The metabolic basis of PAH *and cancer*

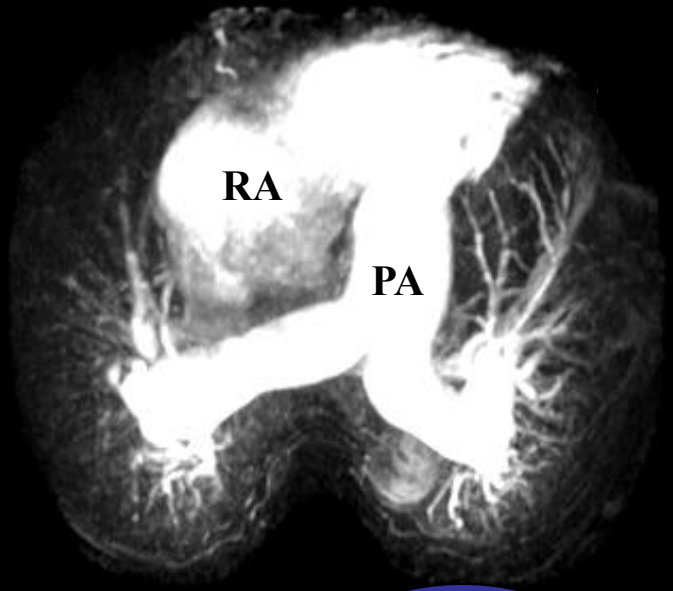
Evangelos D. Michelakis, MD, FACC, FAHA

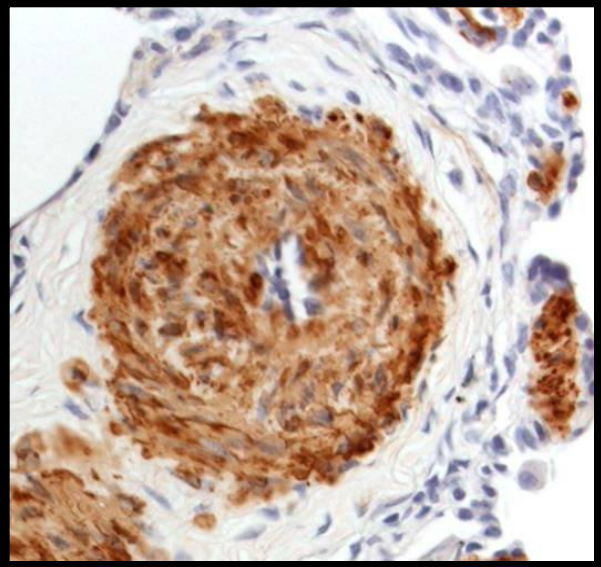
Pulmonary Hypertension Program
University of Alberta

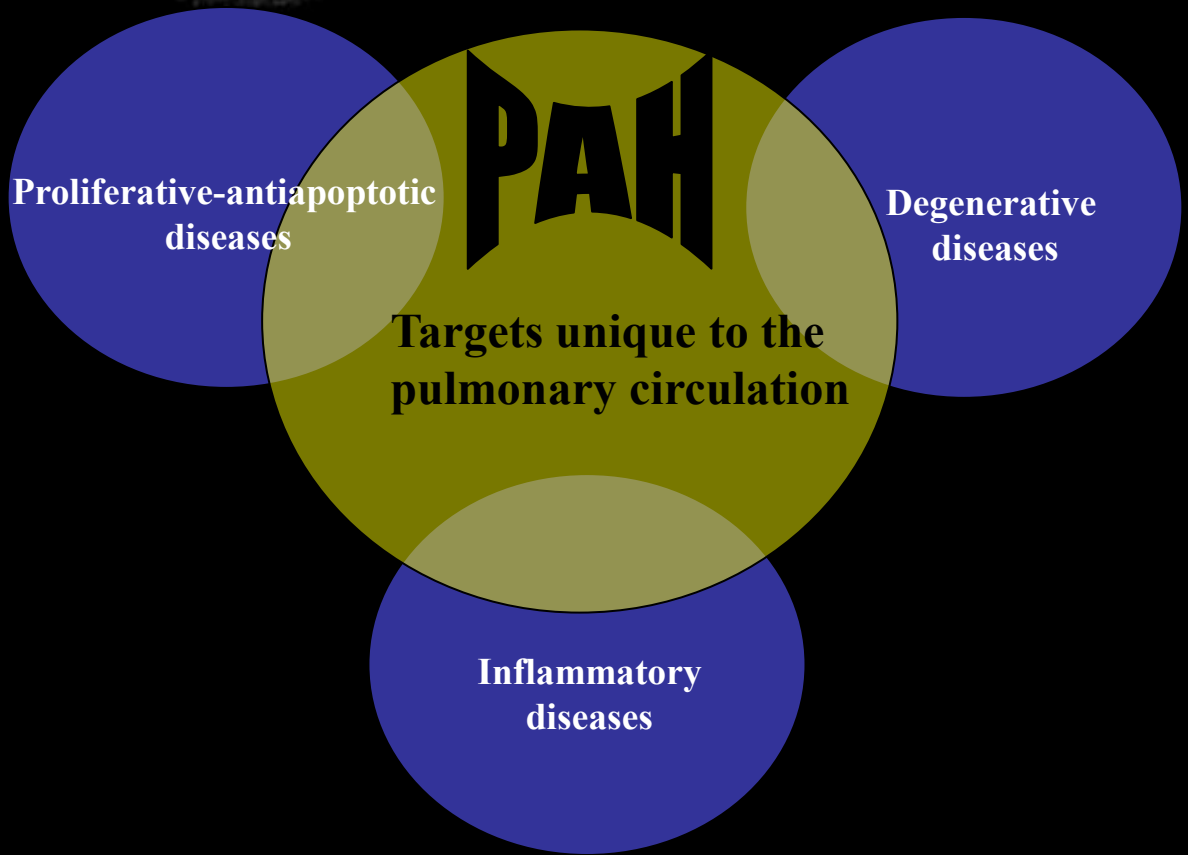
Take a walk in Academia…

Aristotle, a faculty member in Plato's Academy, used to lecture while walking, and founded the Peripatetic School of Philosophy

Peripatos = stroll, walk


RA
PA



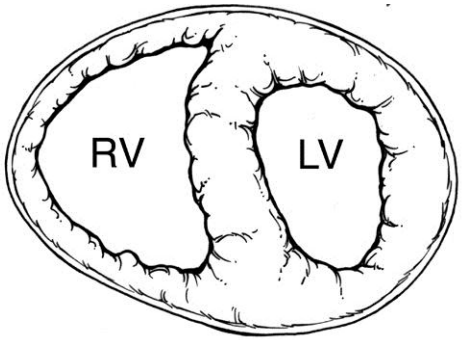

PAH
Proliferative-antiapoptotic diseases
Degenerative diseases
Inflammatory diseases
Targets unique to the pulmonary circulation

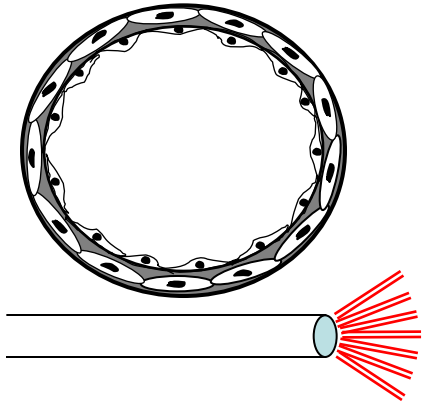
Circulation, 2009

Right Ventricle

Pulmonary Arteries

Normal

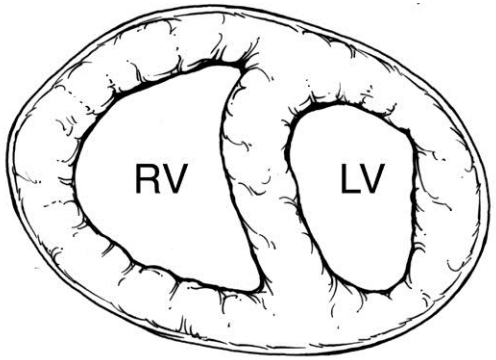


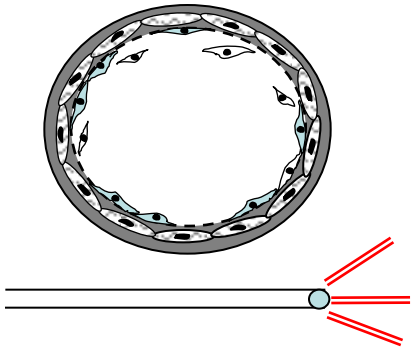


Thin RV
Healthy PA endothelium
Thin walled-relaxed PAs
Large capillary network

Normal CO
Normal PVR
Normal perfusion

Compensation

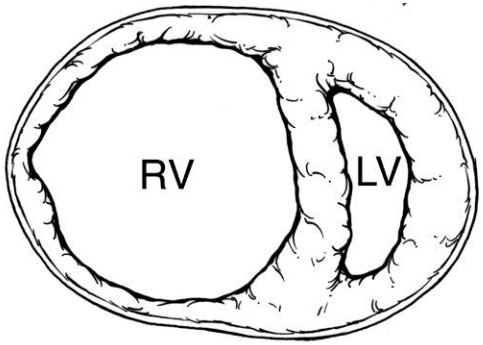


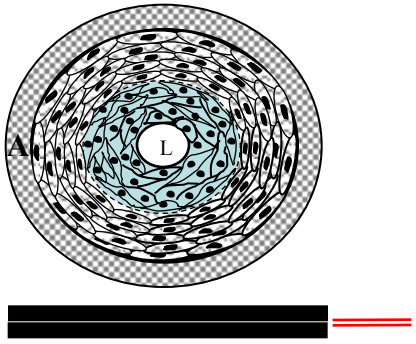


Hypertrophied RV
Abnormal PA endothelium
Constricted-stiff PAs
Loss of microvessels

Normal CO
Mild increase in PVR
Moderate decrease in perfusion

Failure

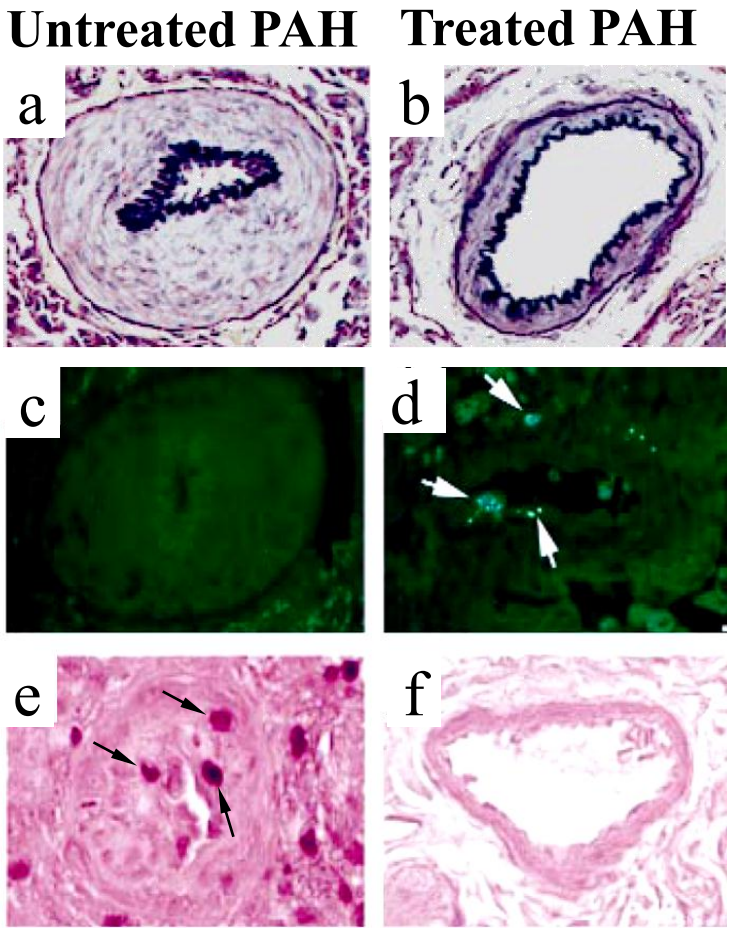




Dilated RV
Cell proliferation in the PA wall
Obliterative PA remodeling

Severe decrease in CO
Severe increase in PVR
Severe decrease in perfusion

Michelakis et al, Circulation, 2008

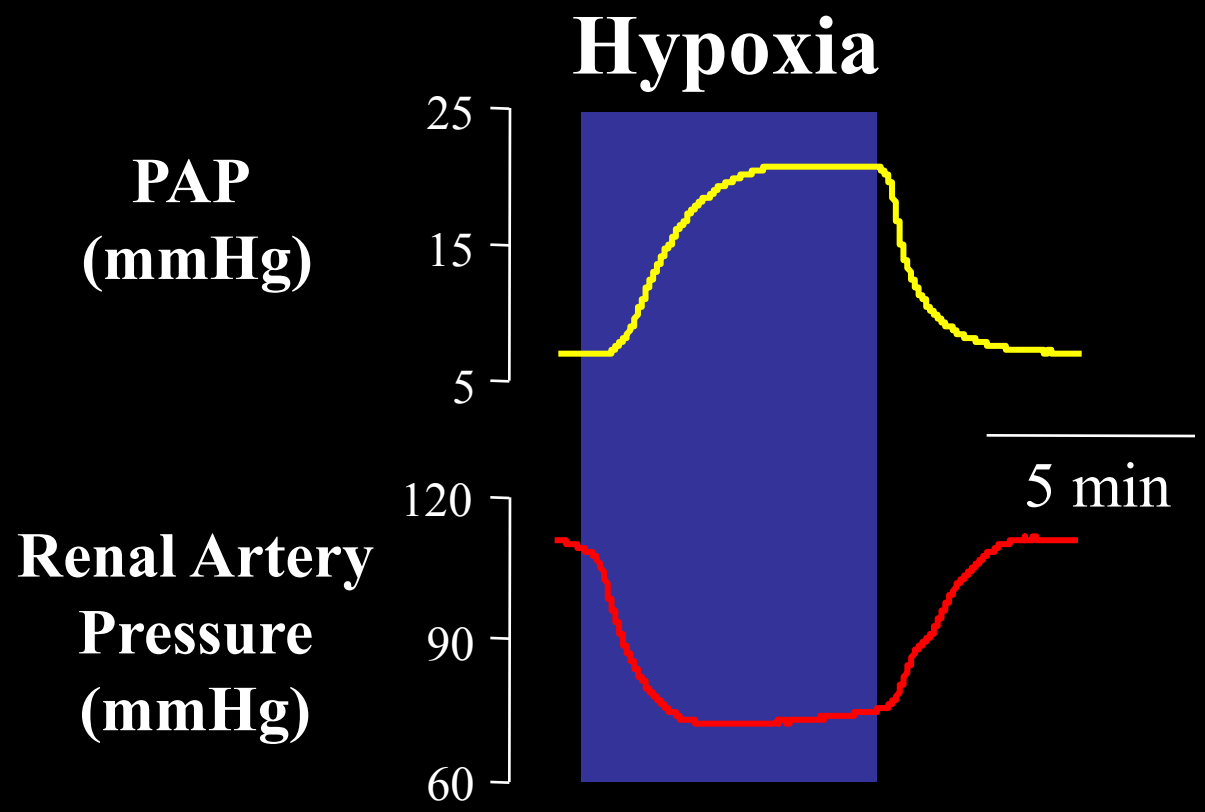


↑ **Apoptosis**
(measured by TUNEL)

↓ **Proliferation**
(measured by PCNA)

PASMC pro-apoptotic therapies

- Elastase inhibitors
- EGF receptor inhibitors
- Dichloroacetate
- Simvastatin
- Anti-survivin
- Imatinib
- Sildenafil
- Cyclosporine



The opposing effects of hypoxia in the PA vs RA are in part due to differences in the O_2 sensor, i.e. the SMC mitochondria

E. Michelakis et al, CircRes, 2002

PAH: a state of insulin resistance?

