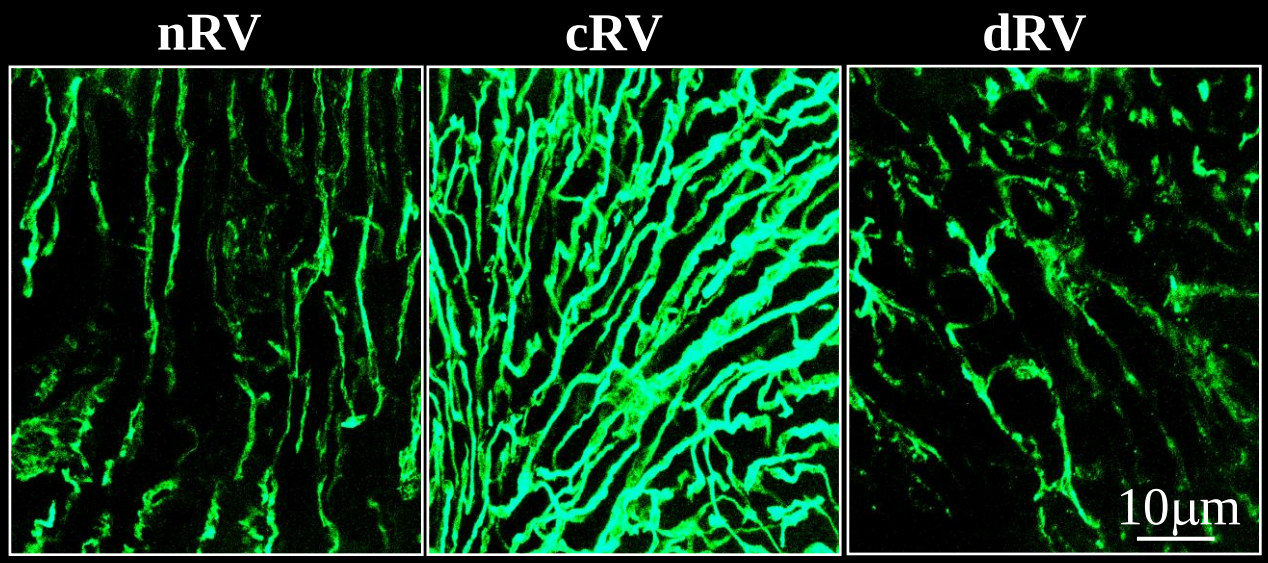




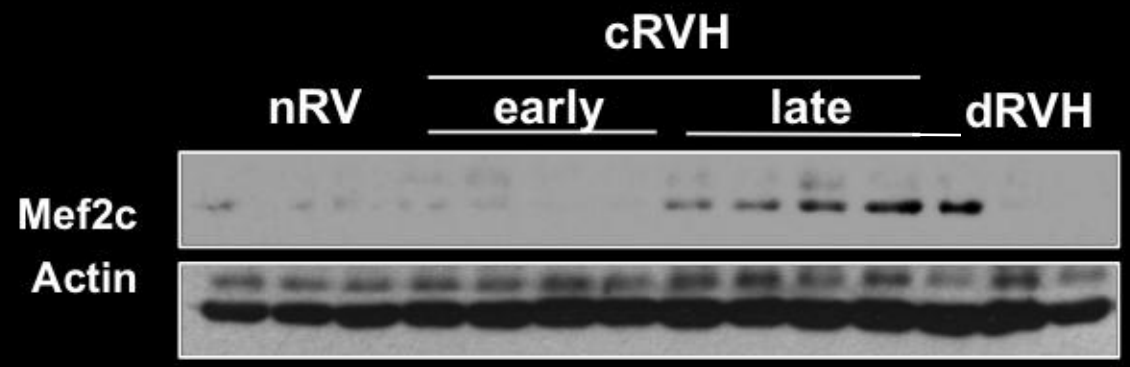
nRV
cRV
dRV

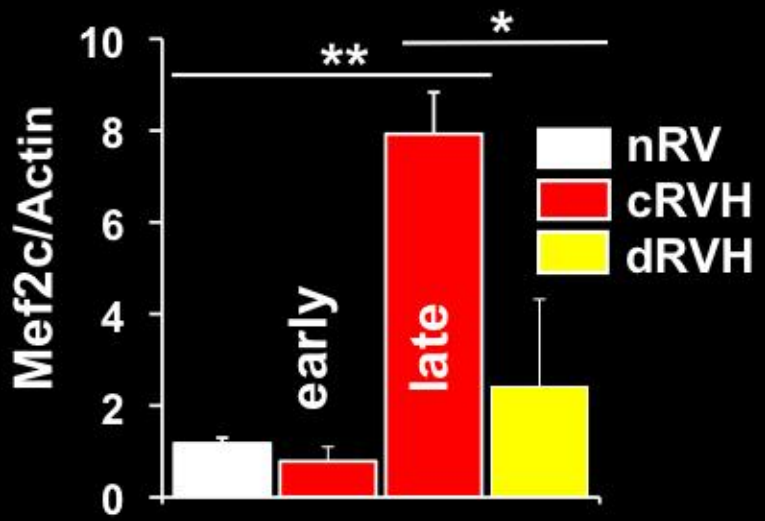


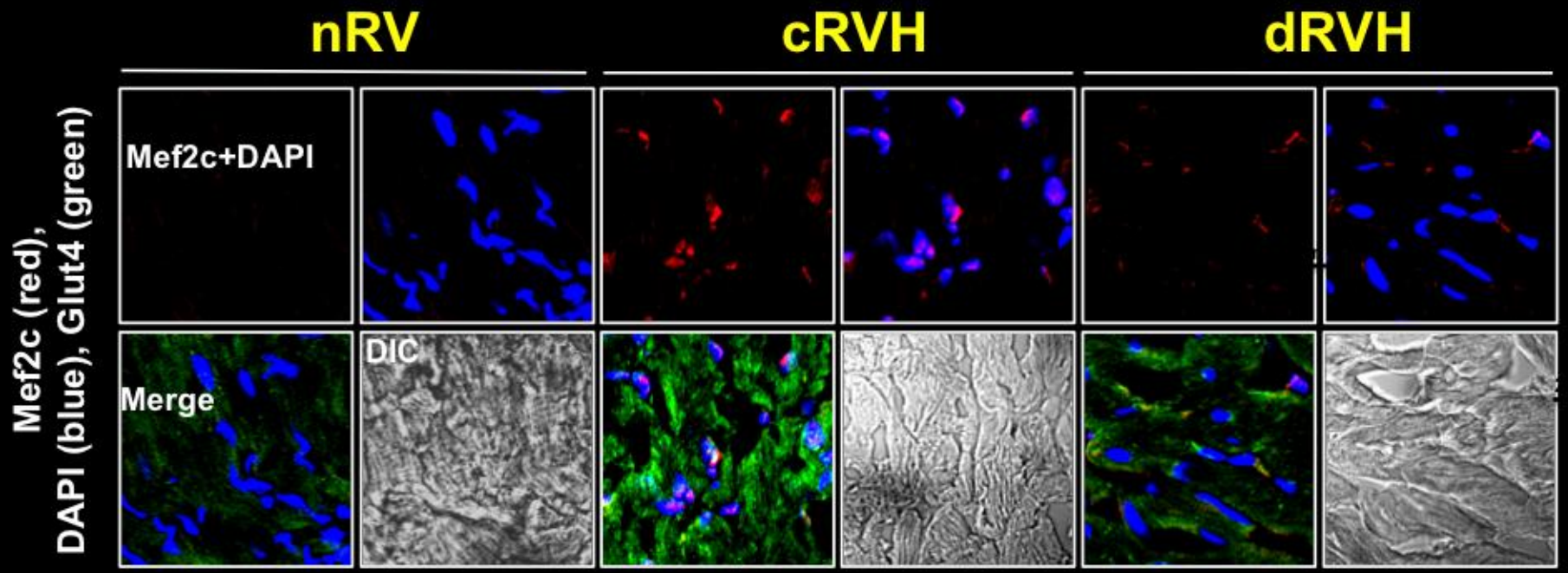
Lectin

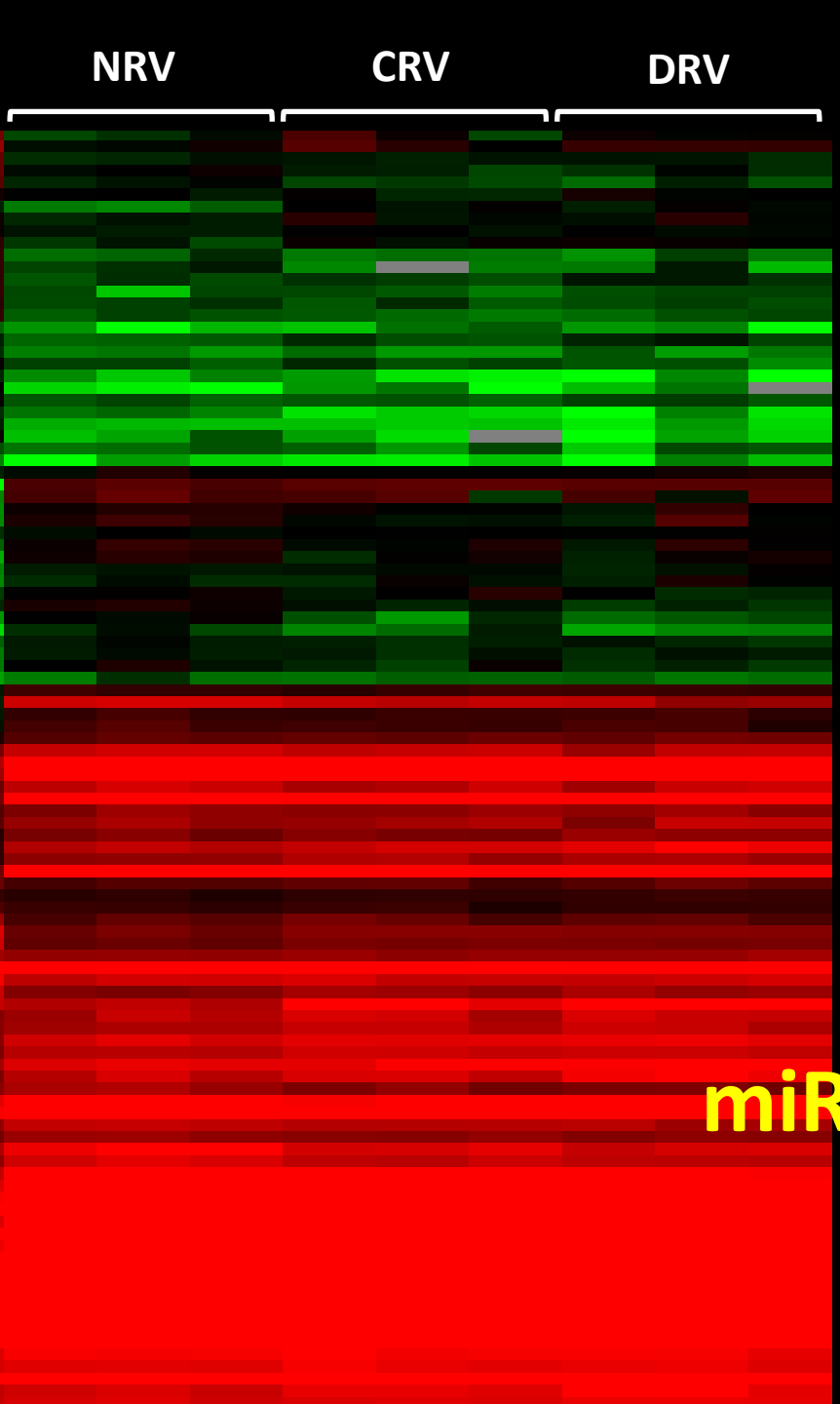


Mef2c is activated during cRVH





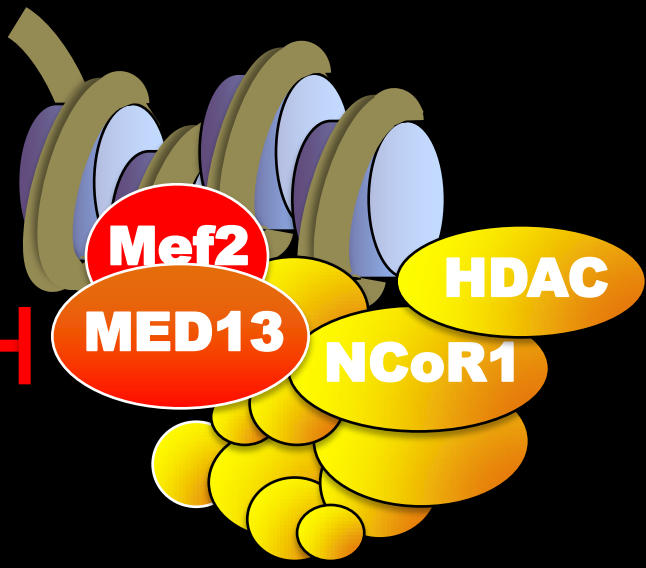


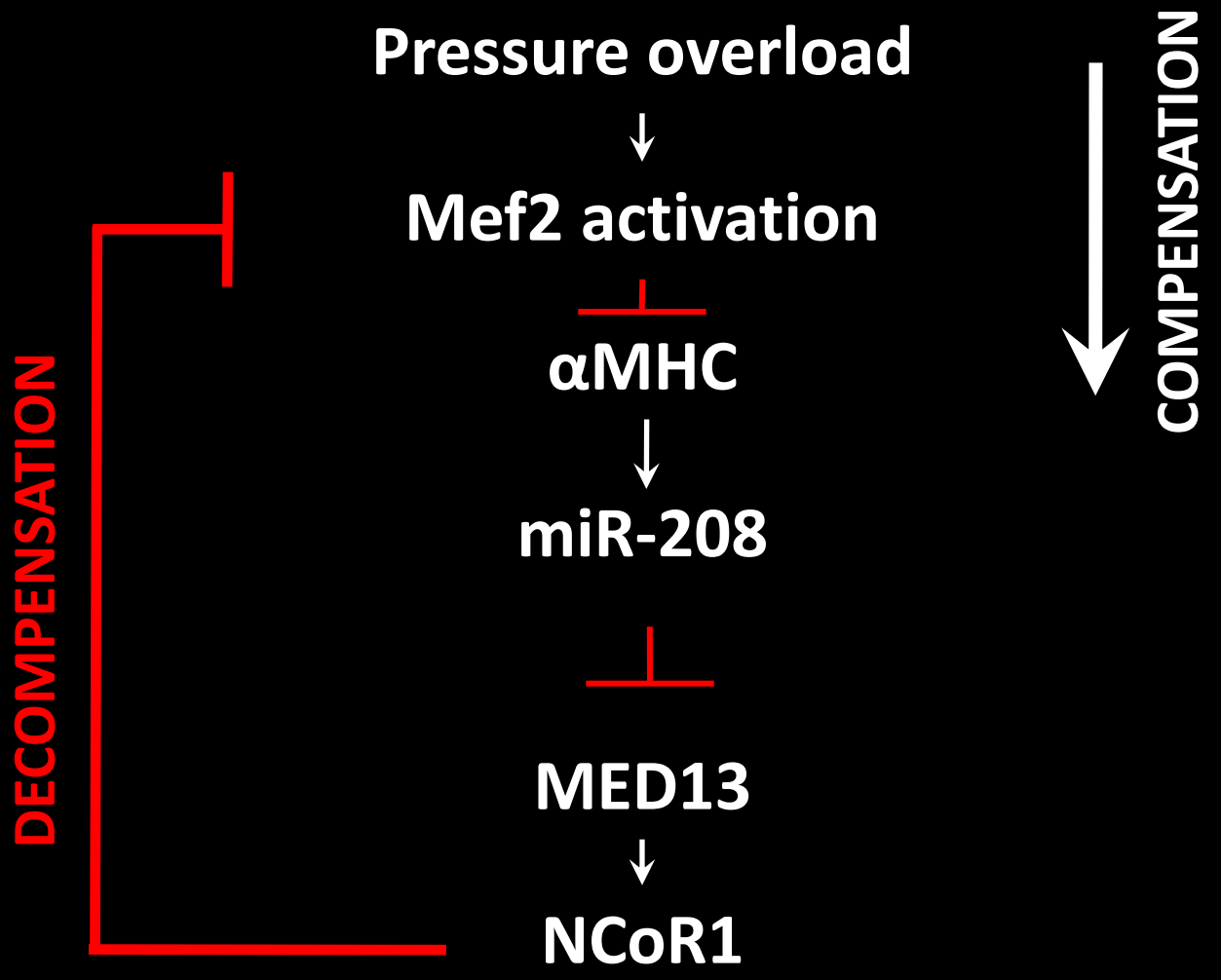