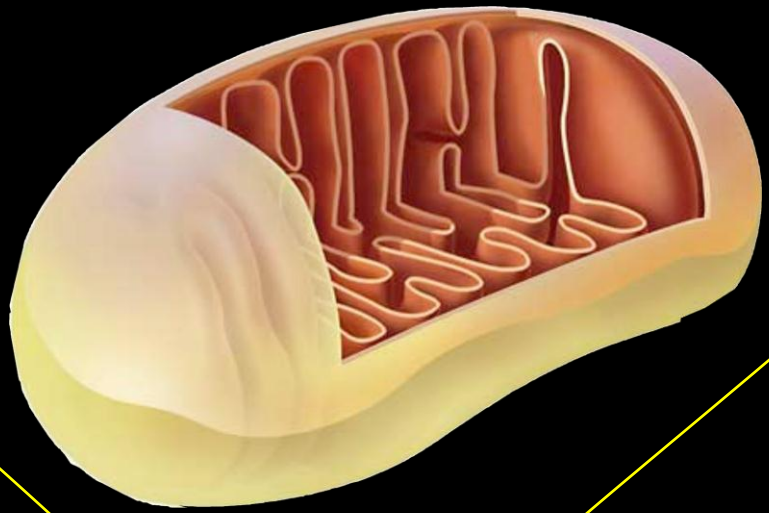
1. Pulmonary arterial hypertension is linked to insulin resistance and reversed by peroxisome proliferator-activated receptor-gamma activation. Hansmann et al, Circulation, 2007

2. An antiproliferative BMP-2/PPARgamma/apoE axis in human and murine SMCs and its role in pulmonary hypertension Hansmann et al, JCI, 2008

- Mice with SMC targeted deletion of PPARγ develop PAH
- PPARγ agonists (rosiglitazone, pioglitazone) can reverse PAH by activating pro-apoptotic and supressing pro-proliferative genes

Sense

(supply of O_2 and demand for fuel)



execute

Can match fuel generation (ATP) with demand

LIVE

Cannot match fuel generation (ATP) with demand

DIE

- Is not he who can best strike a blow in a boxing match or any kind of fighting, best able to ward off a blow?
- Certainly
- And he who is most skilled in preventing or escaping from a disease is best able to create one?
- True
- And is he the best guard of a camp who is best able to steal a march upon the enemy?
- Certainly
- Then he who is a good keeper of everything is also a good thief?
- That I suppose is to be inferred
- Then if the just man is good at keeping money he is good at stealing it
-That is implied in the argument

Socrates and Polemarchus:

- Is not he who can best strike a blow in a boxing match or any kind of fighting, best able to ward off a blow?
- Certainly
- And he who is most skilled in preventing or escaping from a disease is best able to create one?
- True
- And is he the best guard of a camp who is best able to steal a march upon the enemy?
- Certainly
- Then he who is a good keeper of everything is also a good thief?
- That I suppose is to be inferred
- Then if the just man is good at keeping money he is good at stealing it
- That is implied in the argument

The Republic, Plato

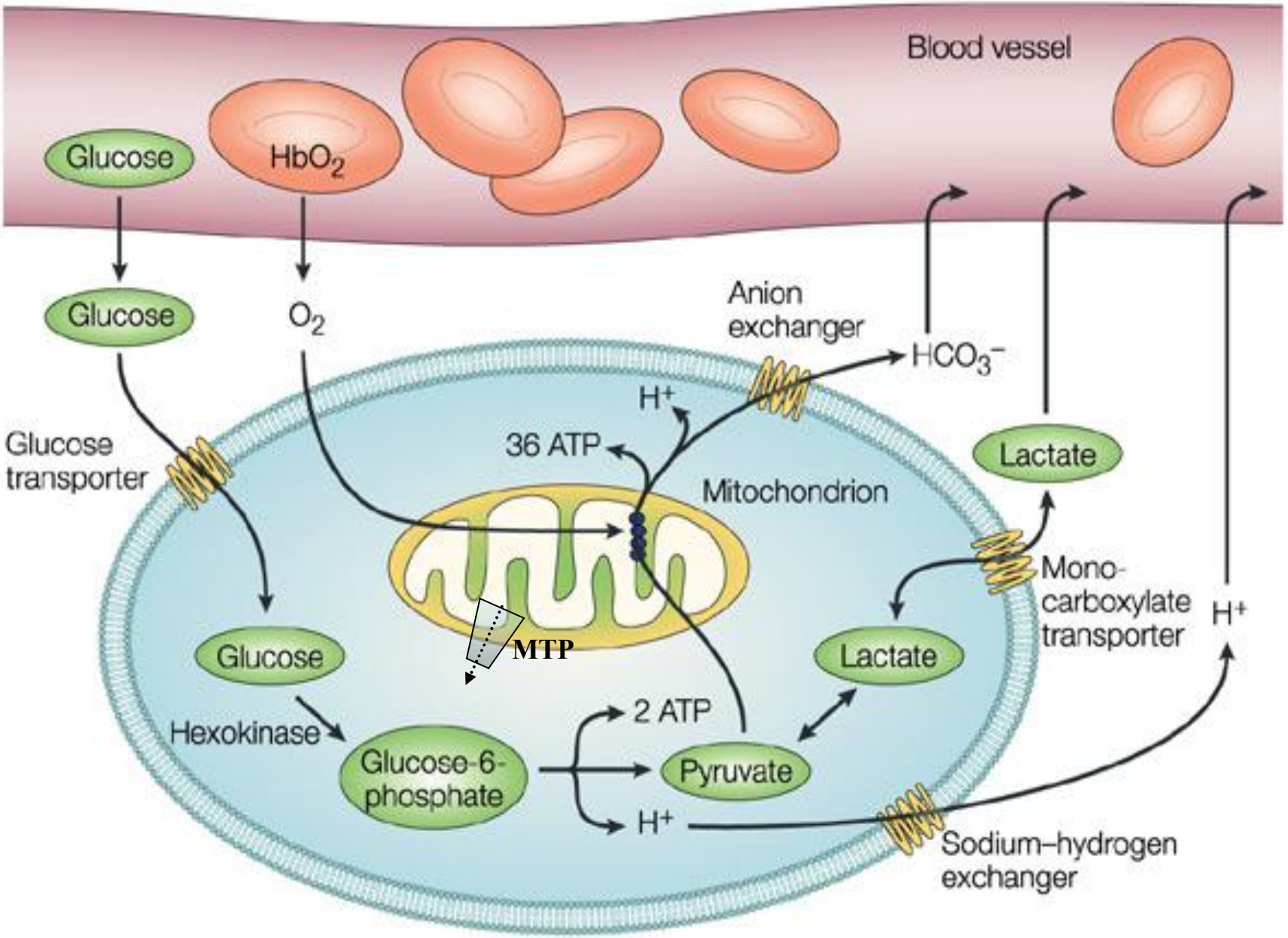
Otto Warburg

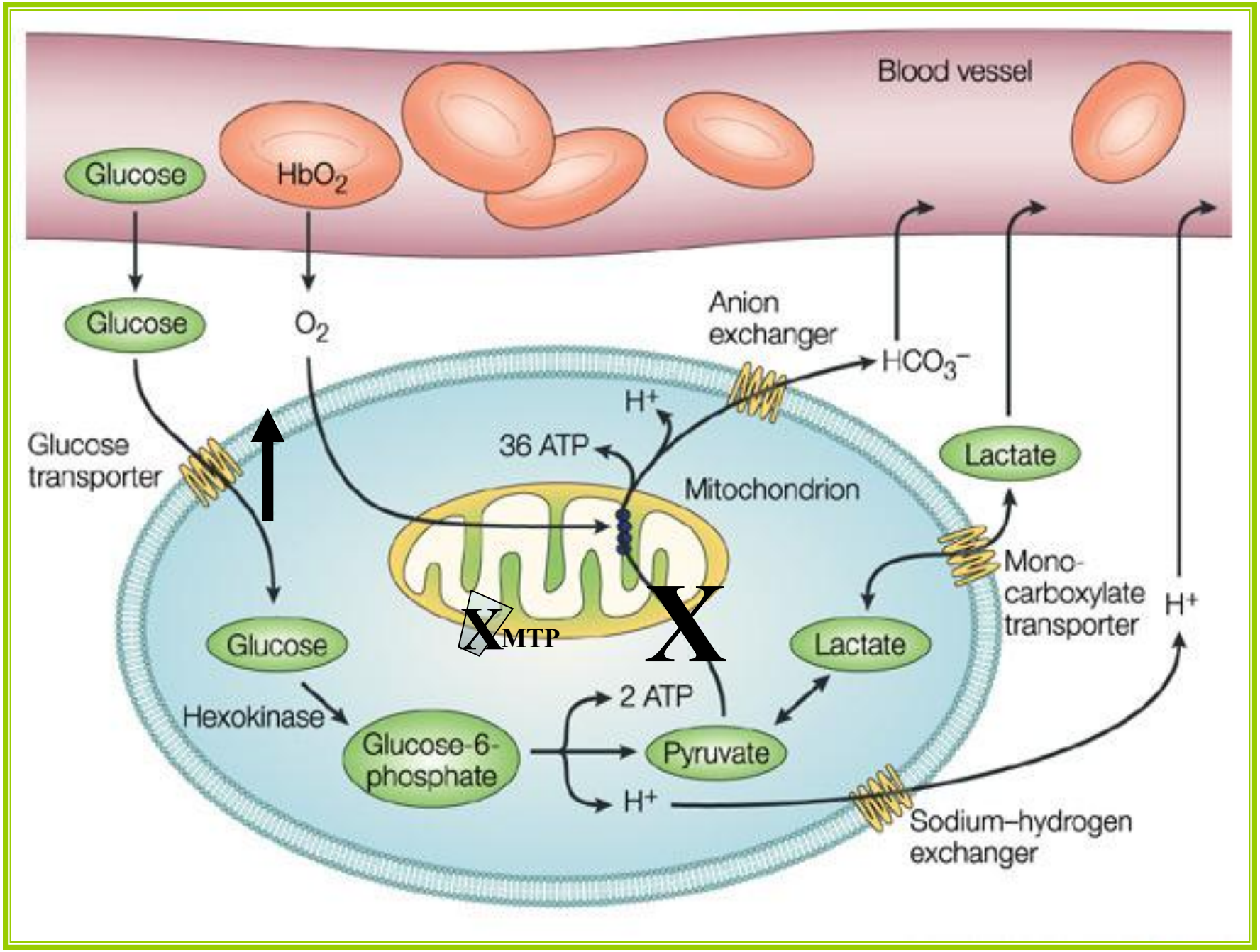
Born October 8 1883, Freiburg
MD in1911, Heidelberg

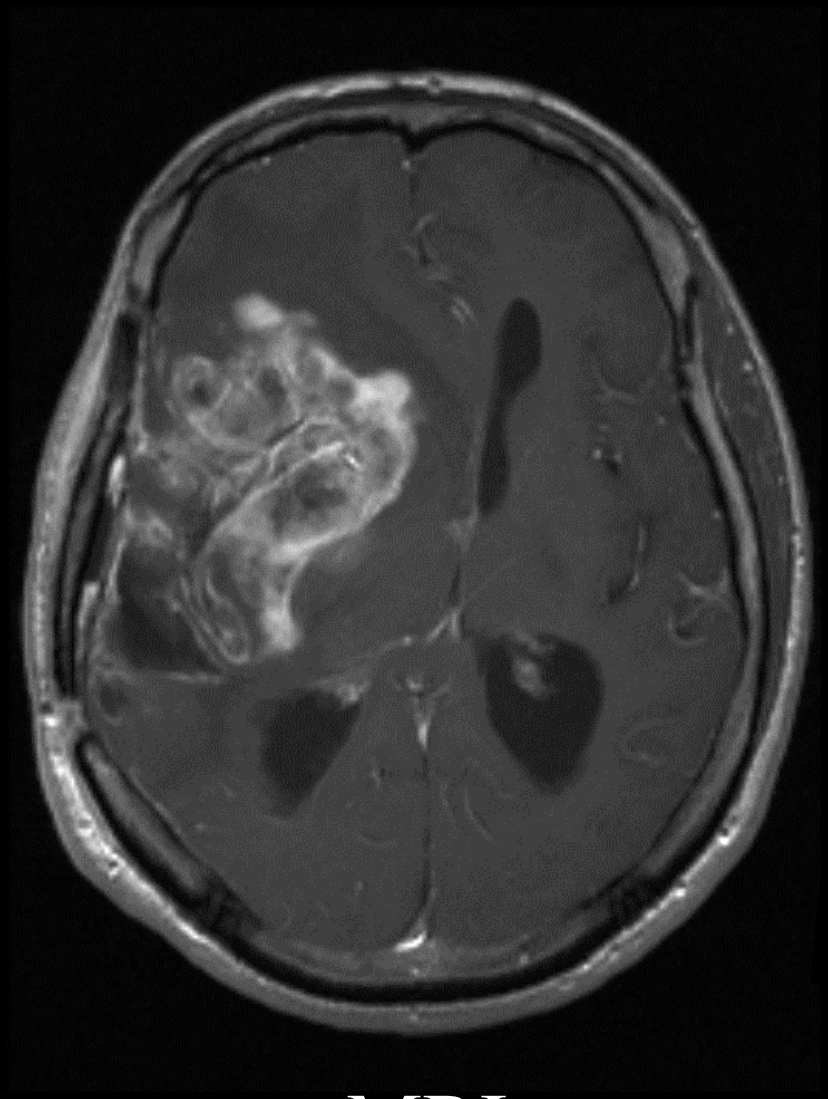
Nobel Prize 1931
" *For his discovery of the nature and mode of action of the respiratory enzyme*"

Stoffwechsel der Tumoren, 1926

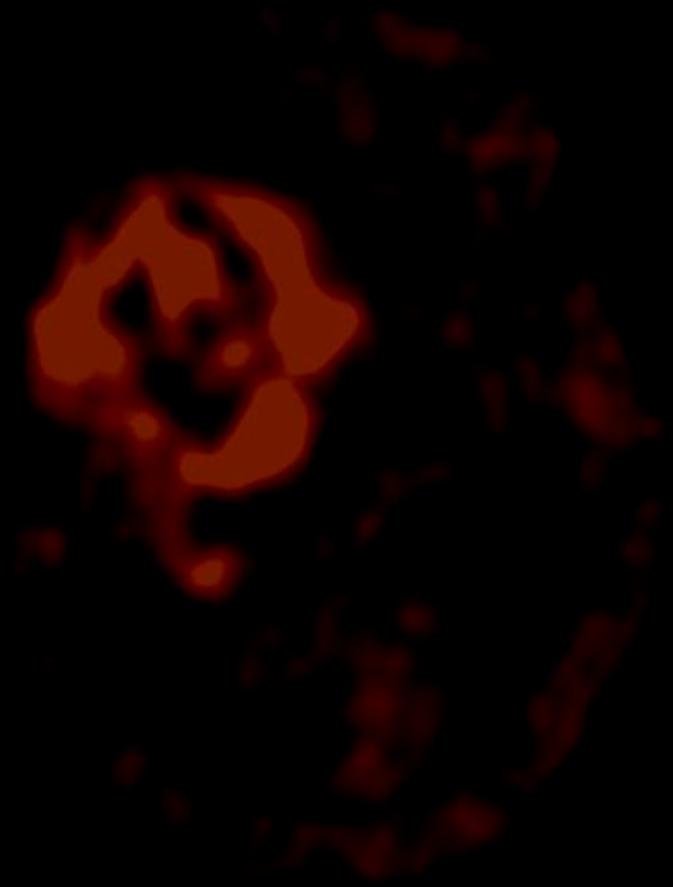
The Warburg effect:
"Cancer is caused by abnormal metabolism of the cells: due to abnormal mitochondria the cancer cells use glycolysis, and not oxidative phosphorylation for energy production, even in the absence of hypoxia".


Blood vessel
Glucose
HbO_2
Glucose
O_2
Anion exchanger
HCO_3^-
H^+
36 ATP
Mitochondrion
Glucose transporter
Lactate
Mono-carboxylate transporter
H^+
MTP
Glucose
Lactate
Hexokinase
2 ATP
Glucose-6-phosphate
Pyruvate
H^+
Sodium–hydrogen exchanger

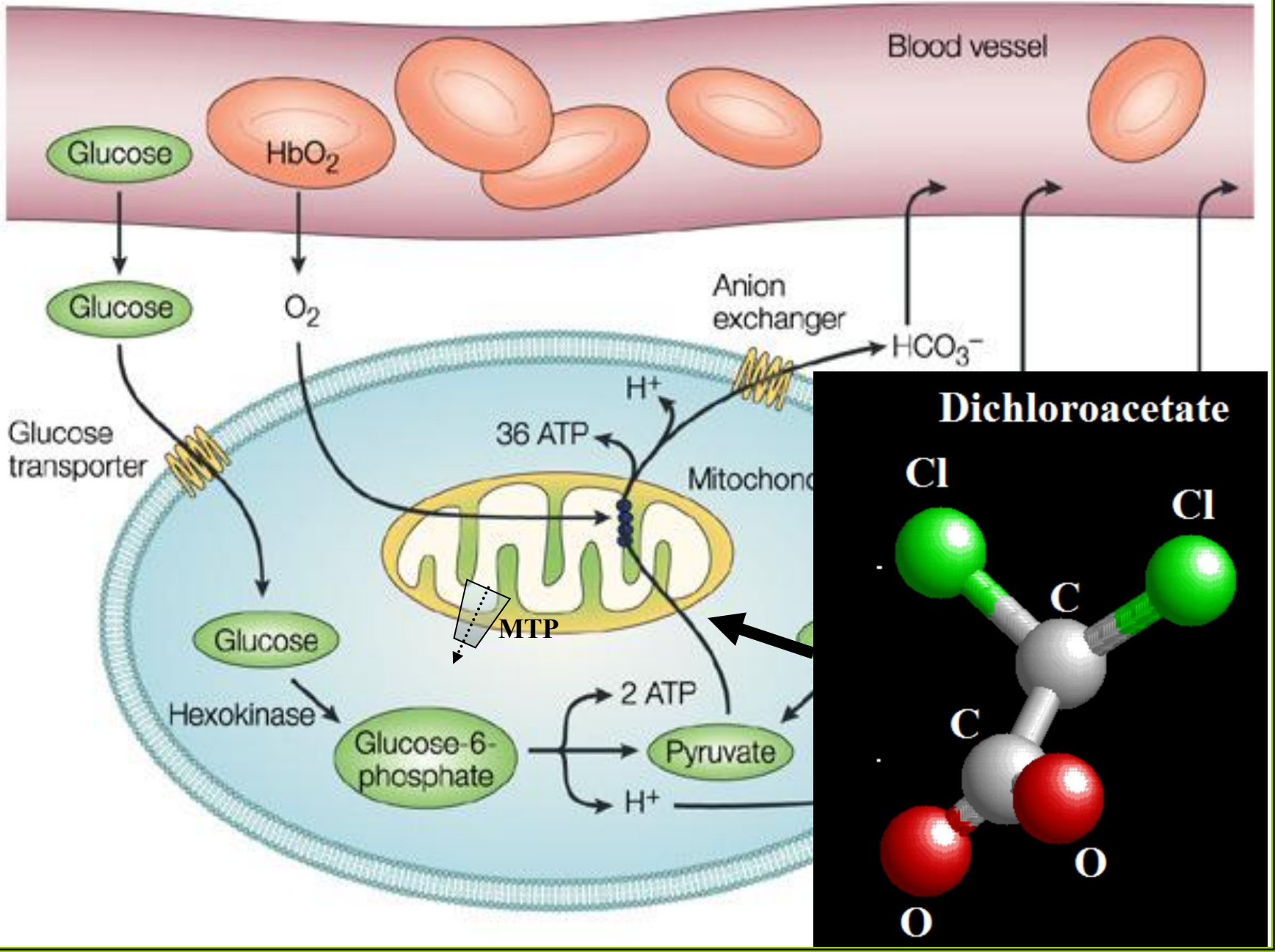

Blood vessel
Glucose
HbO_2
Glucose
O_2
Anion exchanger
HCO_3^-
H^+
36 ATP
Glucose transporter
Mitochondrion
Lactate
Mono-carboxylate transporter
H^+
X_{MTP}
X
Glucose
Lactate
Hexokinase
2 ATP
Glucose-6-phosphate
Pyruvate
H^+
Sodium–hydrogen exchanger



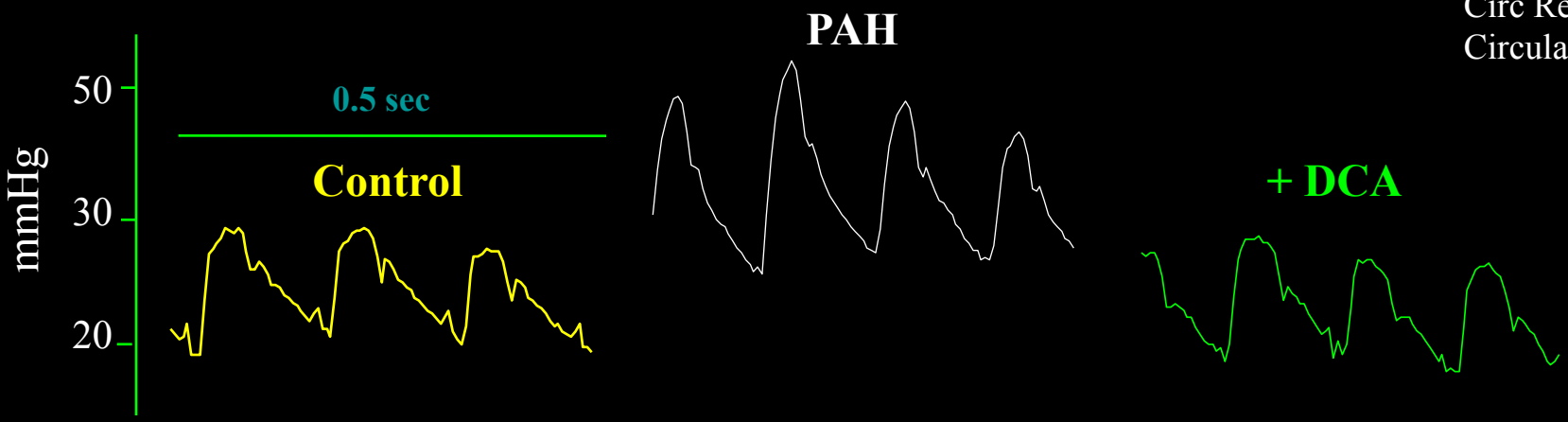
MRI



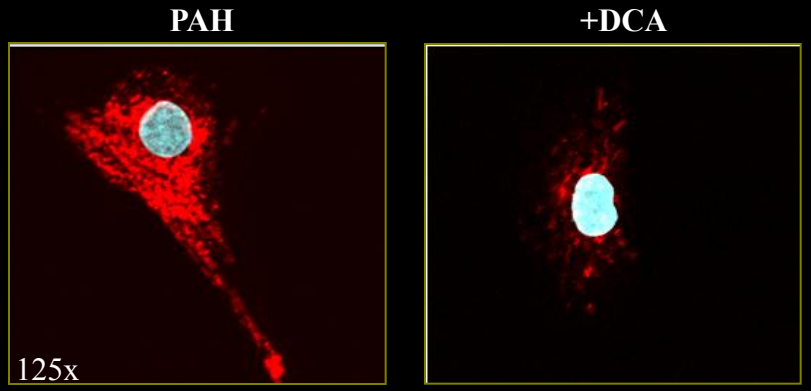
PET


Blood vessel
Glucose
HbO_2
Glucose
O_2
Anion exchanger
HCO_3^-
H^+
36 ATP
Glucose transporter
Mitochond
MTP
Glucose
Hexokinase
Glucose-6-phosphate
2 ATP
Pyruvate
H^+
Dichloroacetate
Cl
Cl
C
C
O
O

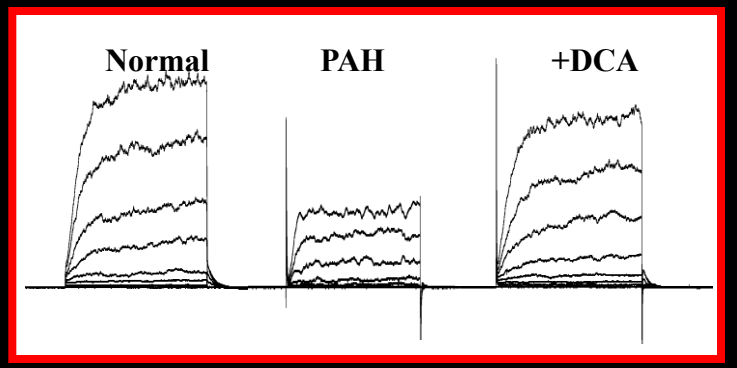
Circulation 2002
Circ Res 2004
Circulation 2006



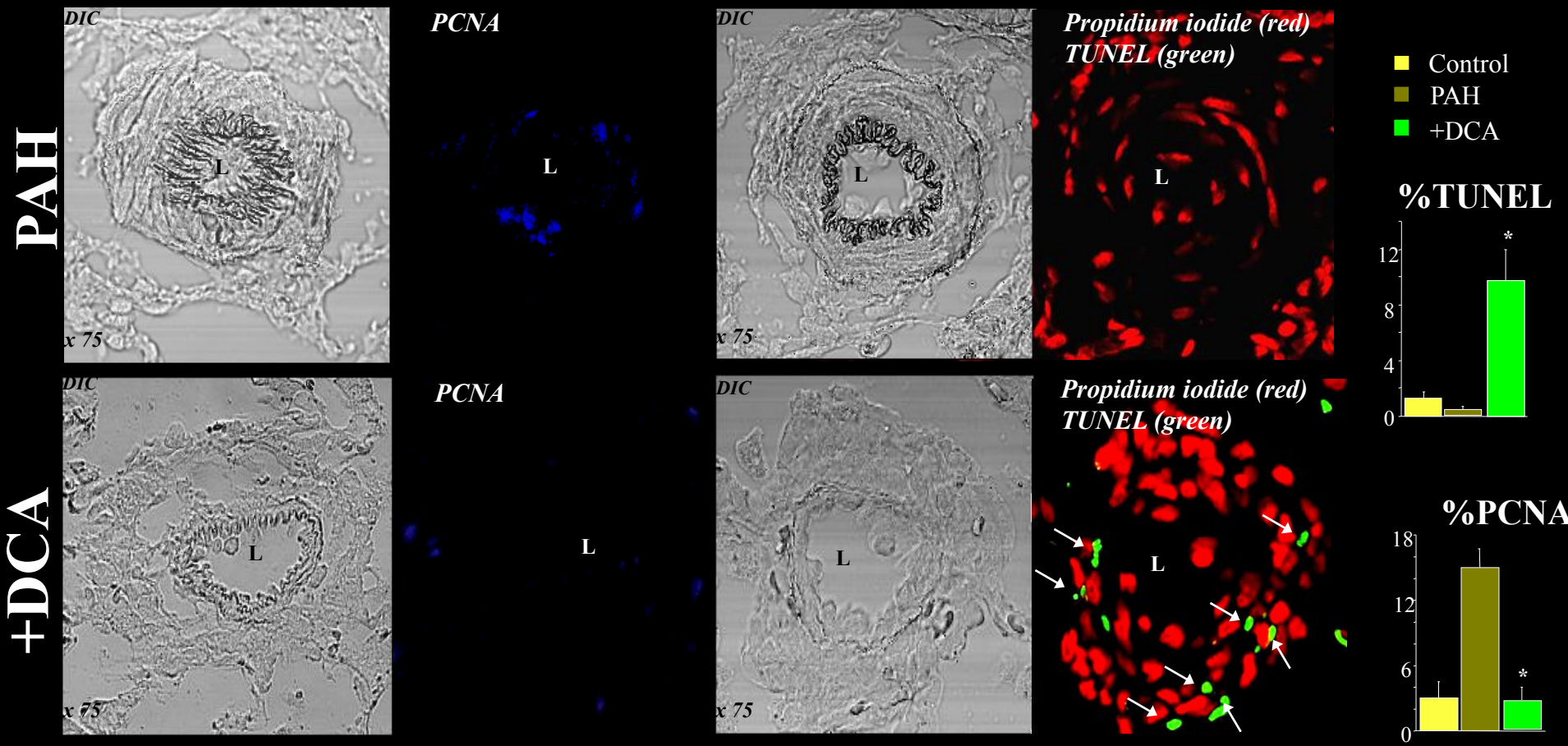
PASMC MITOCHONDRIA



PASMC K^+ CURRENT

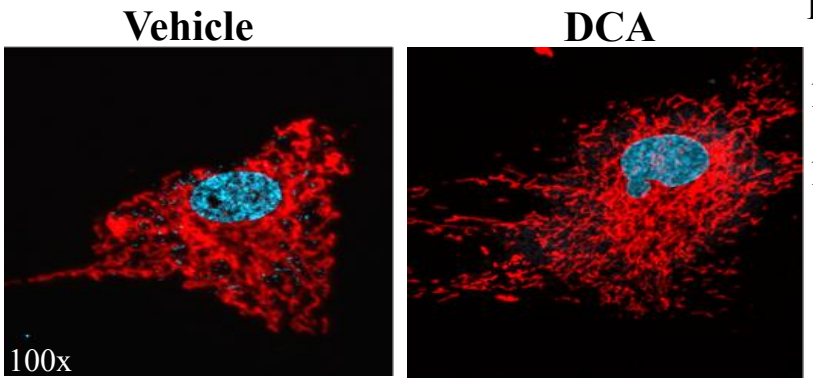


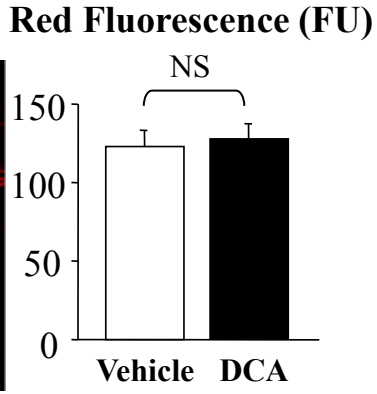
DCA therapy induces apoptosis in the PA wall and reverses vascular remodeling



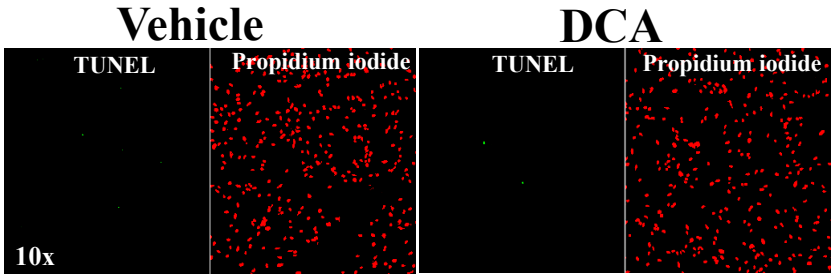
…without affecting normal cells and rats