The cardiac specific miR-208

- Cardiac specific
- hosted by the αMHC
- Maintained during LVH

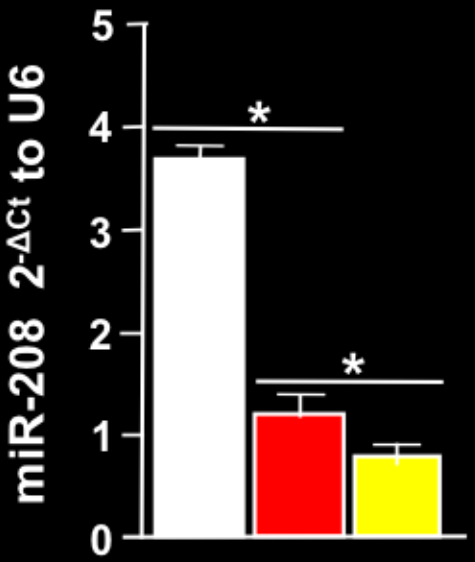
miR-208

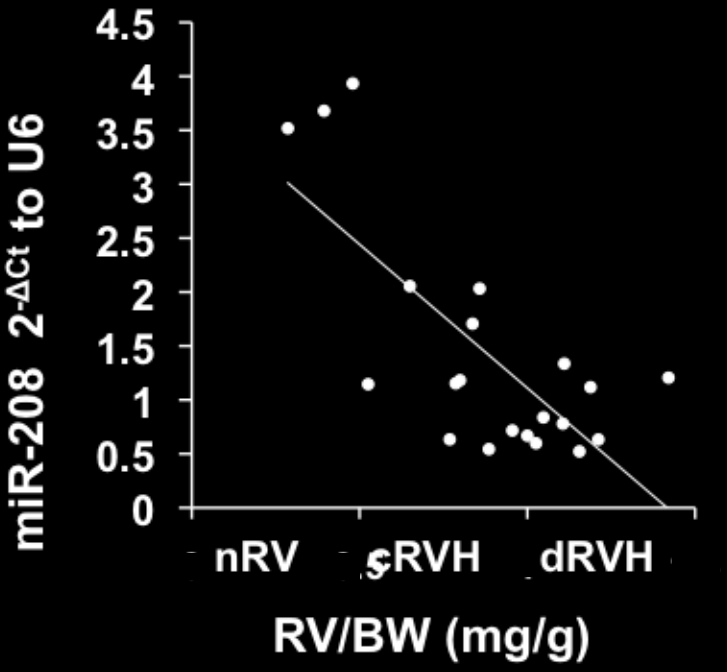


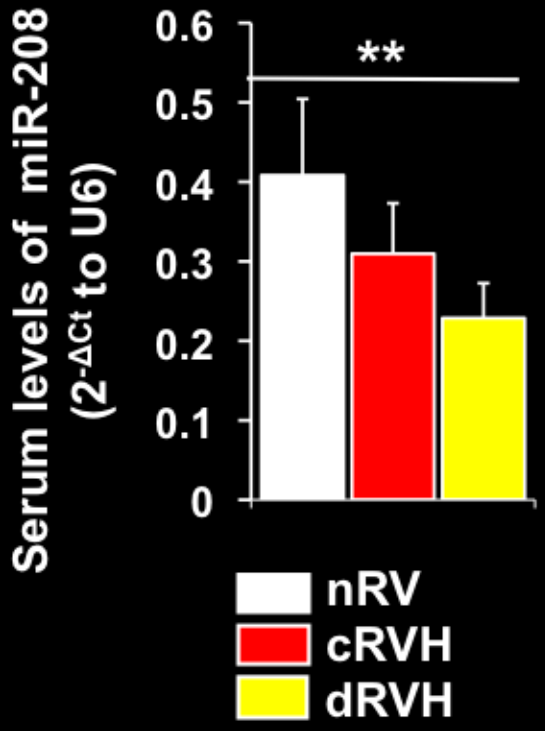

Pressure overload
Mef2 activation
αMHC
miR-208
MED13
NCoR1
DECOMPENSATION
COMPENSATION

The cardiac specific miR-208

An RV failure biomarker?