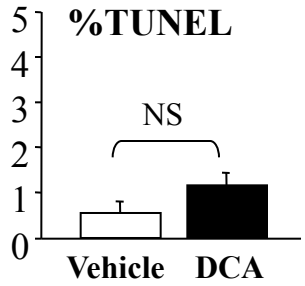
Normal PASMC ΔΨm



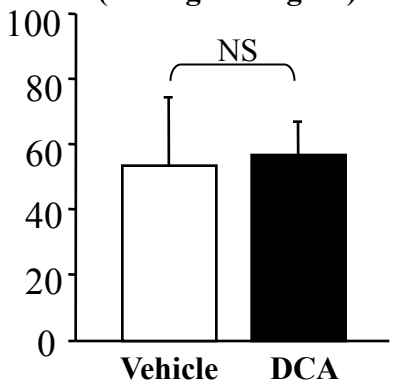


Normal PASMC TUNEL

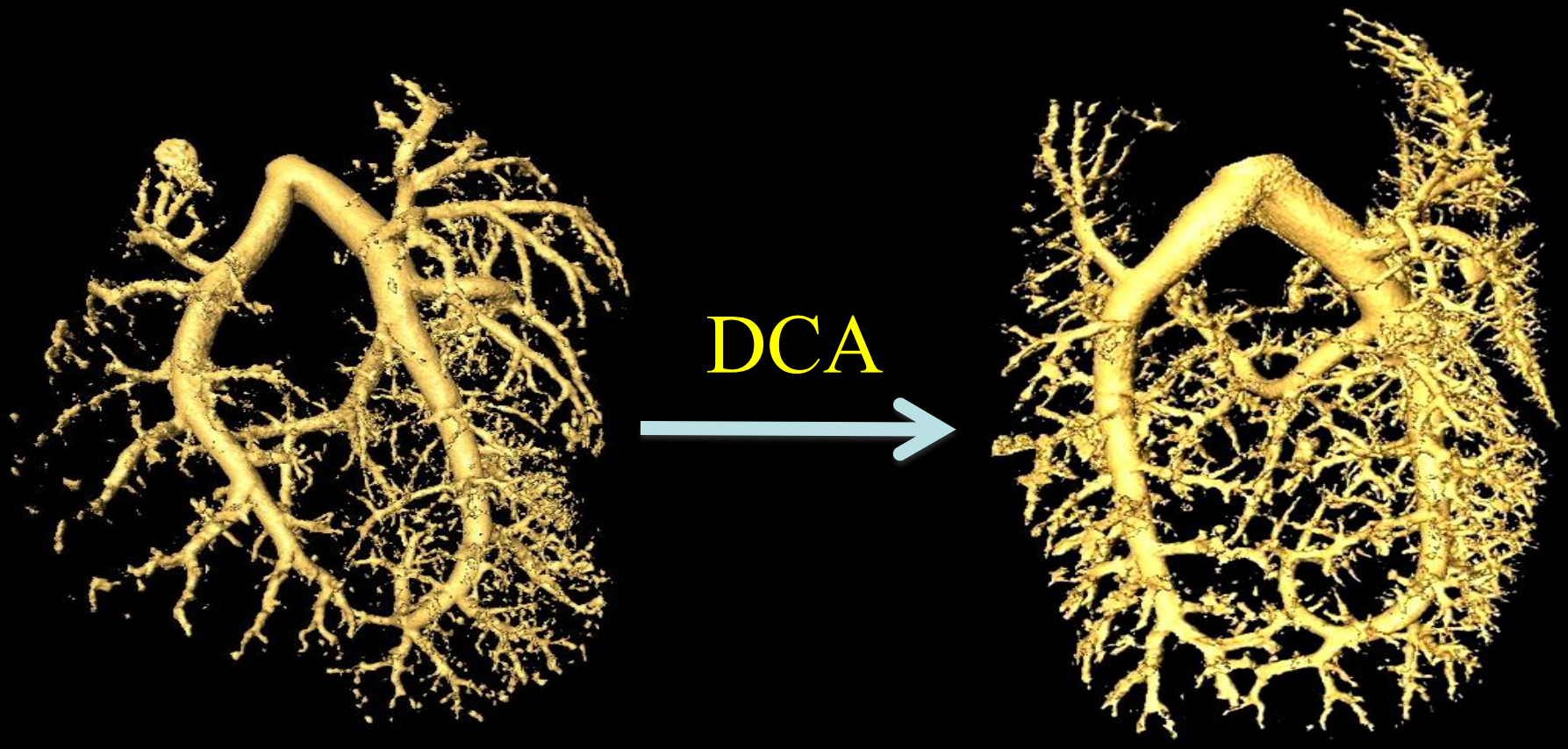




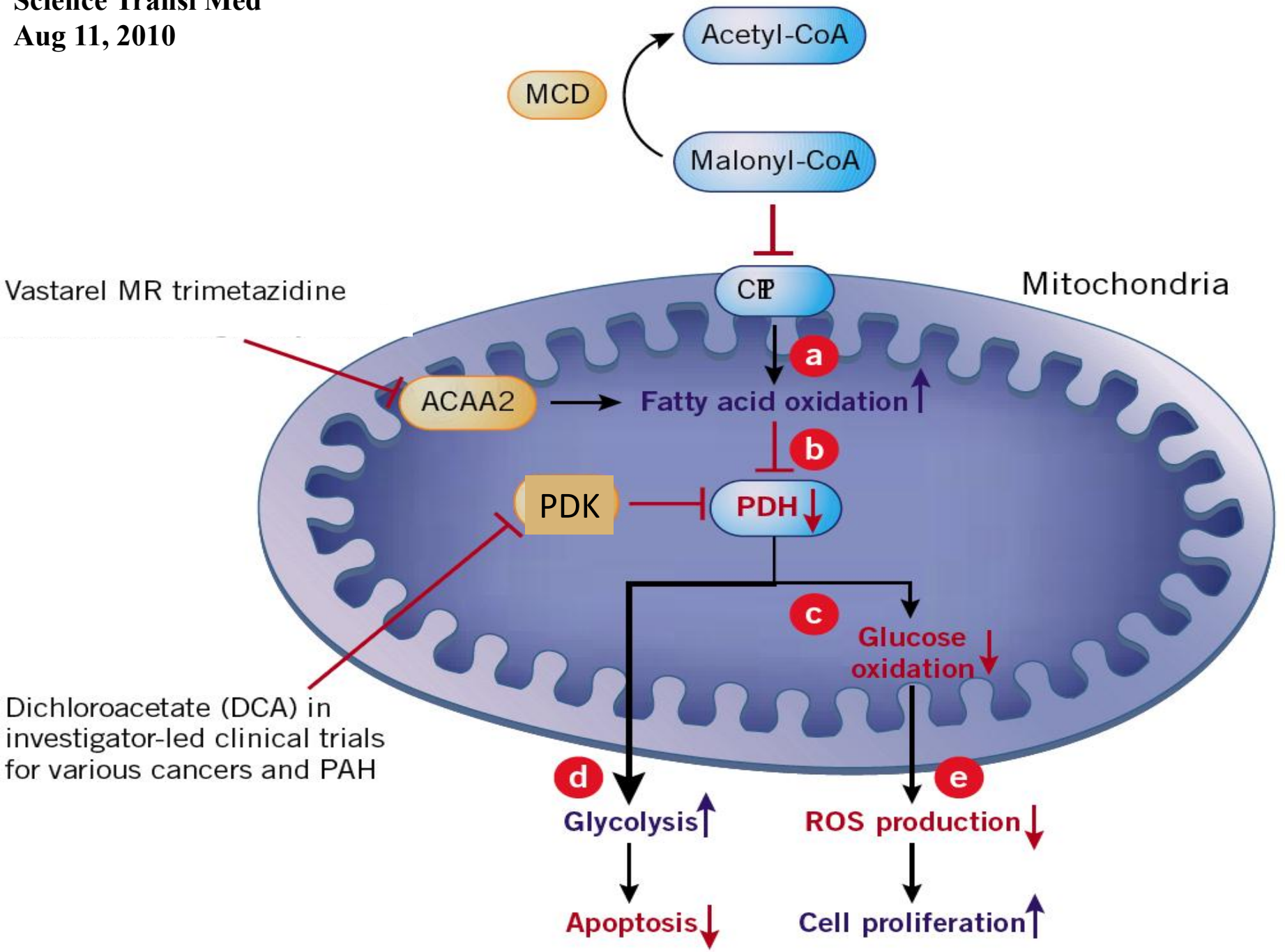
Normal Rat PVRi



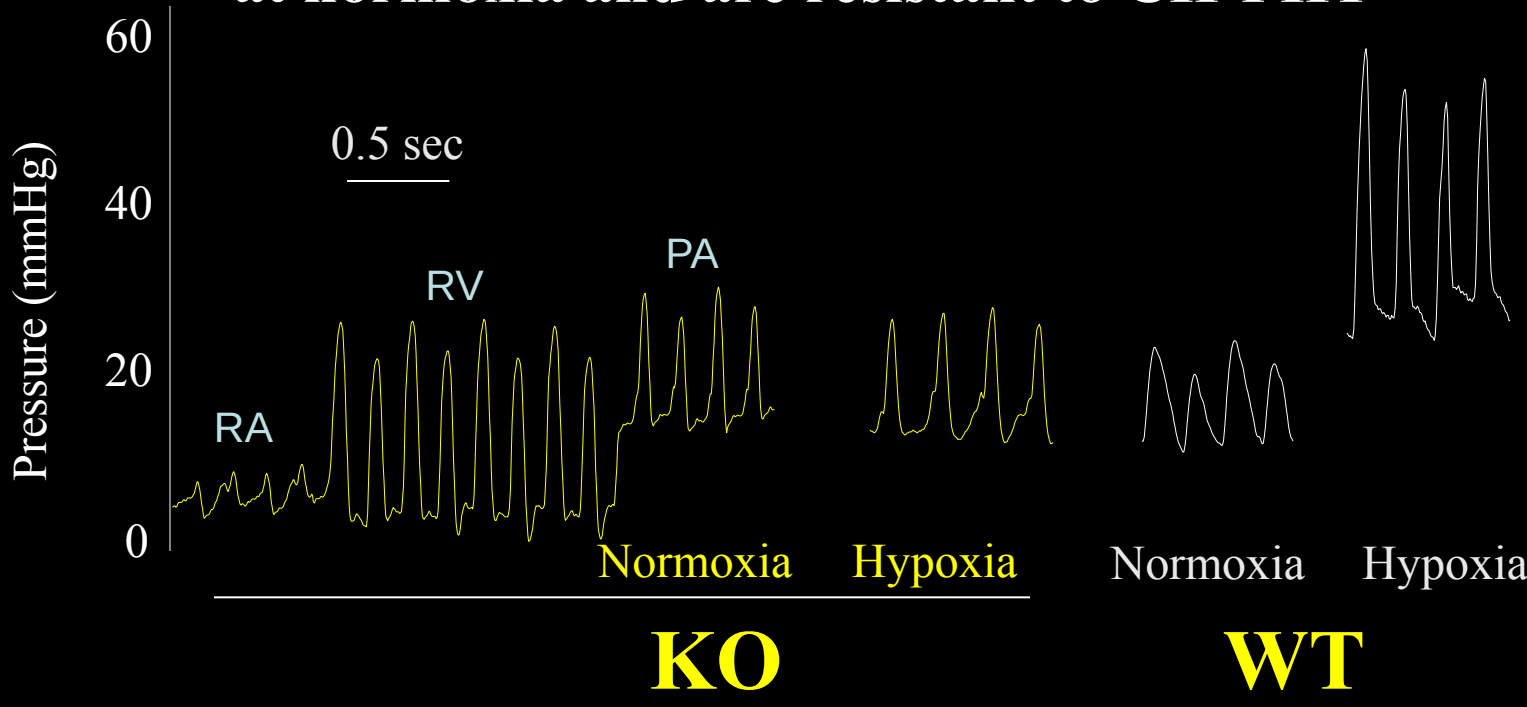
DCA reverses established vascular remodeling in rodent PAH

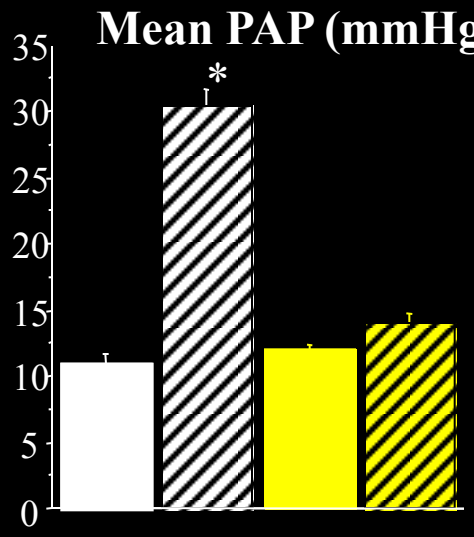


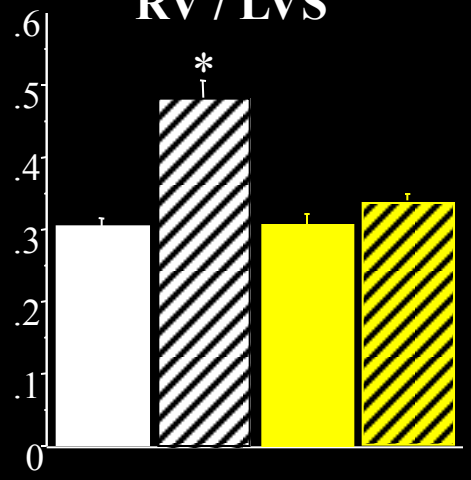
Science Transl Med
Aug 11, 2010

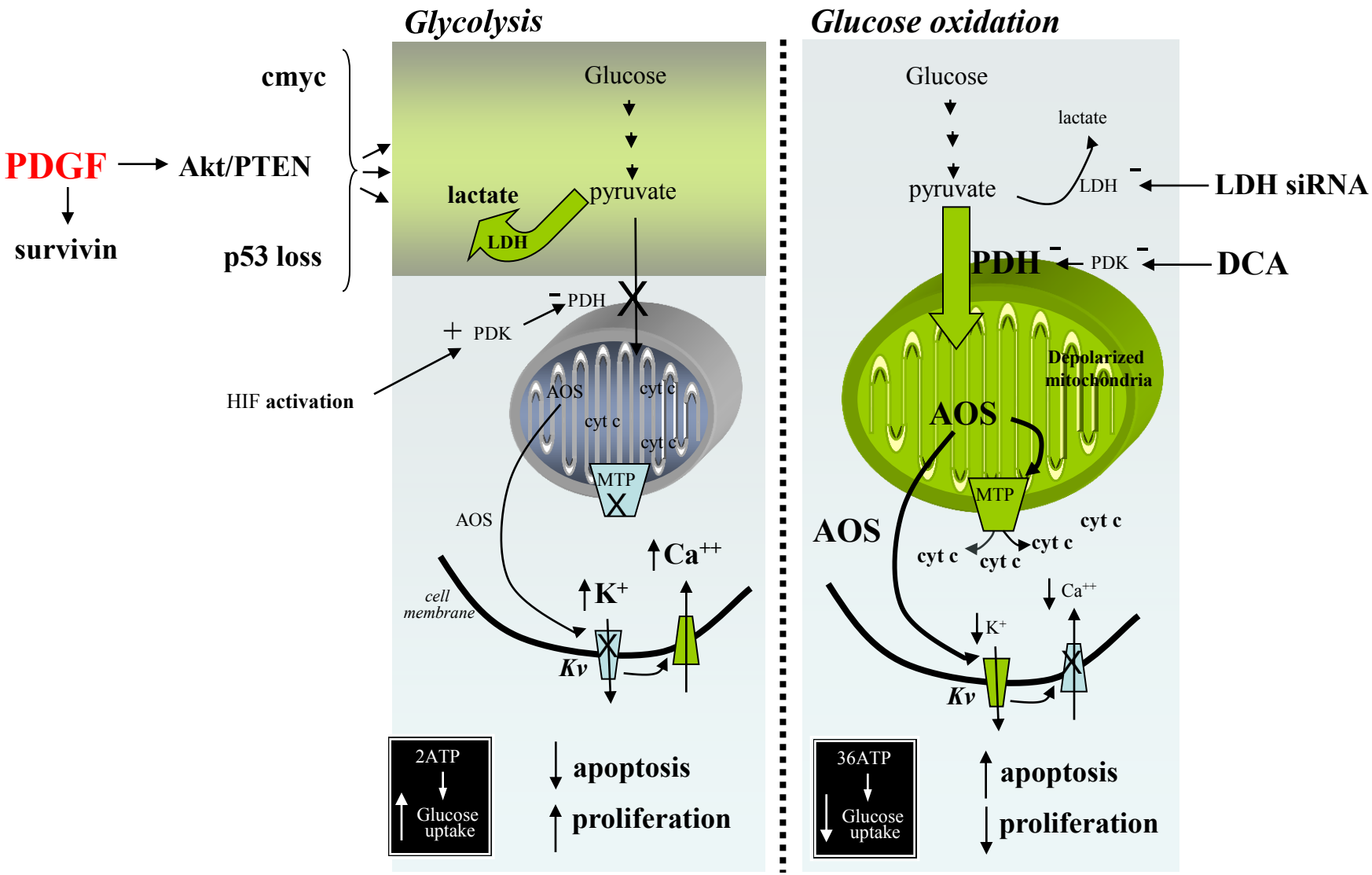


The MCD-KO mice have a normal phenotype at normoxia and are resistant to CH-PHT







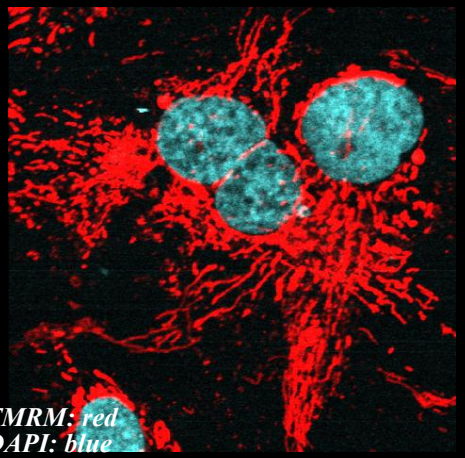


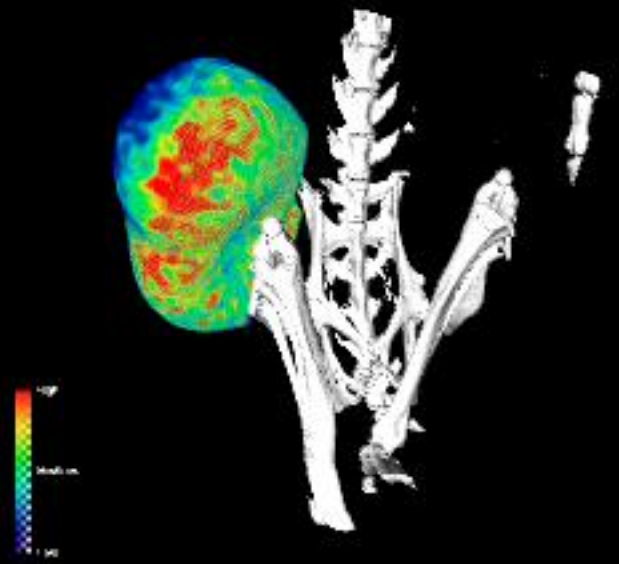
Michelakis, Br J Cancer, 2008

Cancer Cell, 2007

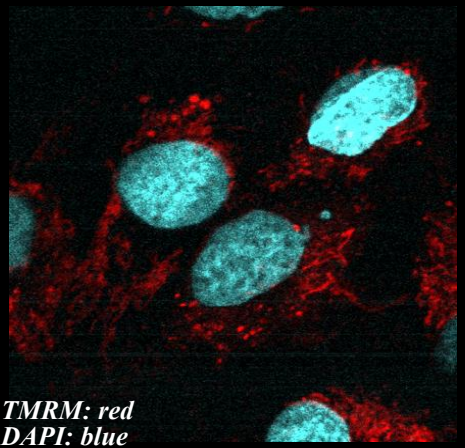
Mitochondrial membrane potential

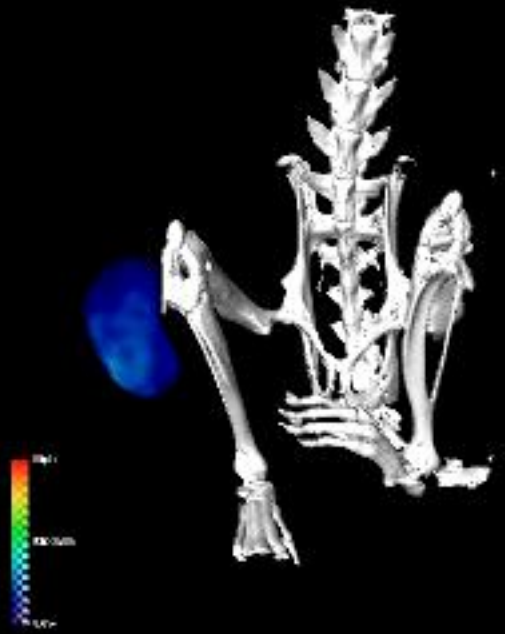
Control
(non small cell lung cancer)





DCA-treated
(non small cell lung cancer)





Economist.com

SCIENCE & TECHNOLOGY

Cancer biology

Cramping tumours

Jan 18th 2007
From The Economist print edition

An old observation about cancer cells may lead to a new treatment

Newsweek

Buzz for a Potential New Cancer Drug

Scientists and patients are buzzing about DCA, an existing drug newly recognized as a potentially powerful cancer treatment. But, of course, more research is needed.

WEB EXCLUSIVE

By Jerry Adler

Newsweek
Updated: 4:46 p.m. MT Jan 23, 2007

Science stke

AAAS

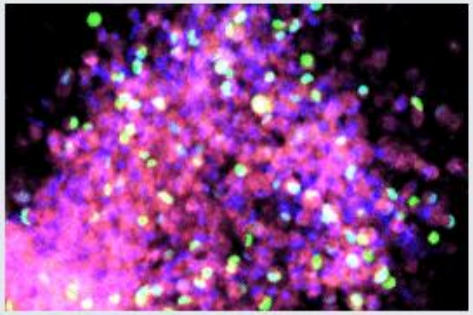
Metabolic Targeting as an Anticancer Strategy: Dawn of a New Era?
James G. Pan and Tak W. Mak (10 April 2007)
Sci. STKE **2007** (381), pe14. [DOI: 10.1126/stke.3812007pe14]

"DCA treatment may be an important example of anticancer intervention through metabolic targeting."

Hello I am Brenna. I made coasters for cancer research. I sold them at school. I raised $75.00. I wanted to change the work. I spool knitted them.

Brenna.


ANTWERP
1920
1924
ST. MORITZ
1928
otoscope
opth
PRESCRIPTION



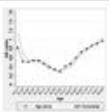
12 MAY 2010
SCI. TRANSL. MED.

METABOLIC MODULATION OF GLIOBLASTOMA WITH DICHLOROACETATE

A metabolic modulator shifts metabolism away from aerobic glycolysis in

PREVIOUS NEXT

NEWS



MAY 17, 2010 | SCIENCENOW

Golden Years Truly Are Golden

Massive phone survey reveals that people are happier after age 50

MAY 17, 2010 | SCIENCEINSIDER

Fruit Bat Sex Chat Prompts Sexual Harassment Spat

Fellatio, fruit bats, and allegations of sexual harassment. These are the ingredients of a scandal boiling over in Ireland at the University College Cork (UCC). Last year, a formal...

MAY 17, 2010 | SCIENCEINSIDER

Obama Adviser John Holdren on Why We Don't Know the Size of the Oil Gusher

Academic scientists quoted in stories late last week by NPR and The New York Times suggested that the amount of oil spewing out from the broken pipe on the...

MAY 14, 2010 | NEWS OF THE WEEK

Herschel's First Images Spark Star-Formation Debate

When the Herschel telescope was launched into space last May, it promised new insights into our universe, detecting far-infrared and submillimeter wavelengths of radiation that have eluded previous missions

SCIENCE

CURRENT ISSUE | PREVIOUS ISSUES | SCIENCE EXPRESS

MAY 14, VOL 328, ISSUE #5980

SPECIAL SECTION
Tuberculosis & Malaria

NEWS FOCUS
The Laser at 50

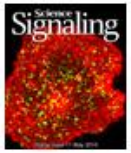
MOLECULAR BIOLOGY
Plant Signaling by Small RNAs

PHYSICS
Multiphoton Entanglement

ECOLOGY
Dwindling Lizard Diversity

- CURRENT ISSUE
- Author Index
- Subject Index
- Top Last Month
- Products

SCIENCE SIGNALING



TCR SIGNALING
Delivering LAT from Below

CELL BIOLOGY
Stabilizing β-catenin with Gβγ

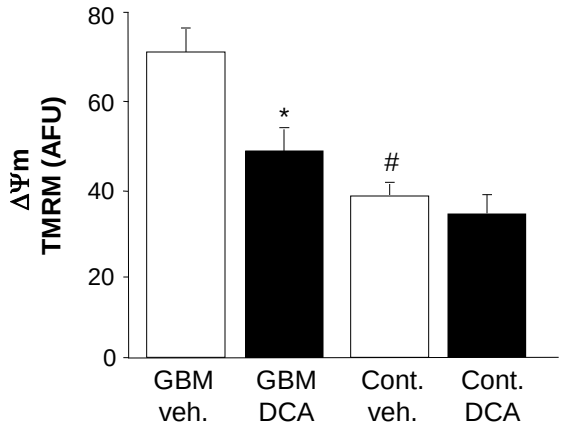
- Current Issue
- Issue Archive

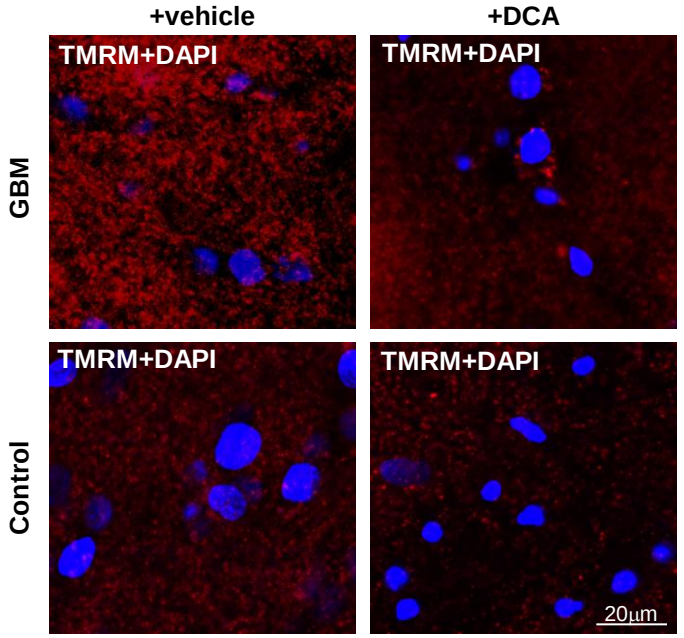
SCIENCE TRANSLATIONAL MEDICINE

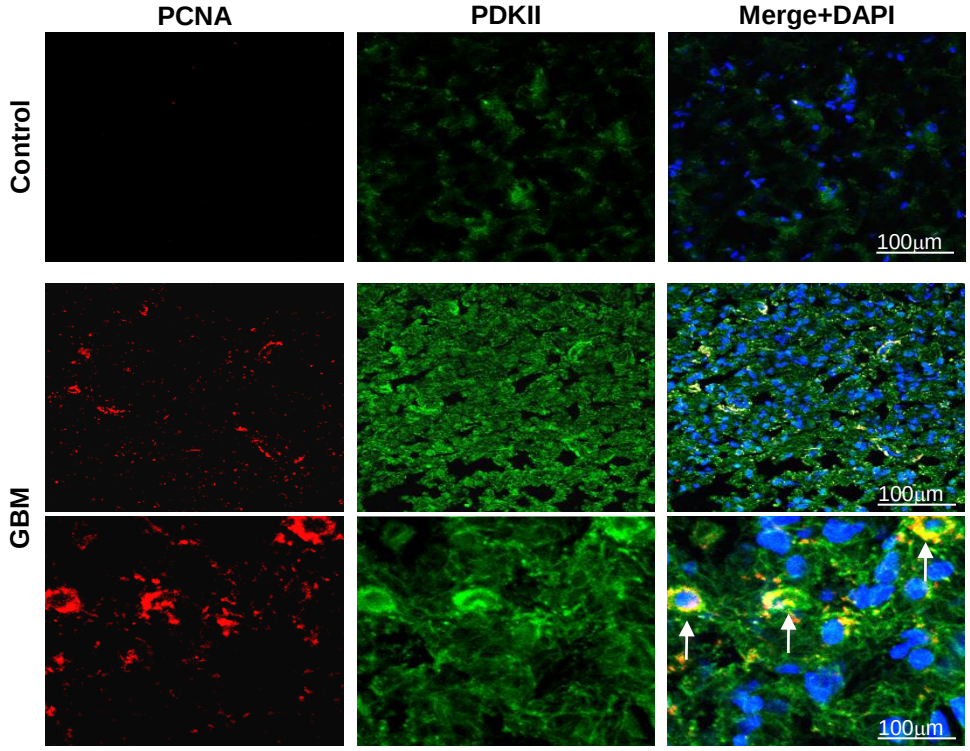
RESEARCH ARTICLE
Can Blue-Light Therapy Help You Sleep?

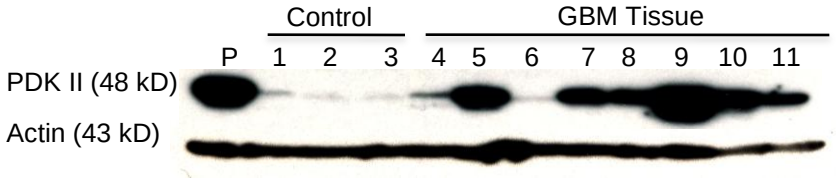
PERSPECTIVE
Defining Mammary Stem Cells

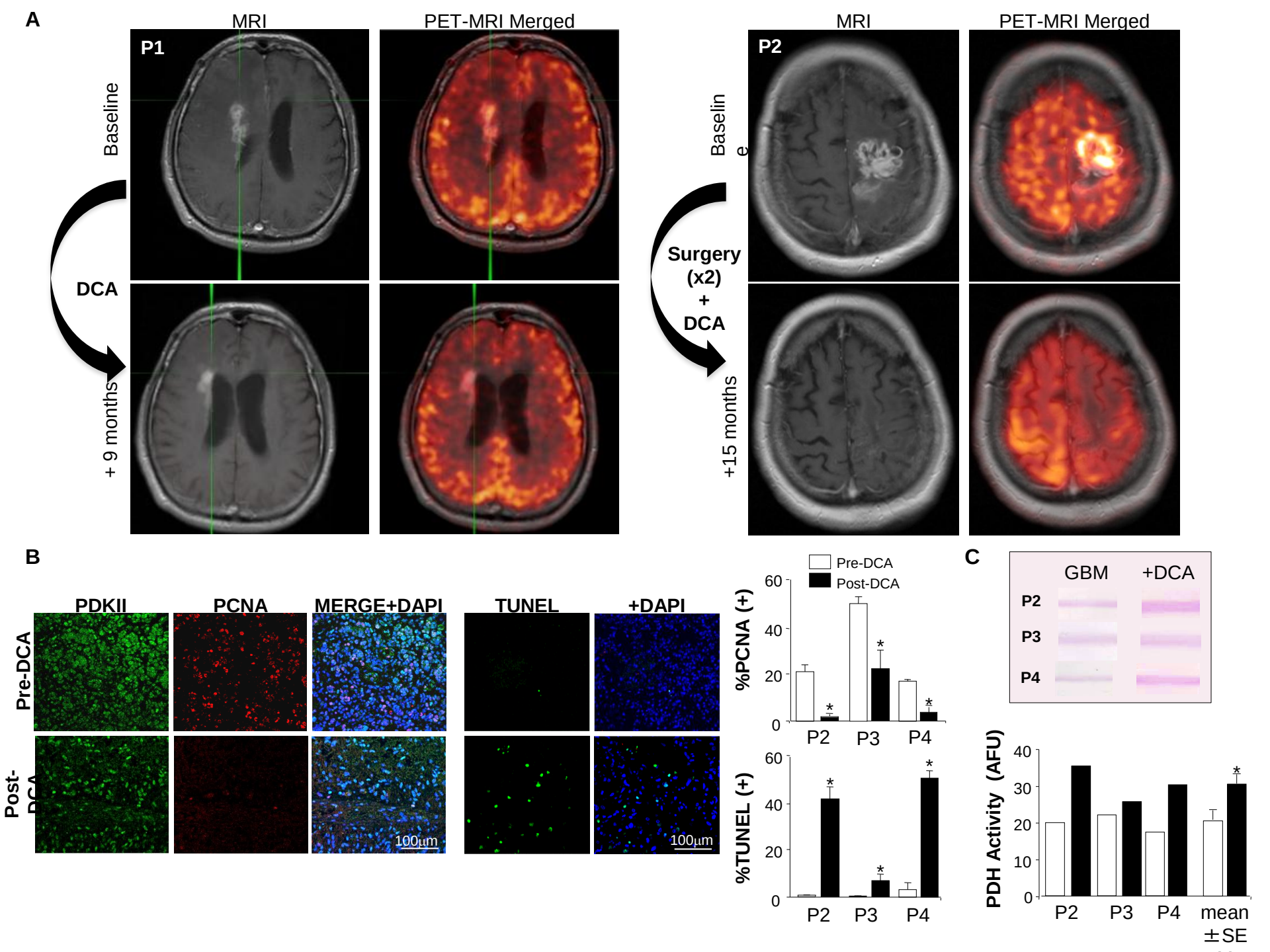
- Current Issue


80
60
40
20
0
ΔΨm
TMRM (AFU)
*
#
GBM
veh.
GBM
DCA
Cont.
veh.
Cont.
DCA


+vehicle
+DCA
GBM
Control
TMRM+DAPI
TMRM+DAPI
TMRM+DAPI
TMRM+DAPI
20μm


PCNA
PDKII
Merge+DAPI
Control
GBM
100μm
100μm
100μm

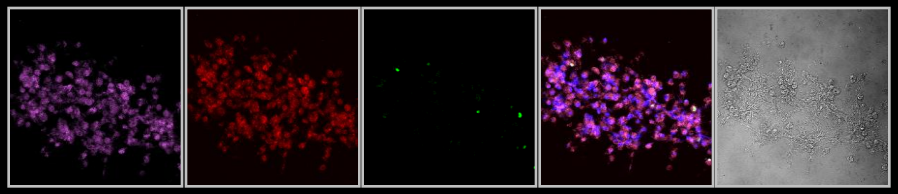

Control
GBM Tissue
P
1
2
3
4
5
6
7
8
9
10
11
PDK II (48 kD)
Actin (43 kD)


A
MRI
PET-MRI Merged
P1
Baseline
DCA
+ 9 months
P2
Surgery
(x2)
+
DCA
+15 months
B
PDKII
PCNA
MERGE+DAPI
TUNEL
+DAPI
Pre-DCA
Post-DCA
100μm
Pre-DCA
Post-DCA
%PCNA (+)
%TUNEL (+)
P2
P3
P4
C
GBM
+DCA
PDH Activity (AFU)
mean
±SE