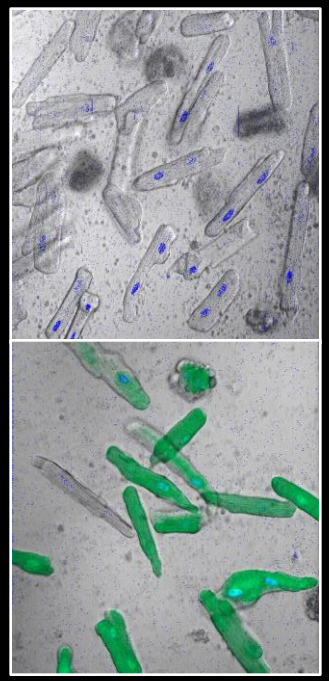


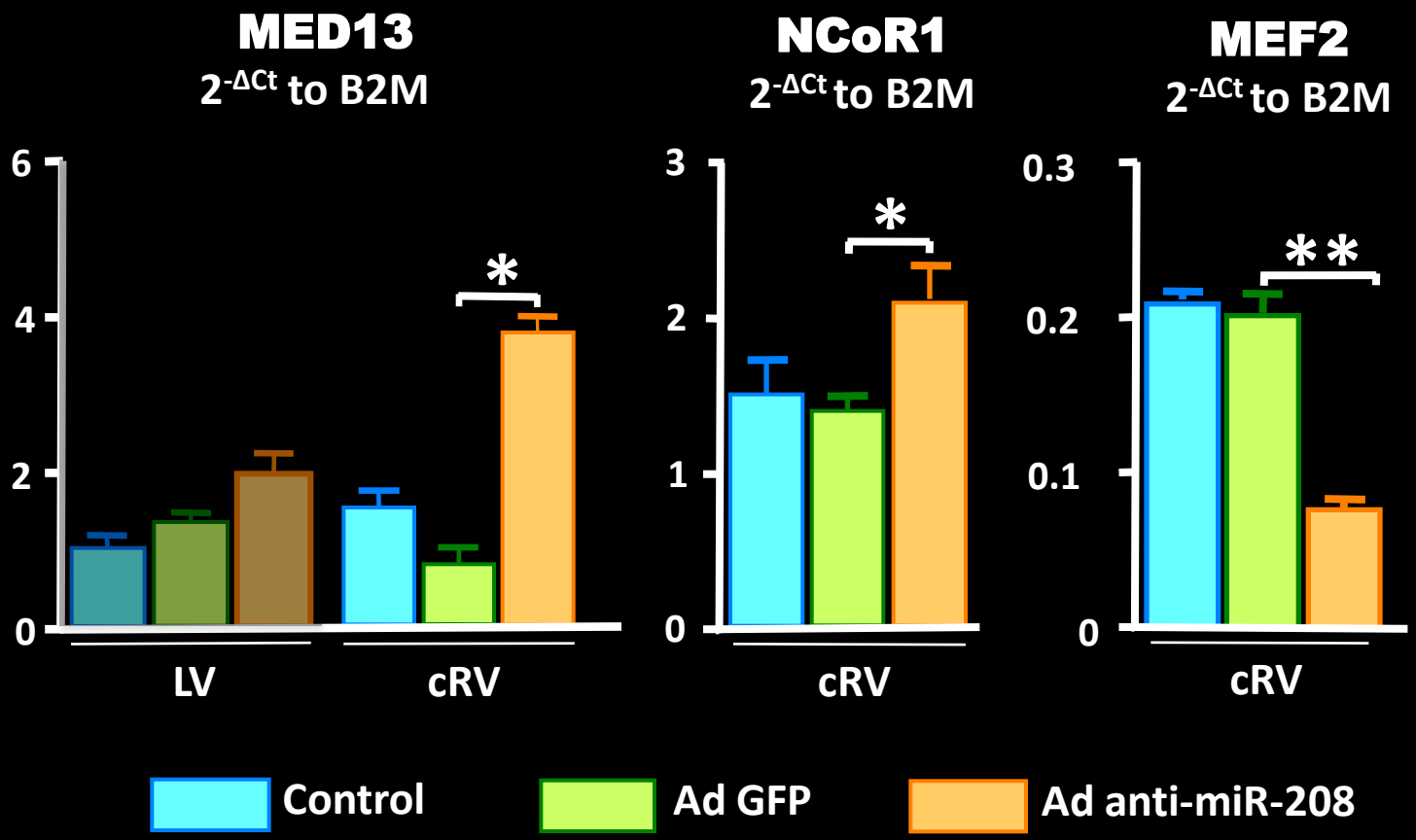


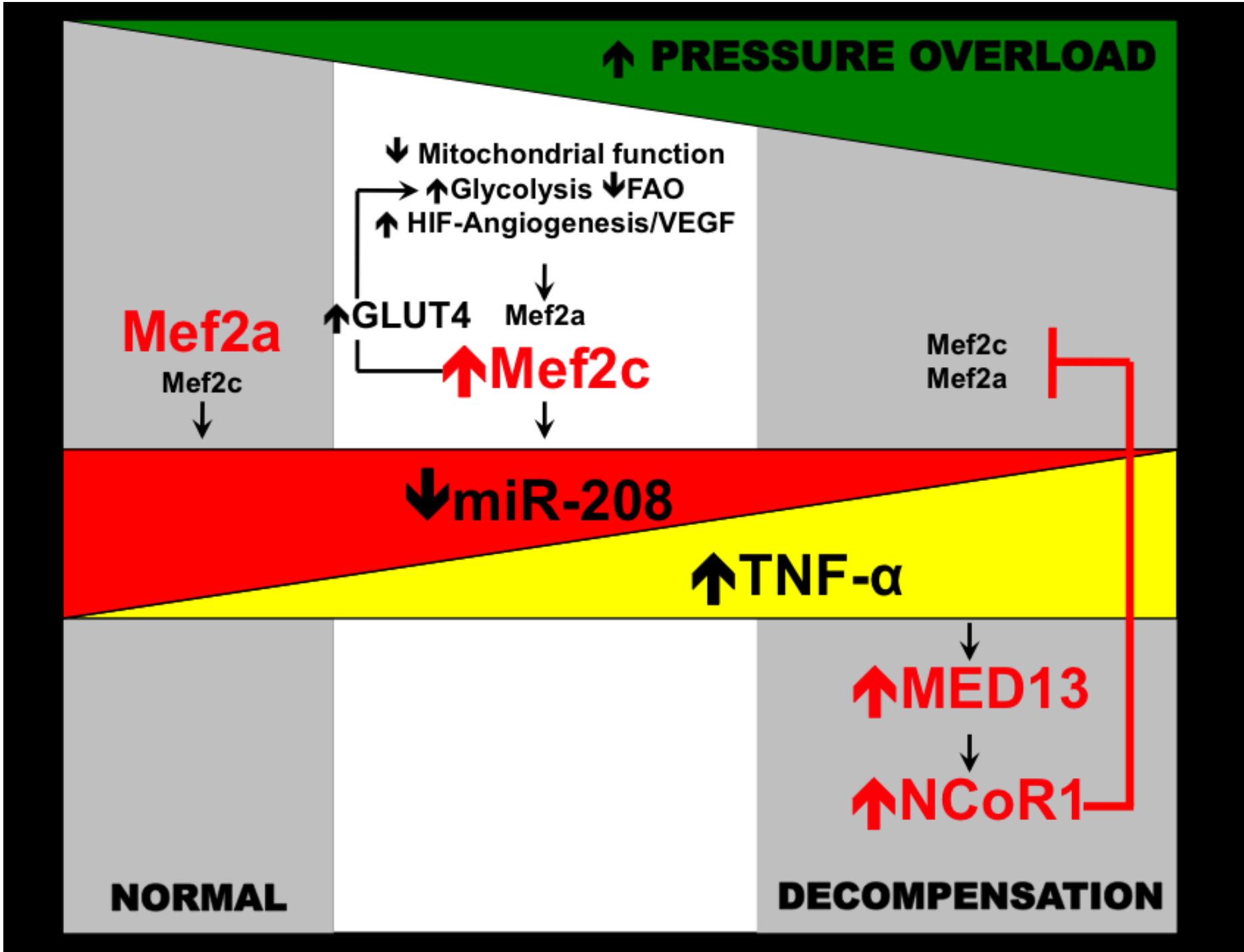


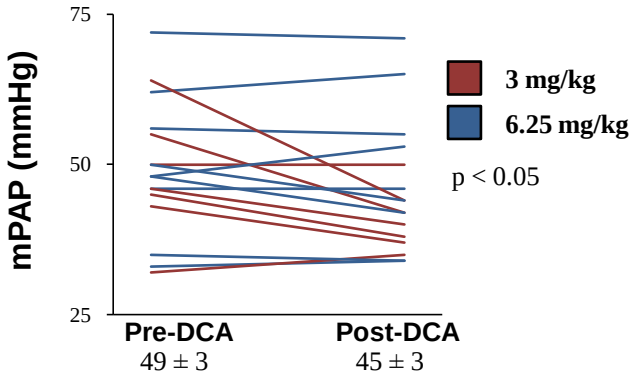
miR-208 inhibition transforms a cRV cardiomyocyte into a dRV one

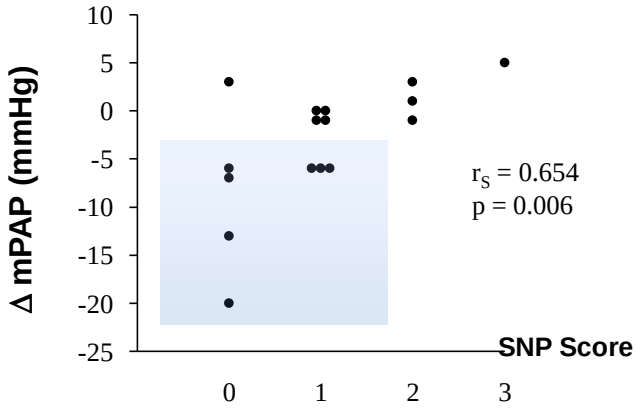
Adult rat cardiomyocytes from CRV-MCT rats