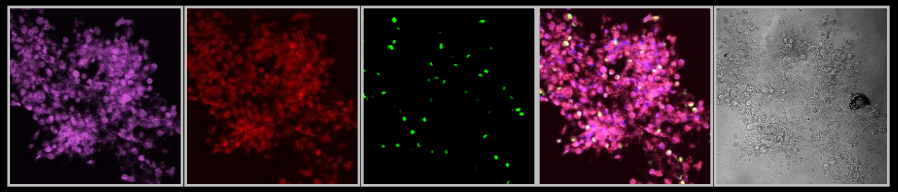
In Vitro

CONTROL - CSC

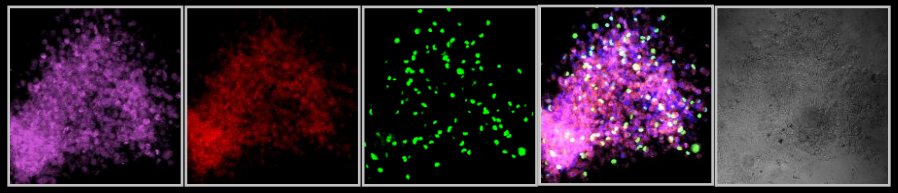
CD133 | NESTIN | TUNEL | MERGE | DIC



DCA



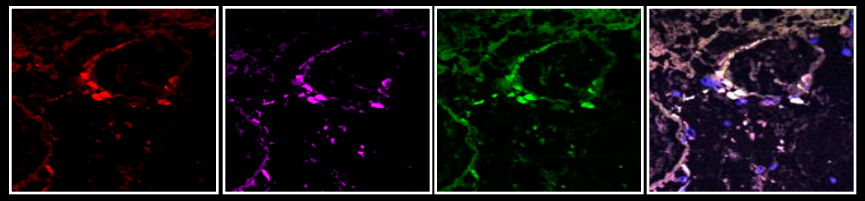
DCA+TMZ



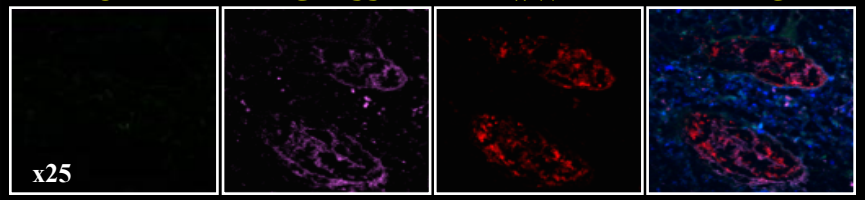
In Vivo

Pre DCA

NESTIN | CD133 | PDKII | MERGE

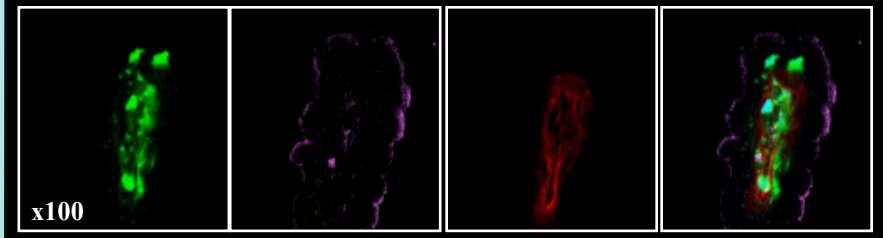


TUNEL | CD133 | wWF | MERGE

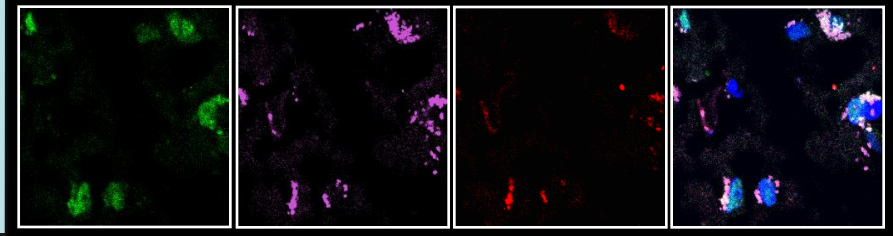


Post DCA

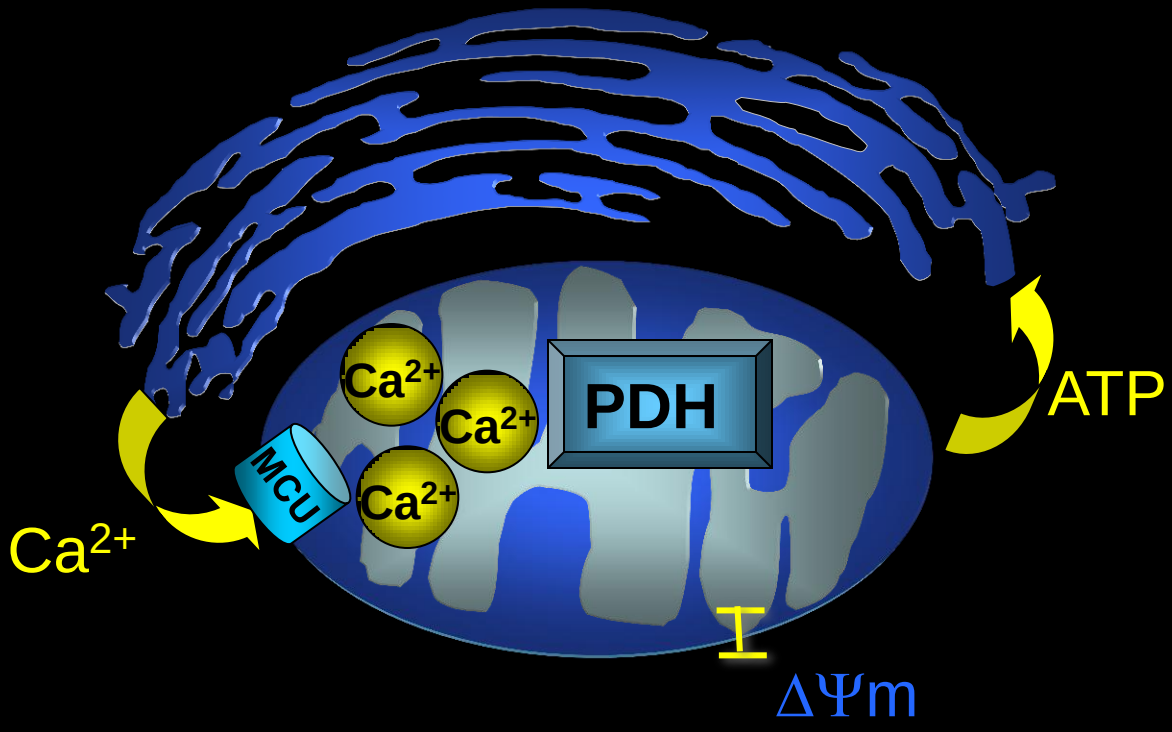
TUNEL | CD133 | wWF | MERGE

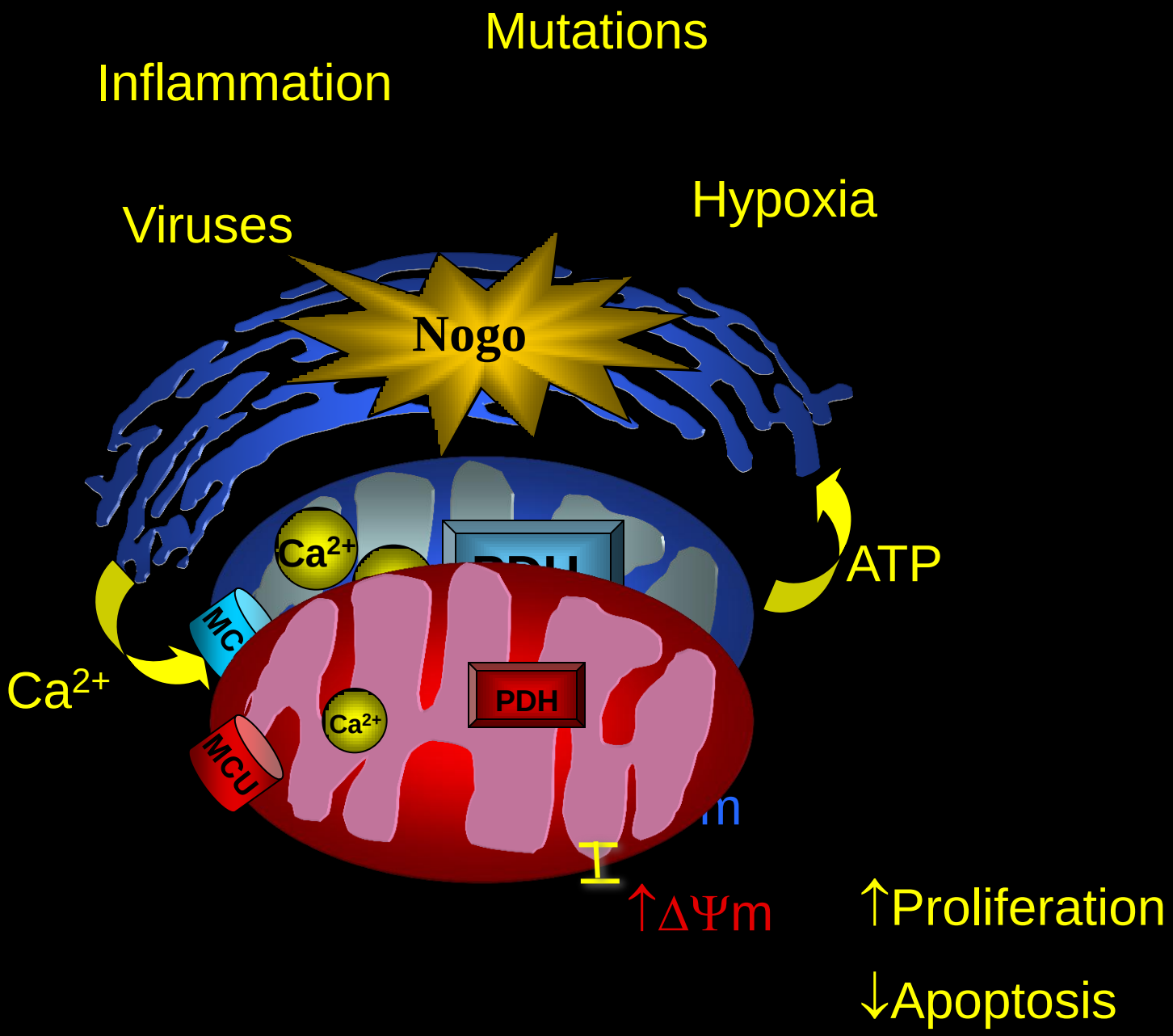


TUNEL | CD133 | NESTIN | MERGE



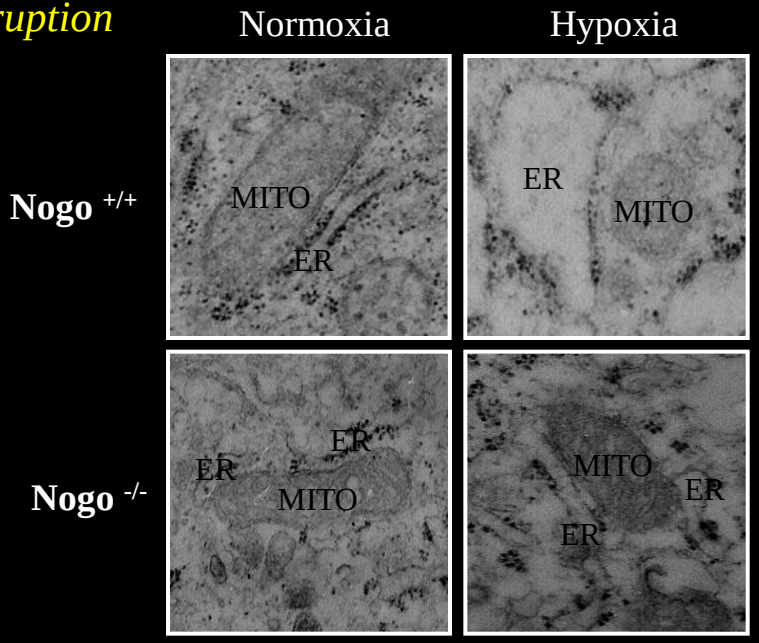
Normal

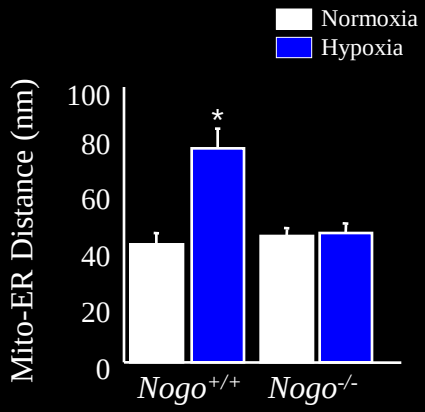



Mutations
Inflammation
Hypoxia
Viruses
Nogo
ATP
Ca2+
MC
Ca2+
PDH
Ca2+
MCU
↑ΔΨm
↑Proliferation
↓Apoptosis

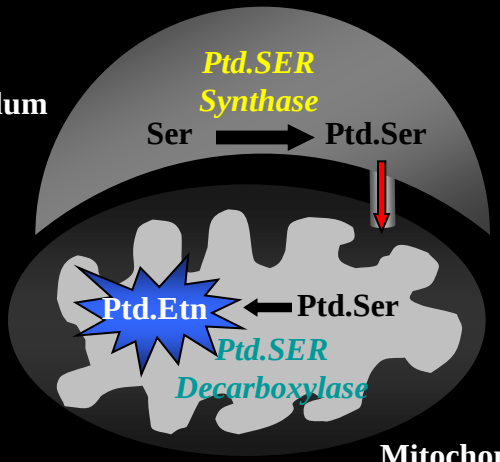
Nogo$^{-/-}$ PASMCs Are Resistant To Hypoxia-Induced ER-Mito Separation

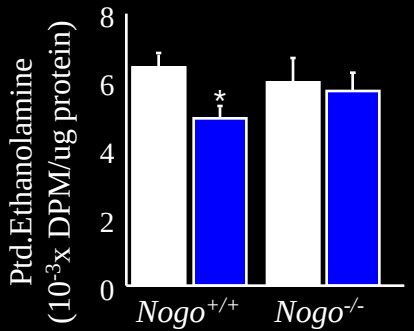
Structural Disruption



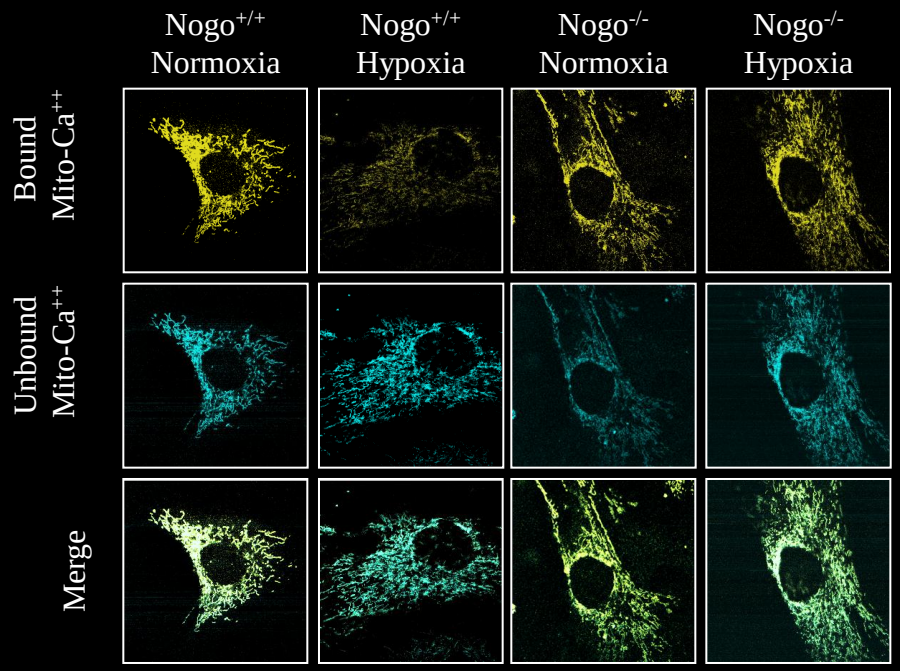


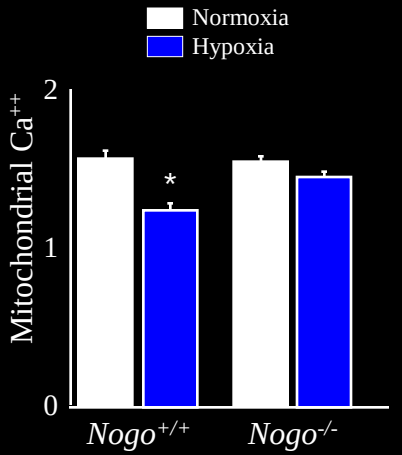
Functional Disruption

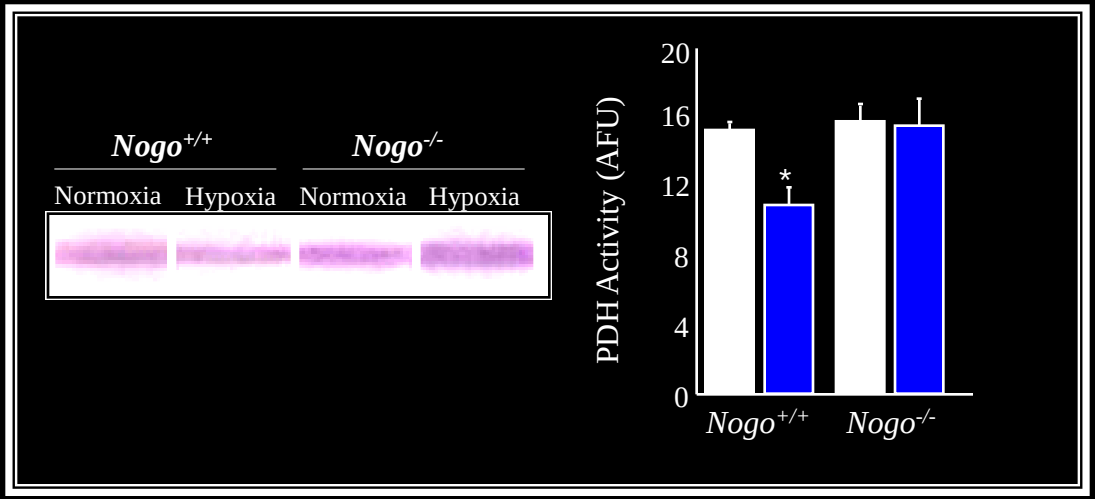


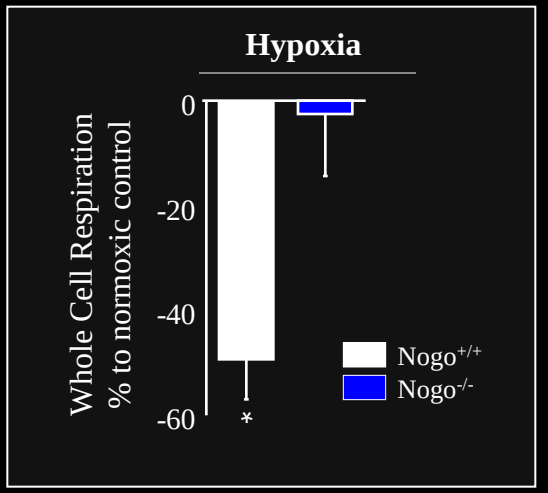


Nogo K.O. PASMCs maintain mitochondrial Ca^{++} and Ca^{++}-sensitive enzymes in hypoxia