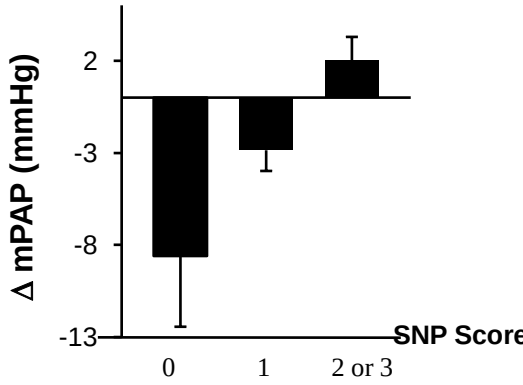


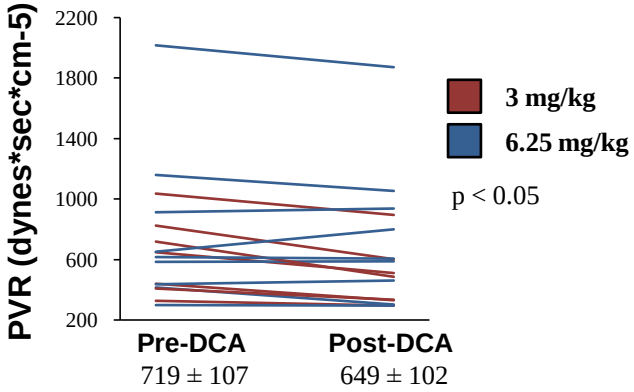


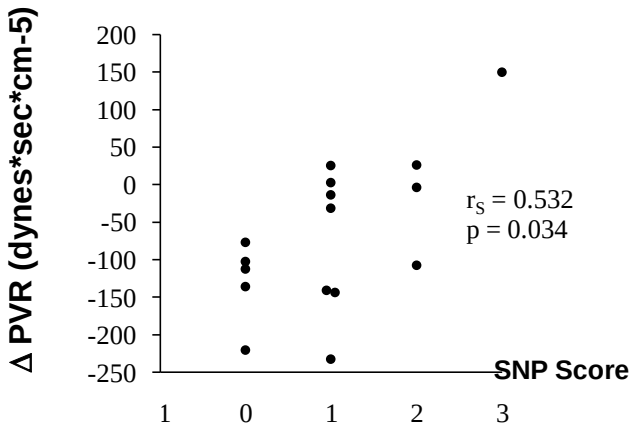

↑ PRESSURE OVERLOAD
↓ Mitochondrial function
↑Glycolysis ↓FAO
↑ HIF-Angiogenesis/VEGF
↑GLUT4
Mef2a
↑Mef2c
Mef2a
Mef2c
Mef2c
Mef2a
↓miR-208
↑TNF-α
↑MED13
↑NCoR1
NORMAL
DECOMPENSATION

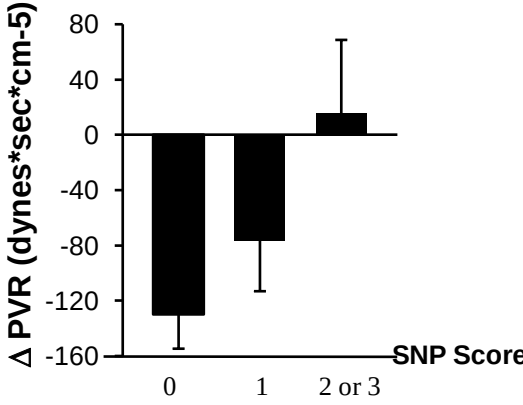

mPAP (mmHg)
75
50
25
Pre-DCA
49 ± 3
Post-DCA
45 ± 3
3 mg/kg
6.25 mg/kg
p < 0.05

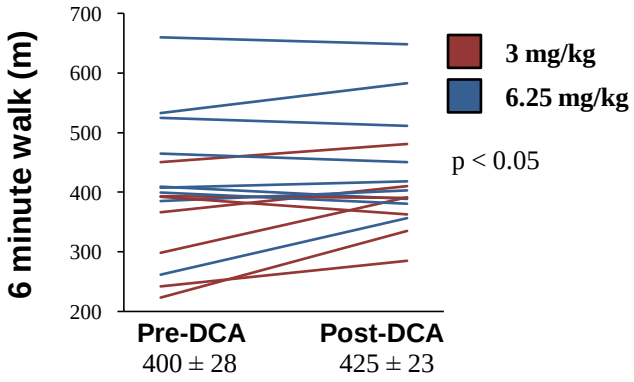

Δ mPAP (mmHg)
10
5
0
-5
-10
-15
-20
-25
rS = 0.654
p = 0.006
SNP Score
0
1
2
3

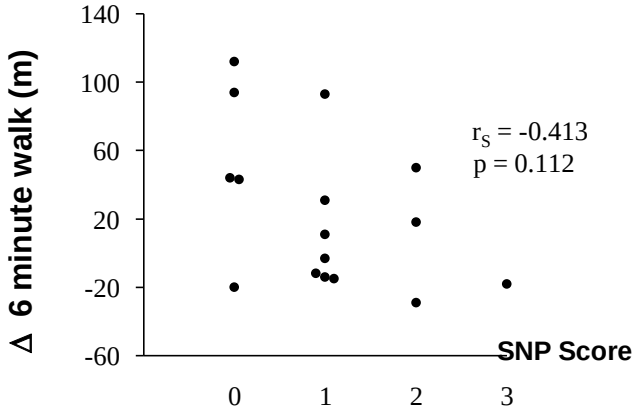

Δ mPAP (mmHg)
2
-3
-8
-13
SNP Score
0
1
2 or 3

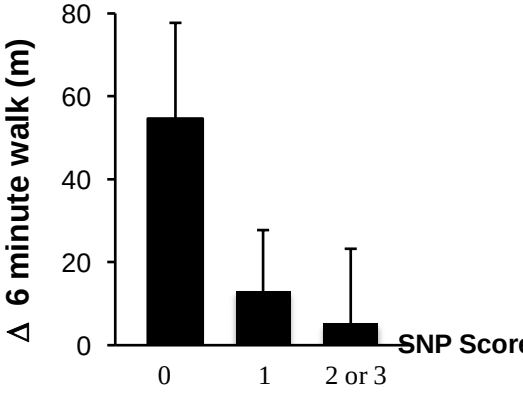

PVR (dynes*sec*cm-5)
2200
1800
1400
1000
600
200
Pre-DCA
719 ± 107
Post-DCA
649 ± 102
3 mg/kg
6.25 mg/kg
p < 0.05

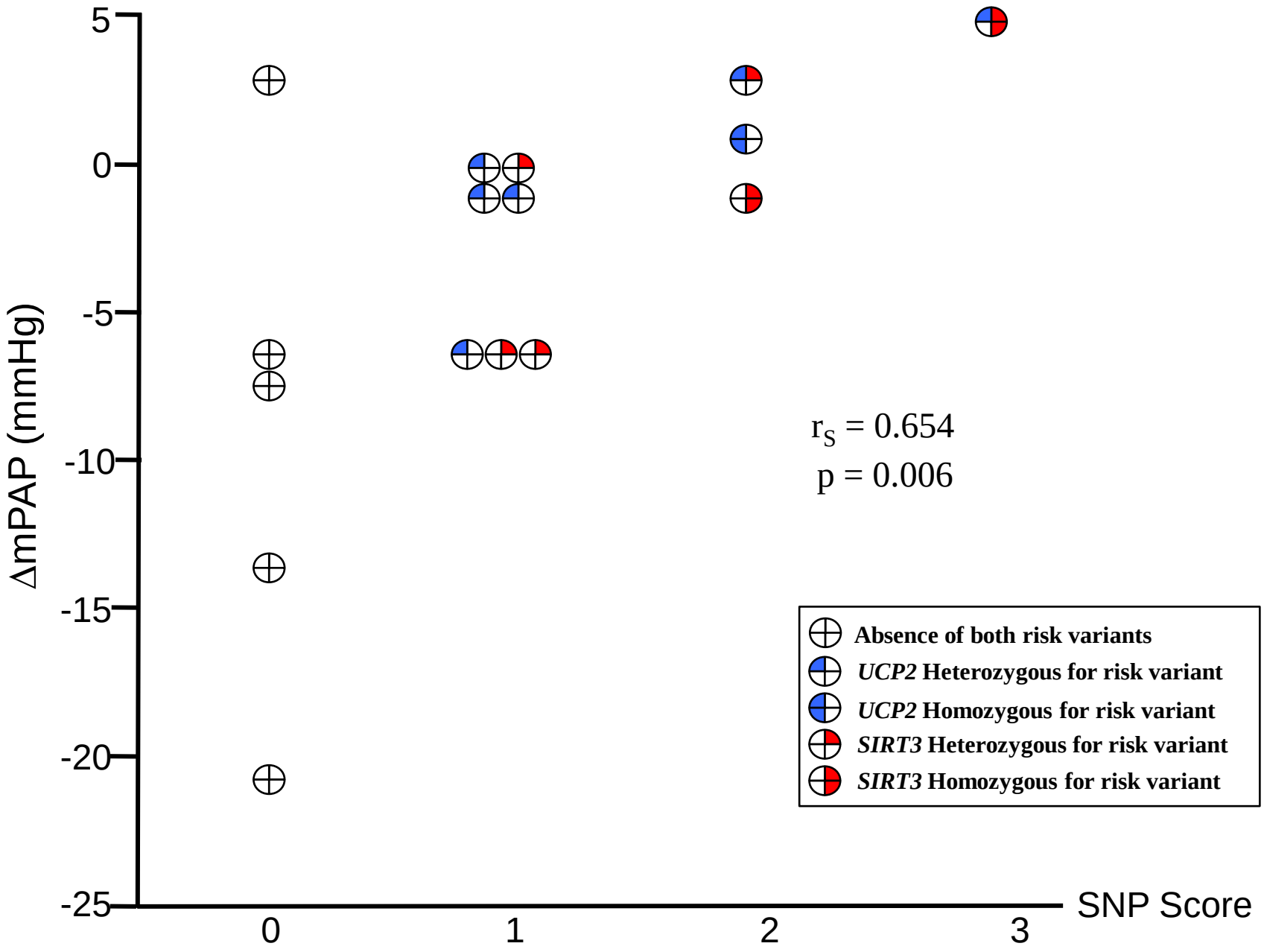

Δ PVR (dynes*sec*cm-5)
200
150
100
50
0
-50
-100
-150
-200
-250
rS = 0.532
p = 0.034
SNP Score
1
0
1
2
3


Δ PVR (dynes*sec*cm-5)
80
40
0
-40
-80
-120
-160
SNP Score
0
1
2 or 3


6 minute walk (m)
700
600
500
400
300
200
Pre-DCA
400 ± 28
Post-DCA
425 ± 23
3 mg/kg
6.25 mg/kg
p < 0.05


Δ 6 minute walk (m)
140
100
60
20
-20
-60
rS = -0.413
p = 0.112
SNP Score
0
1
2
3


Δ 6 minute walk (m)
80
60
40
20
0
SNP Score
0
1
2 or 3


5
0
-5
-10
-15
-20
-25
ΔmPAP (mmHg)
0
1
2
3
SNP Score
r_S = 0.654
p = 0.006
Absence of both risk variants
UCP2 Heterozygous for risk variant
UCP2 Homozygous for risk variant
SIRT3 Heterozygous for risk variant
SIRT3 Homozygous for risk variant

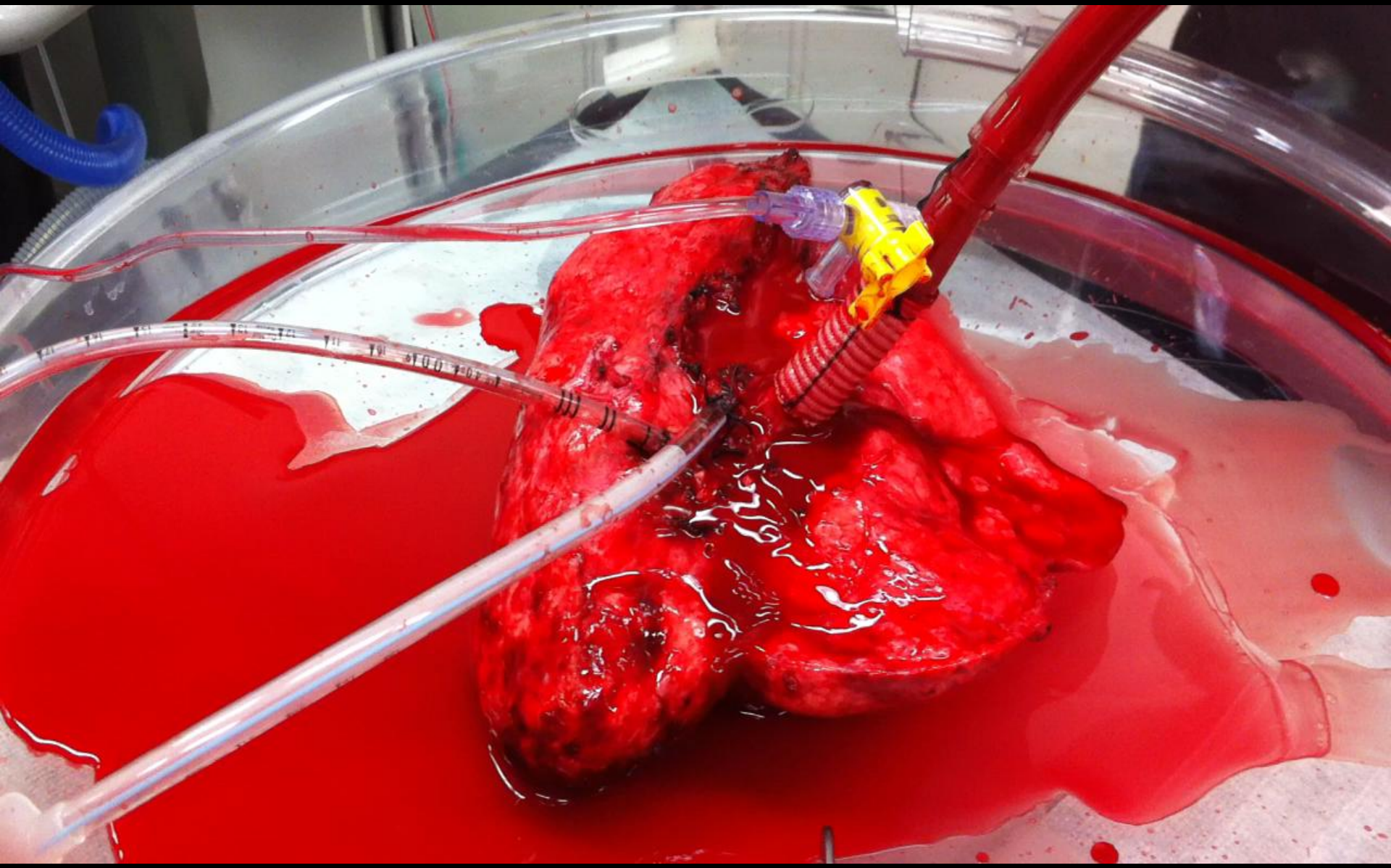
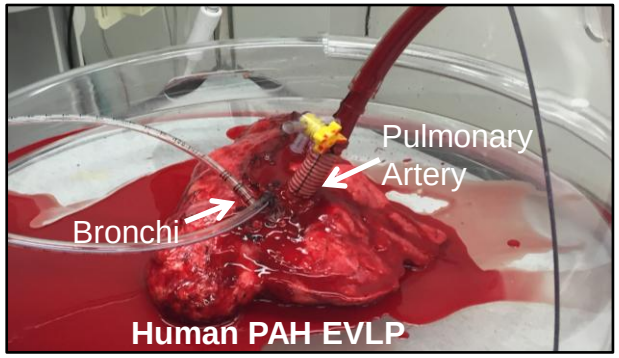
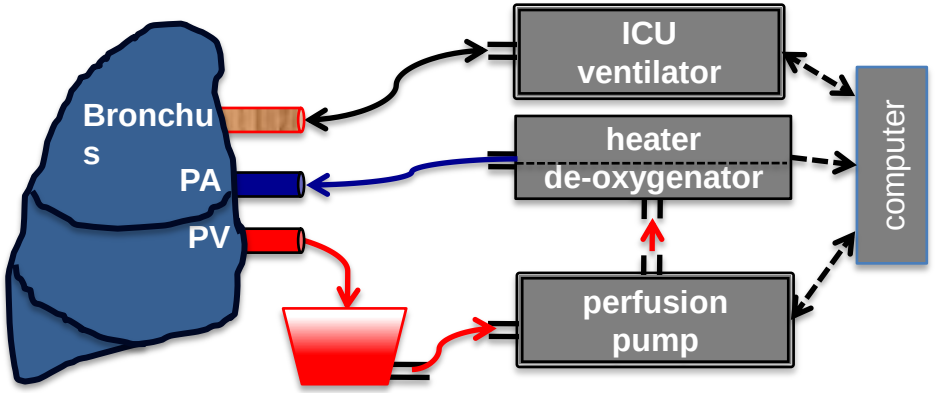


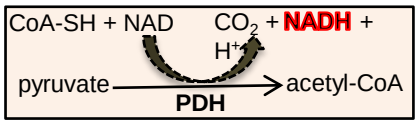
Fig. 2

A

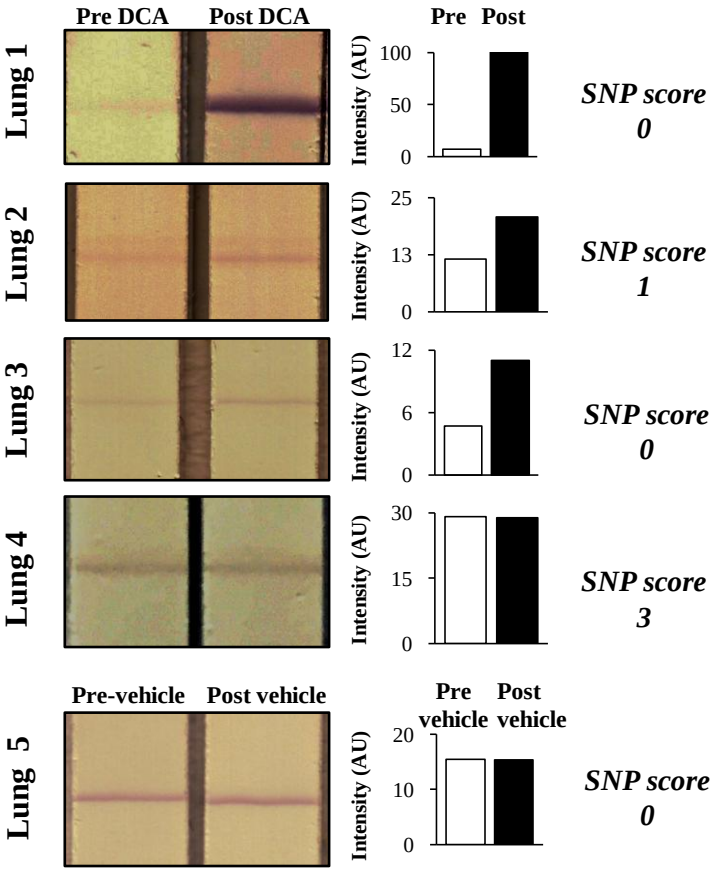




B

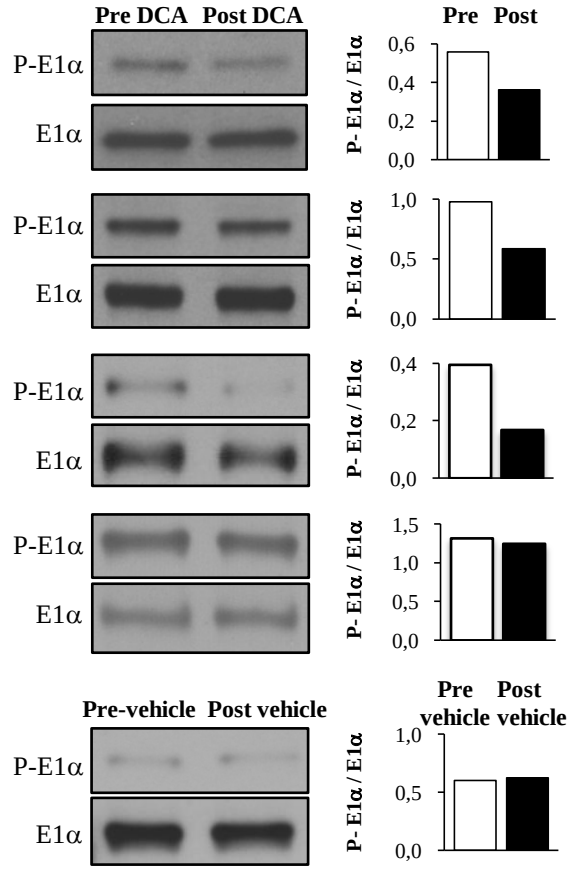


PDH Activity (dipstick assay)