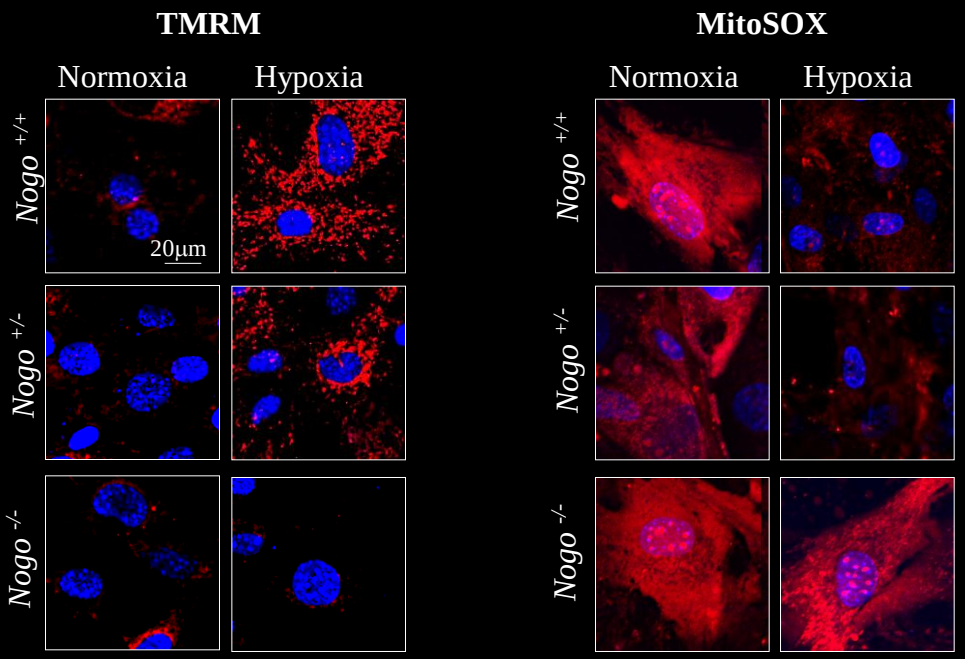


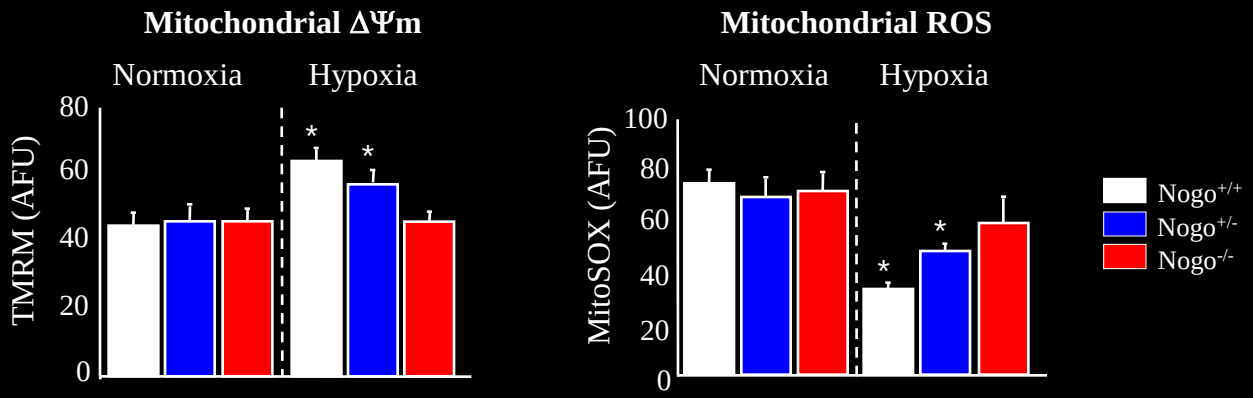




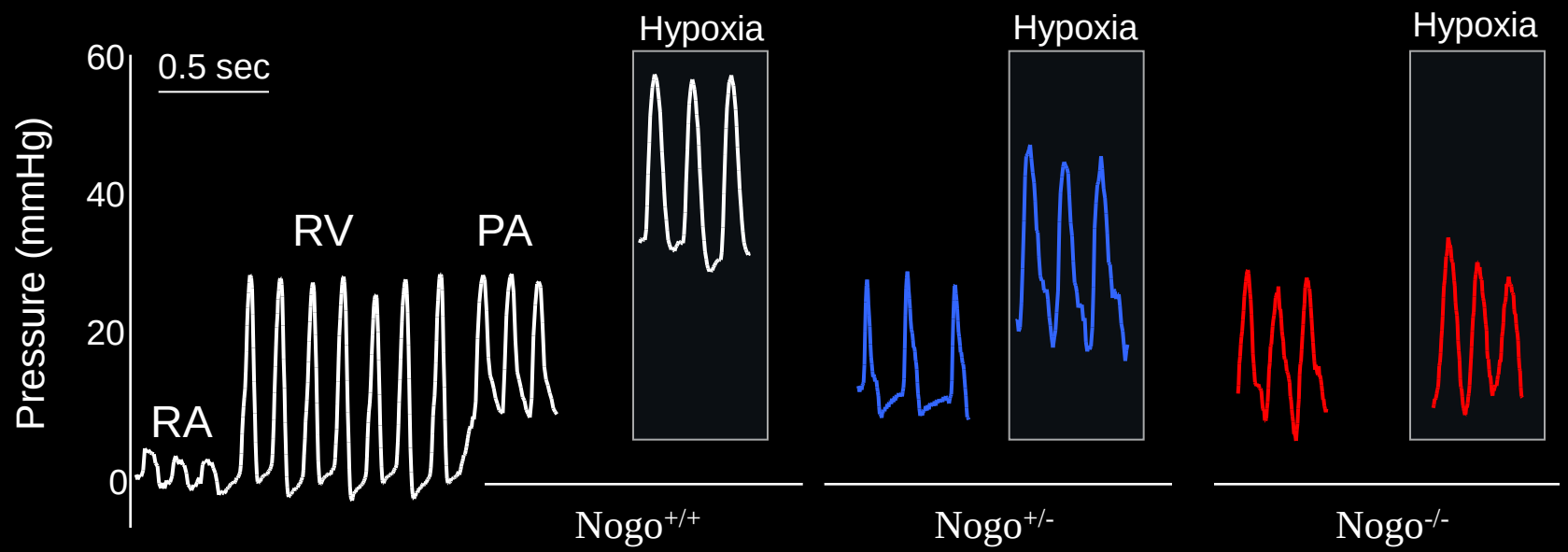


Nogo$^{-/-}$ PASMC are resistant to hypoxia induced mitochondrial hyperpolarization and decreased mitochondrial ROS

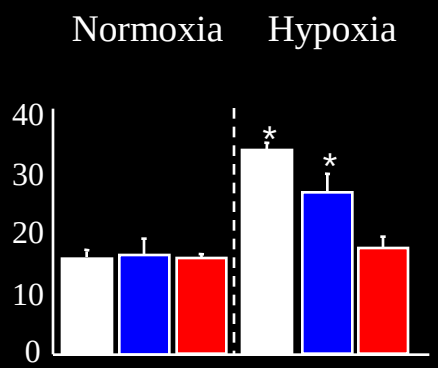




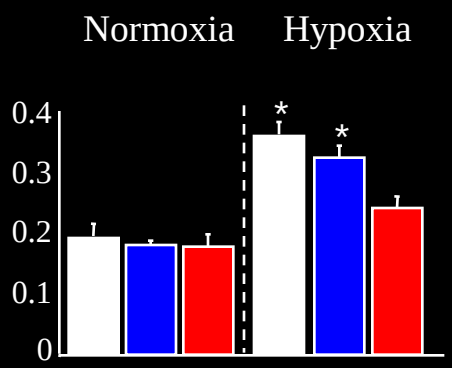
Nogo$^{-/-}$ mice are resistant to chronic-hypoxia PHT



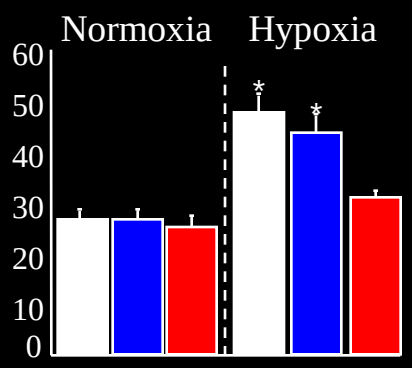
Mean PAP (mmHg)



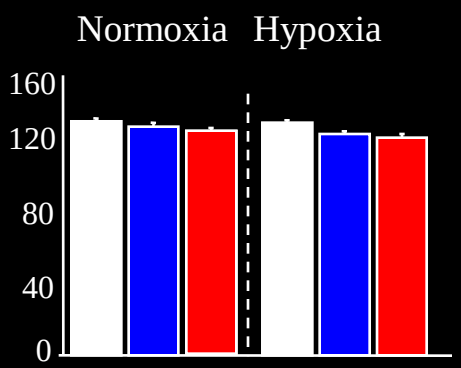
RV/(LV+Septum)



% Medial Wall Thickness

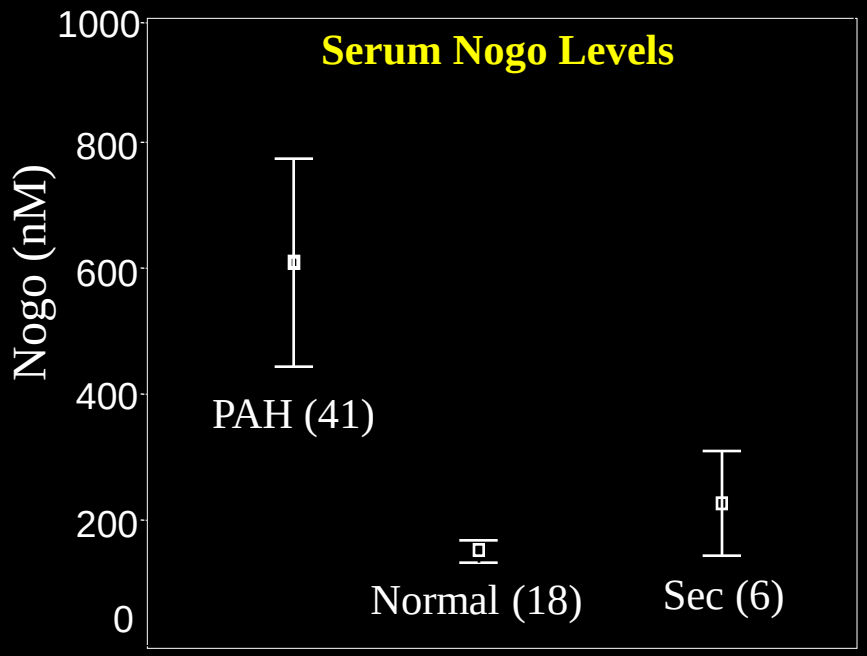


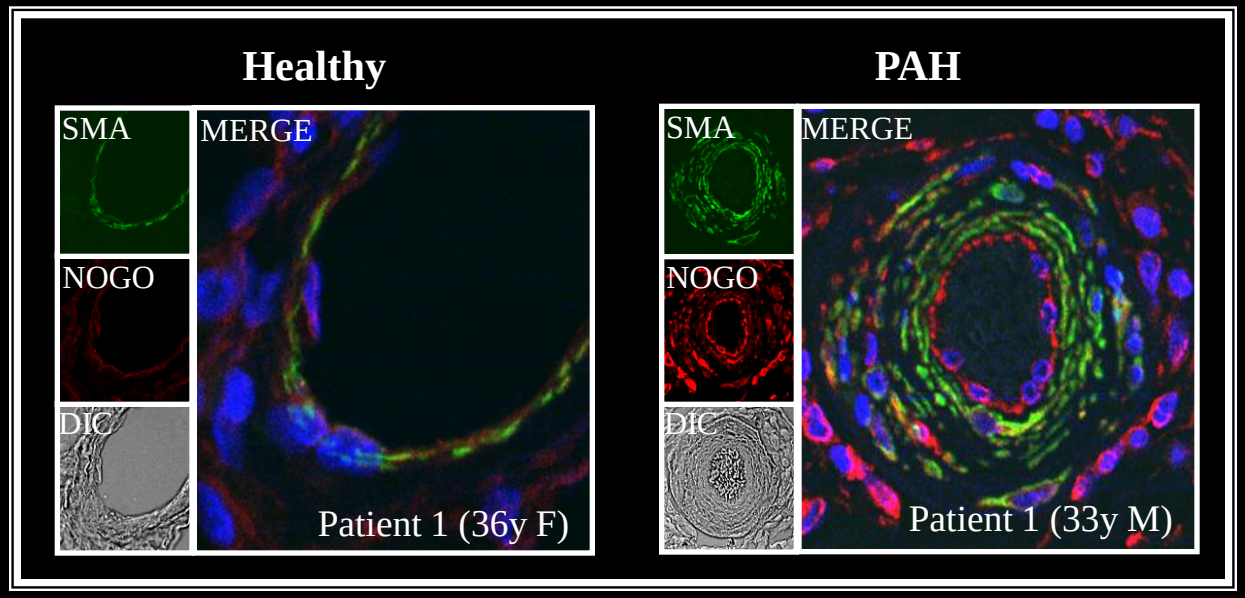
Systemic B.P. (mmHg)