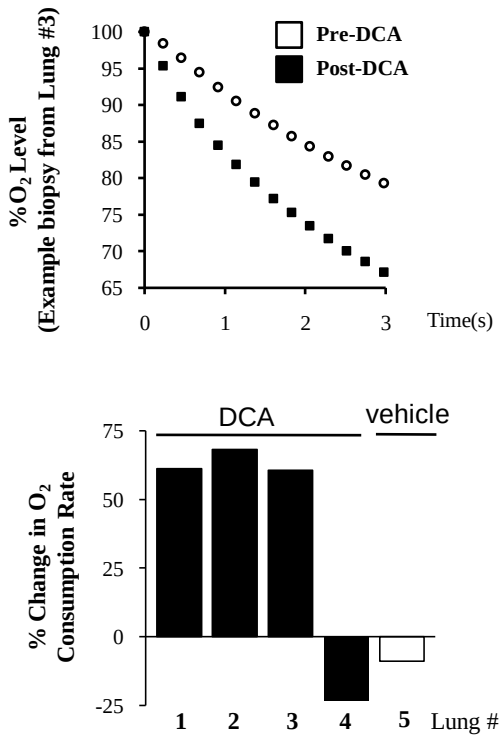
C

PDH Activity (phosphorylation immunoblot)



D

Lung Respiration (Seahorse)



Cover story: Progress for PAH

Metabolic modulation with dichloroacetate improves hemodynamics in genetically susceptible patients with idiopathic pulmonary arterial hypertension

E. Michelakis/University of Alberta

Contents

25 OCTOBER 2017
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RESEARCH ARTICLES

Inhibition of pyruvate dehydrogenase kinase improves pulmonary arterial hypertension in genetically susceptible patients

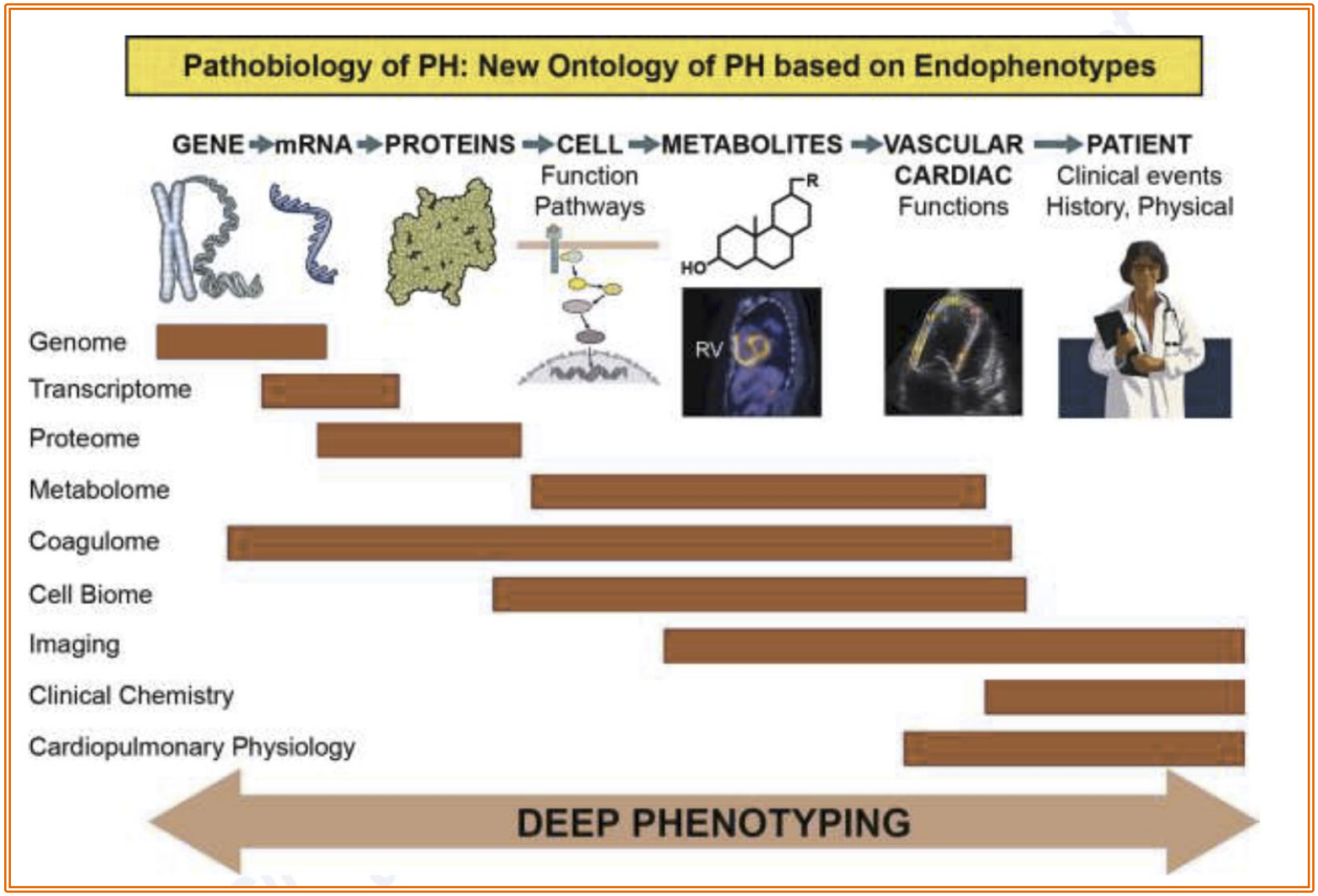
BY EVANGELOS D. MICHELAKIS, VIKRAM GURTU, LINDA WEBSTER, GARETH BARNES, GEOFFREY WATSON, LUKE HOWARD, JOHN CUPITT, IAN PATERSON, RICHARD B. THOMPSON, KELVIN CHOW, DECLAN P. O'REGAN, LAN ZHAO, JOHN WHARTON, DAVID G. KIELY, ADAM KINNAIRD, ARISTEIDIS E. BOUKOURIS, CHRIS WHITE, JAYAN NAGENDRAN, DARREN H. FREED, STEPHEN J. WORT, J. SIMON R. GIBBS, MARTIN R. WILKINS
SCIENCE TRANSLATIONAL MEDICINE | 25 OCT 2017 |

Metabolic modulation with dichloroacetate improves hemodynamics in genetically susceptible patients with idiopathic pulmonary arterial hypertension.

Challenging the WHO classification: The PVDOMICS initiative

n = 1000 PHT, 400 PHT-at-risk, 100 healthy

Cleveland Clinic, Brigham-Women's, Columbia/Cornell,
Johns Hopkins, Mayo Clinic, U of Arizona, Vanderbilt



Personal Omics Profiling Reveals Dynamic Molecular and Medical Phenotypes

Rui Chen,[1,11] George I. Mias,[1,11] Jennifer Li-Pook-Than,[1,11] Lihua Jiang,[1,11] Hugo Y.K. Lam,[1,12] Rong Chen,[2,12] Elana Miriami,[1] Konrad J. Karczewski,[1] Manoj Hariharan,[1] Frederick E. Dewey,[3] Yong Cheng,[1] Michael J. Clark,[1] Hogune Im,[1] Lukas Habegger,[6,7] Suganthi Balasubramanian,[6,7] Maeve O'Huallachain,[1] Joel T. Dudley,[2] Sara Hillenmeyer,[1] Rajini Haraksingh,[1] Donald Sharon,[1] Ghia Euskirchen,[1] Phil Lacroute,[1] Keith Bettinger,[1] Alan P. Boyle,[1] Maya Kasowski,[1] Fabian Grubert,[1] Scott Seki,[2] Marco Garcia,[2] Michelle Whirl-Carrillo,[1] Mercedes Gallardo,[9,10] Maria A. Blasco,[9] Peter L. Greenberg,[4] Phyllis Snyder,[1] Teri E. Klein,[1] Russ B. Altman,[1,5] Atul J. Butte,[2] Euan A. Ashley,[3] Mark Gerstein,[6,7,8] Kari C. Nadeau,[2] Hua Tang,[1] and Michael Snyder[1,*]

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[3]Center for Inherited Cardiovascular Disease, Division of Cardiovascular Medicine

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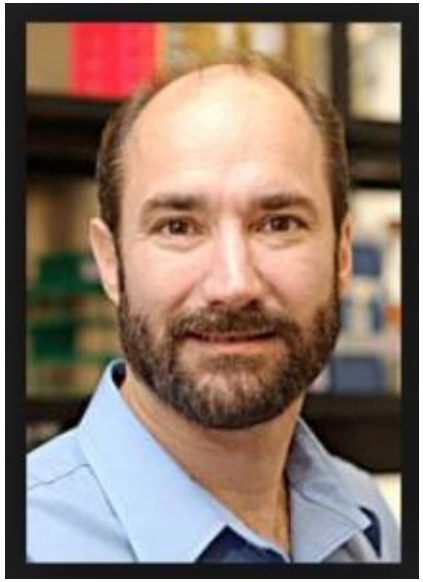
DOI 10.1016/j.c

Cell *148*, 1293–1307, March 16, 2012



Michael Snyder, PhD
Head, Medical Genetics, Stanford
A healthy and fit 54 year old male

- Studied 20 serial samples of his blood during a 14-month period and performed deep WGS, transcriptomic, proteomic and metabolomic analysis, developing the first "**integrative personal omics profile" (iPOP**).

- During the 14-month period he suffered two minor viral infections (with a rhinovirus and RSV).

- His team tracked ~20,000 transcripts coding 12,000 genes and measured more than 6,000 proteins and 1,000 metabolites in Snyder's blood.

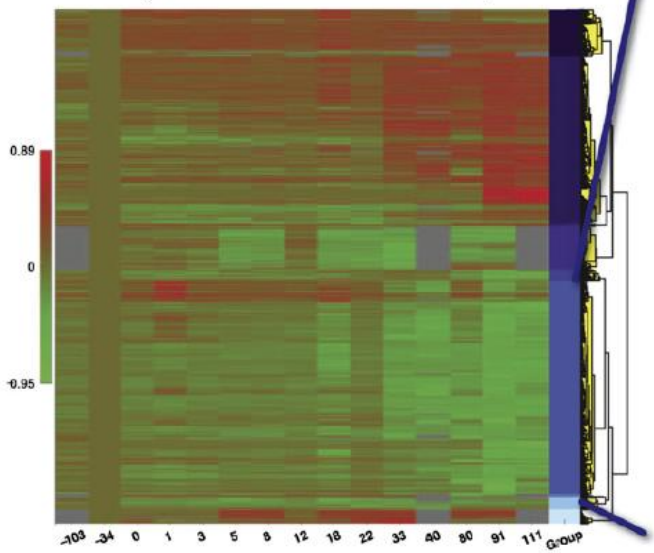
- They identified ~2,000 genes that were expressed at higher levels during the viral infections, and ~2,200 genes expressed at lower levels, including some involved in insulin signaling.

Integrated Omics clustering

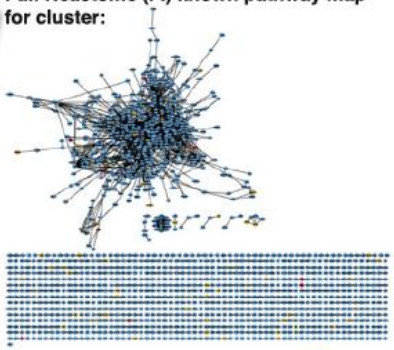
Transcriptome
Proteome
Metabolome

→ RSV Infection → Healthy: Integrated omics

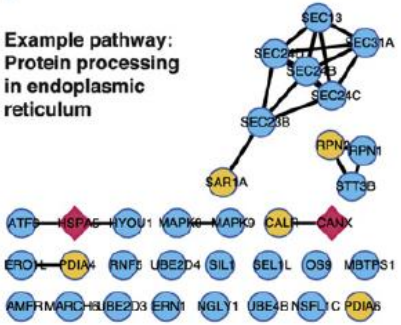
(I) Autocorrelated data clusters



Full Reactome (FI) known pathway map for cluster:

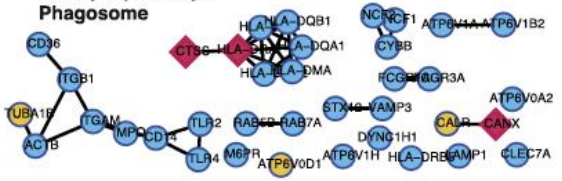


Example pathway: Protein processing in endoplasmic reticulum

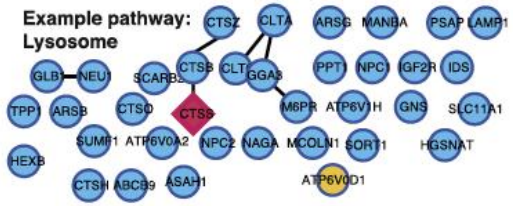


Dynamic expression pattern observed in:
RNA Protein Both RNA + Protein

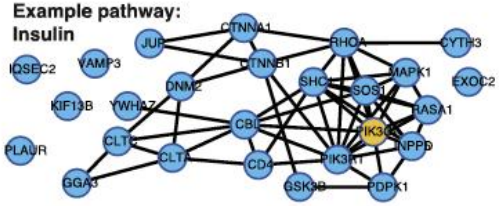
Example pathway: Phagosome



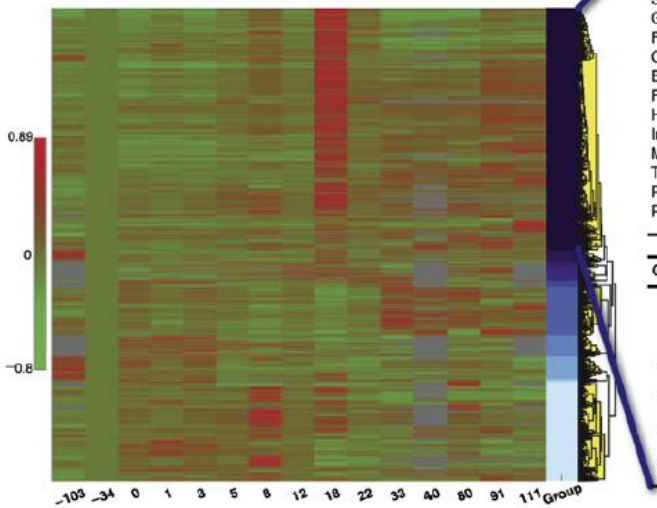
Example pathway: Lysosome



Example pathway: Insulin



(II) Spike maxima data clusters



Eg. Pathway Analysis Results - FDR < 5e-02:

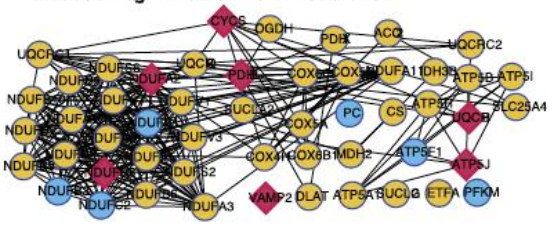
Spliceosome(K)
Glucose Regulation of Insulin Secretion(R)
Formation and Maturation of mRNA Transcript(R)
Oxidative phosphorylation(K)
Electron Transport Chain(R)
Parkinson's disease(K)
Huntington's disease(K)
Influenza Life Cycle(R)
Metabolism of non-coding RNA(R)
Transport of Mature Transcript to Cytoplasm(R)
Protein export(K)
Pyruvate metabolism and TCA cycle(R)

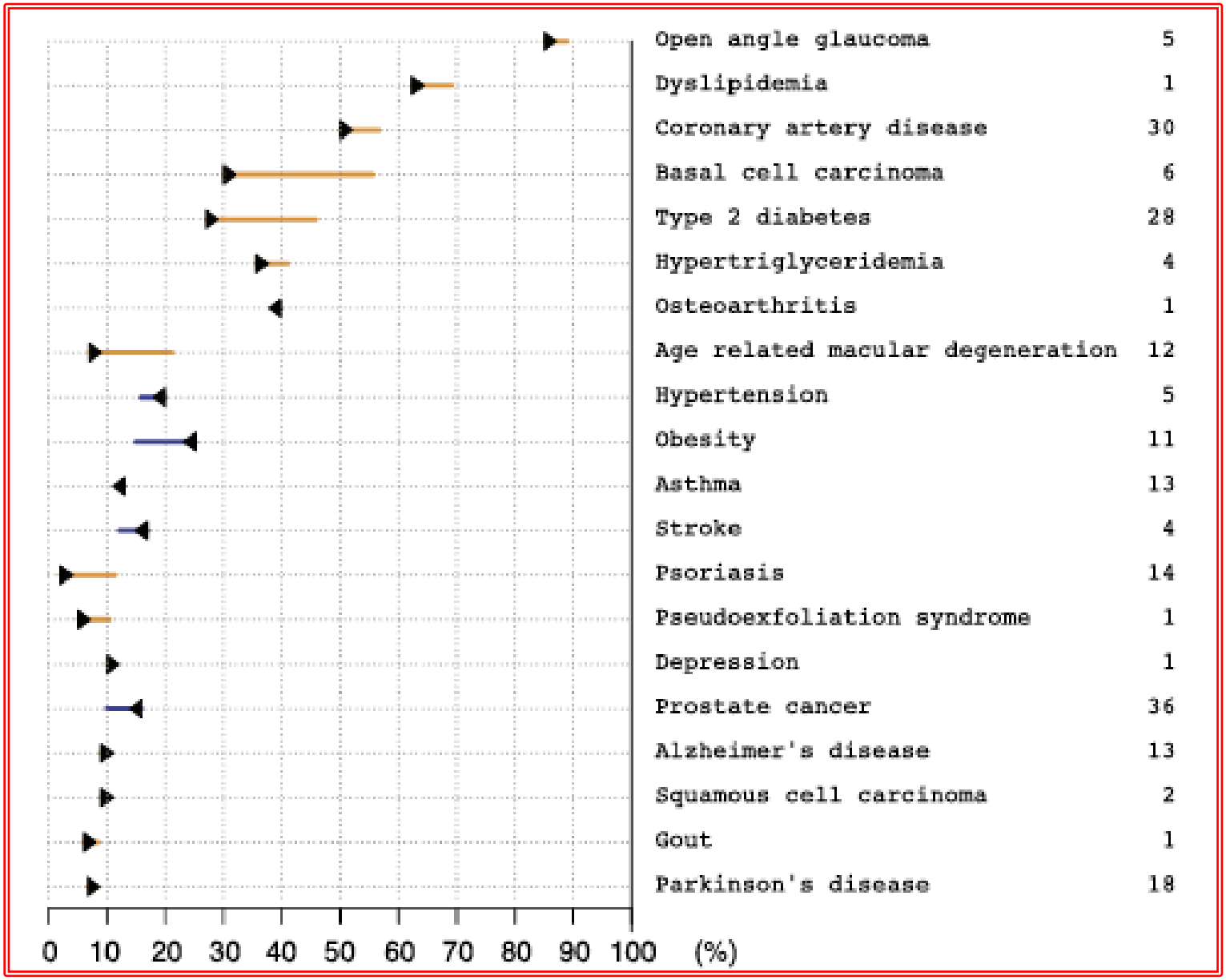
GO-ID	corr p-value	Description
8380	3.59E-71	RNA splicing
6396	2.53E-57	RNA processing
16070	5.93E-54	RNA metabolic process
16071	6.10E-50	mRNA metabolic process
10467	1.74E-48	gene expression
90304	1.78E-45	nucleic acid metabolic process

Eg. Metabolites in Cluster

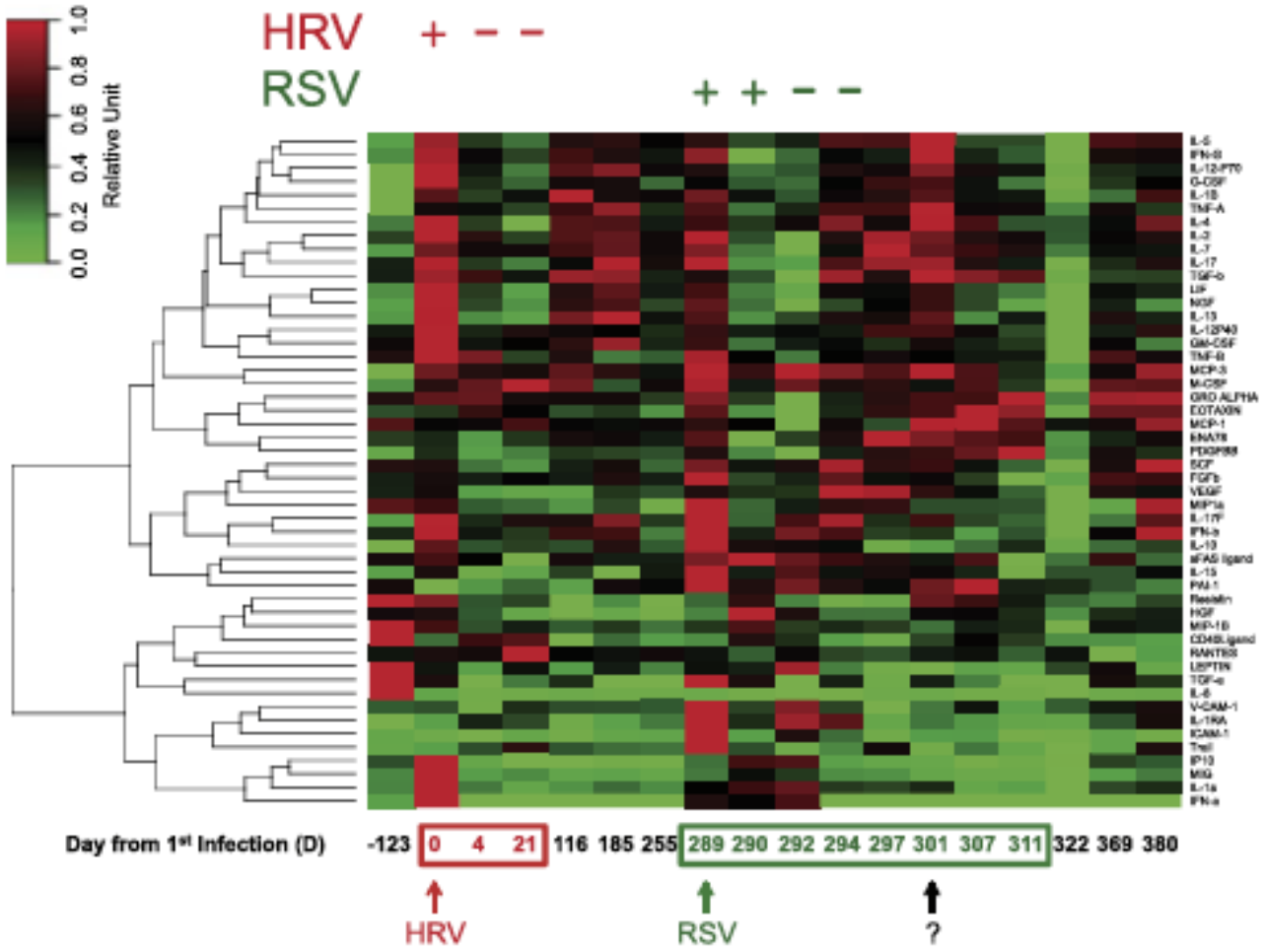
3R-hydroxy-5Z-dodecenoic acid
5,6-DiHETrE-EA
7-Ethoxycoumarin
Lauric acid
1-O-(1Z-tetradecenyl)-2-(9Z-octadecenoyl)-sn-glycerol
(23R)-1alpha,23,25-trihydroxy-24-oxovitamin D3 / (23R)-1alpha,23,25-trihydroxy-24-oxocholecalciferol
1alpha-hydroxy-26,27-dinorvitamin D3 25-carboxylic acid / 1alpha-hydroxy-26,27-dinorcholecalciferol
12-oxo-9-octadecynoic acid
GPCho(O-16:0/O-4:0[U])
19-hydroxy-17-oxoandrost-5-en-3-beta-yl sulfate - 11.538899

Example Pathway: Glucose Regulation of Insulin Secretion

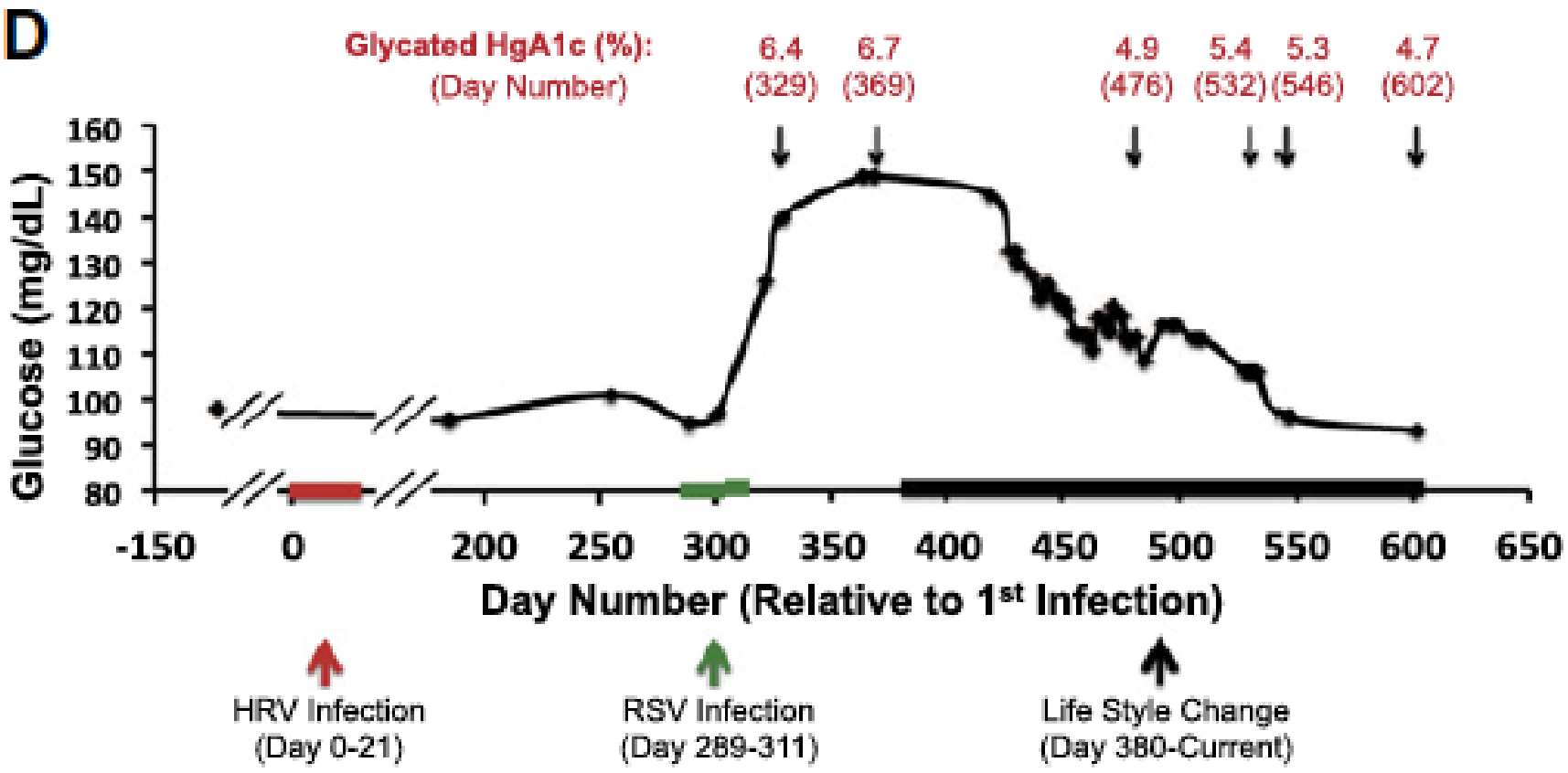



Open angle glaucoma 5
Dyslipidemia 1
Coronary artery disease 30
Basal cell carcinoma 6
Type 2 diabetes 28
Hypertriglyceridemia 4
Osteoarthritis 1
Age related macular degeneration 12
Hypertension 5
Obesity 11
Asthma 13
Stroke 4
Psoriasis 14
Pseudoexfoliation syndrome 1
Depression 1
Prostate cancer 36
Alzheimer's disease 13
Squamous cell carcinoma 2
Gout 1
Parkinson's disease 18
0 10 20 30 40 50 60 70 80 90 100 (%)

"Day-to-day variability in Snyder's genomics profile



- Another striking finding was that extensive heteroallelic changes occurred during healthy and diseased states (the two alleles in each gene behaved differently) and unexpected dynamic RNA editing mechanisms were discovered.


D
Glycated HgA1c (%):
(Day Number)
6.4 (329)
6.7 (369)
4.9 (476)
5.4 (532)
5.3 (546)
4.7 (602)
Glucose (mg/dL)
160
150
140
130
120
110
100
90
80
-150
0
200
250
300
350
400
450
500
550
600
650
Day Number (Relative to 1st Infection)
HRV Infection
(Day 0-21)
RSV Infection
(Day 289-311)
Life Style Change
(Day 380-Current)