Nogo$^{+/+}$
Nogo$^{+/-}$
Nogo$^{-/-}$

Nogo Expression Increases in Human PAH





Ballarina II, Joan Miro, 1925

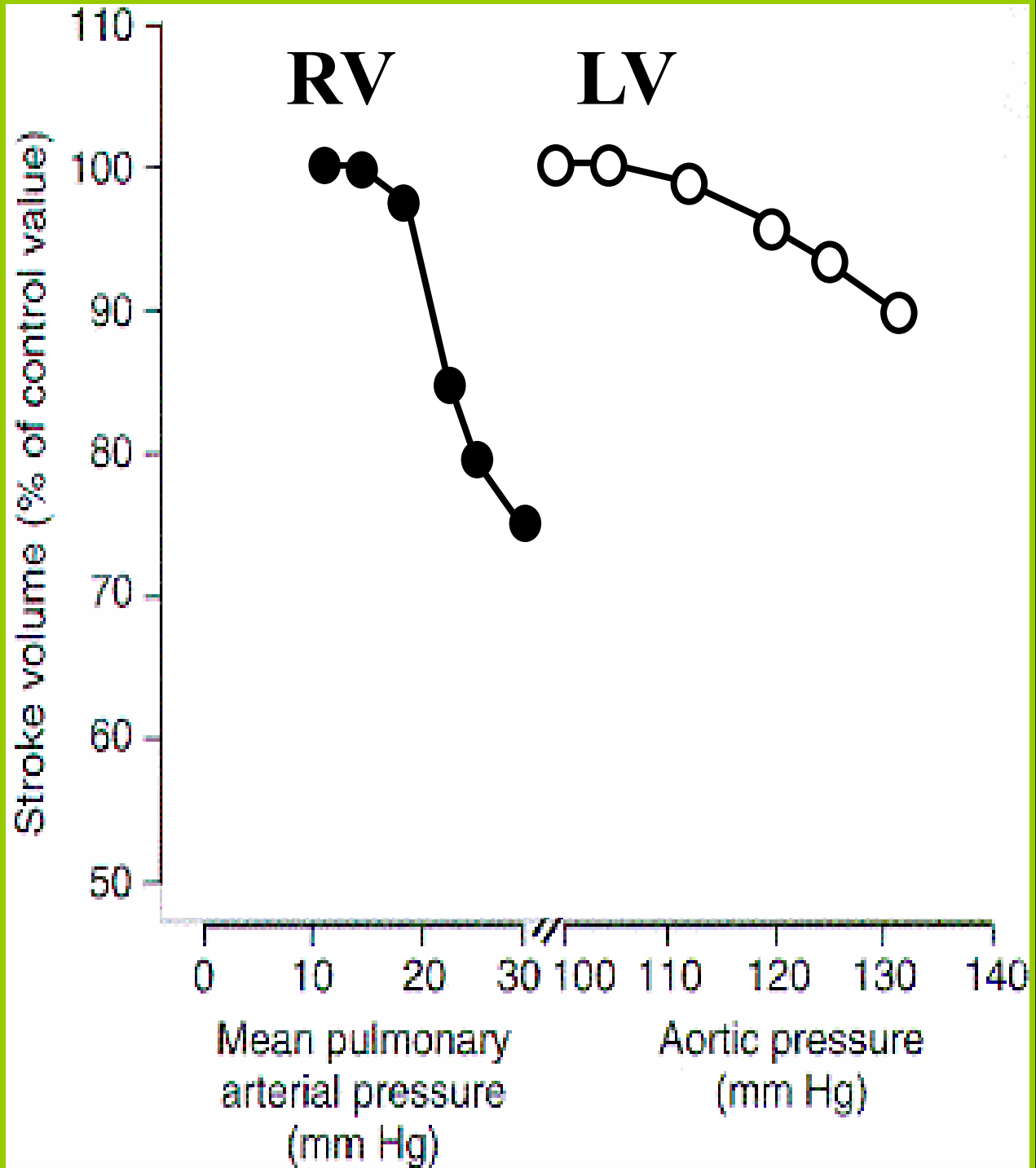
Thank you

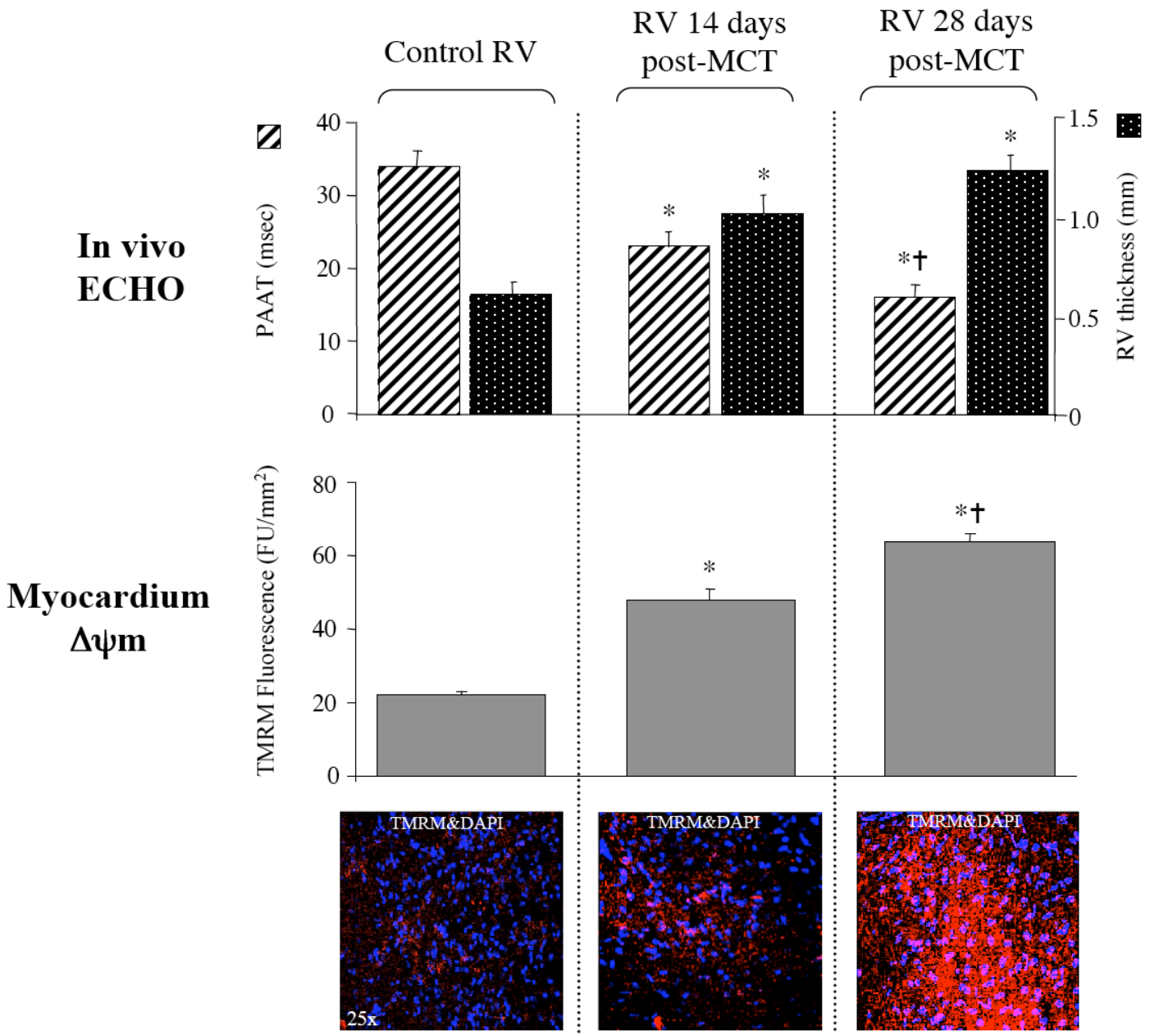
Sebastien Bonnet
Sean McMurtry
Ken Petruk
Gopi Sutendra
Peter Dromparis
Jayan Nagendran
Linda Webster

The RV and the LV are embryologically different

Zaffran et al, *Circ Res* 2004.

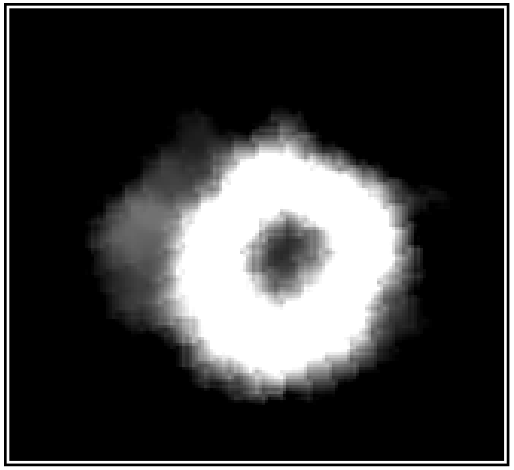
The molecular and metabolic profile of the normal RV is different compared to RVH

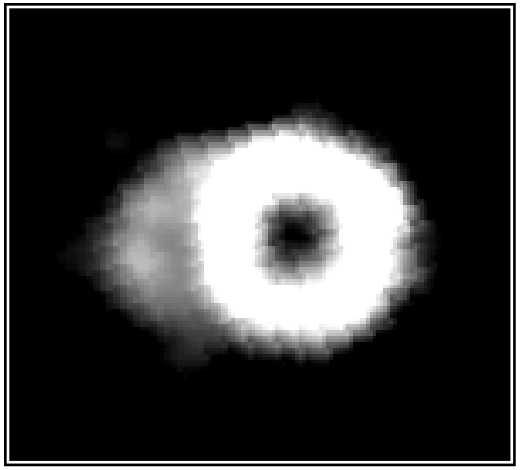




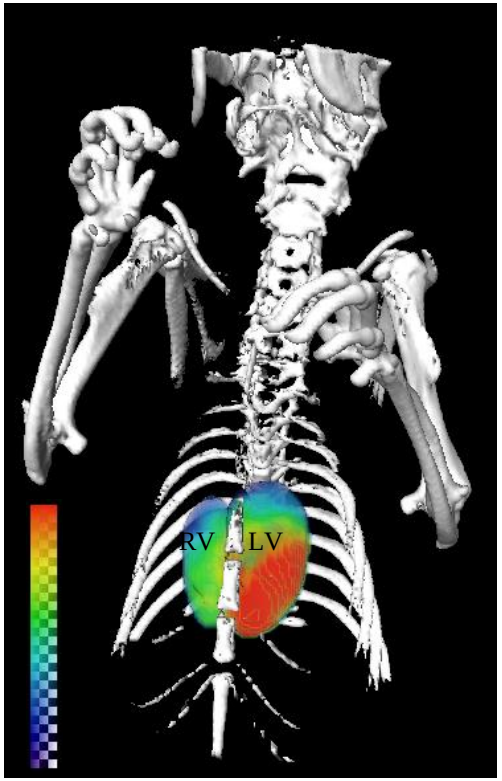
Nagendran et al, JTCS, 2008

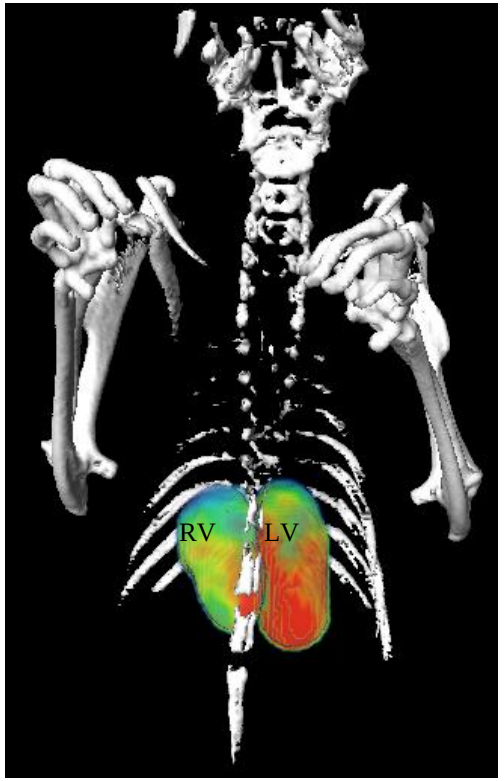
baseline **RVH-PHT**





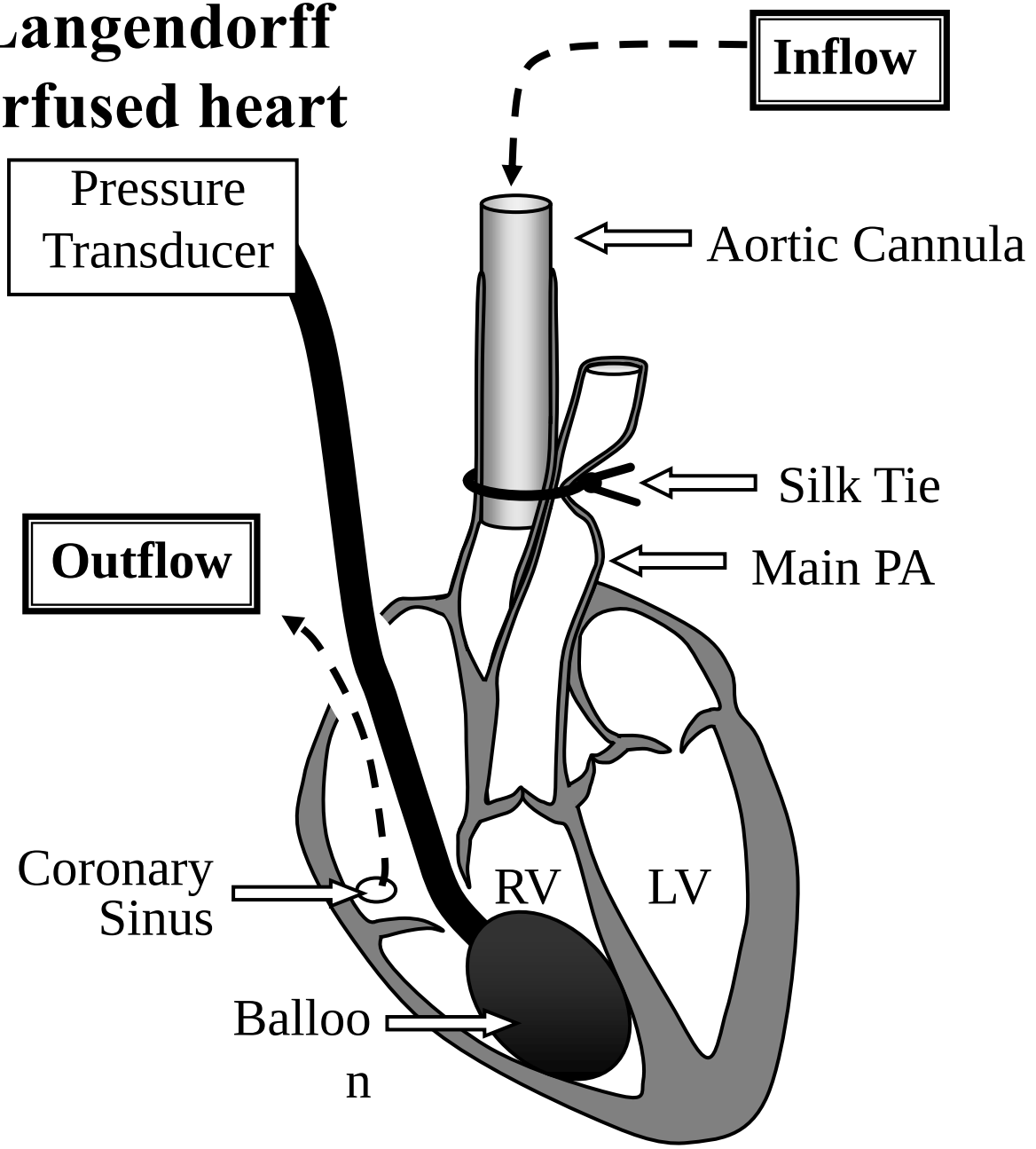
baseline **RVH-PHT**



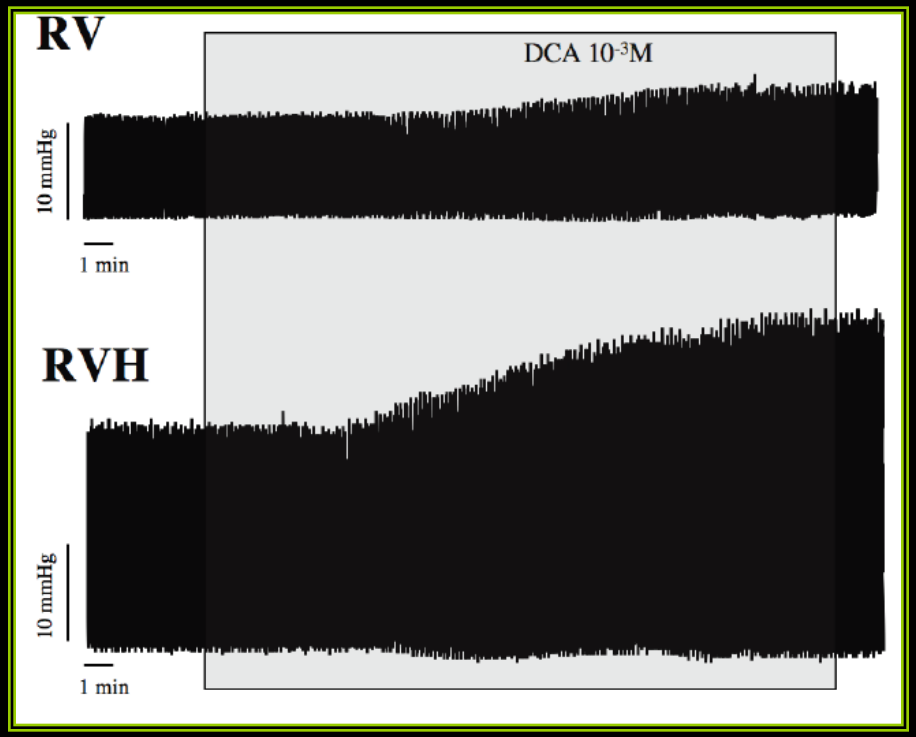


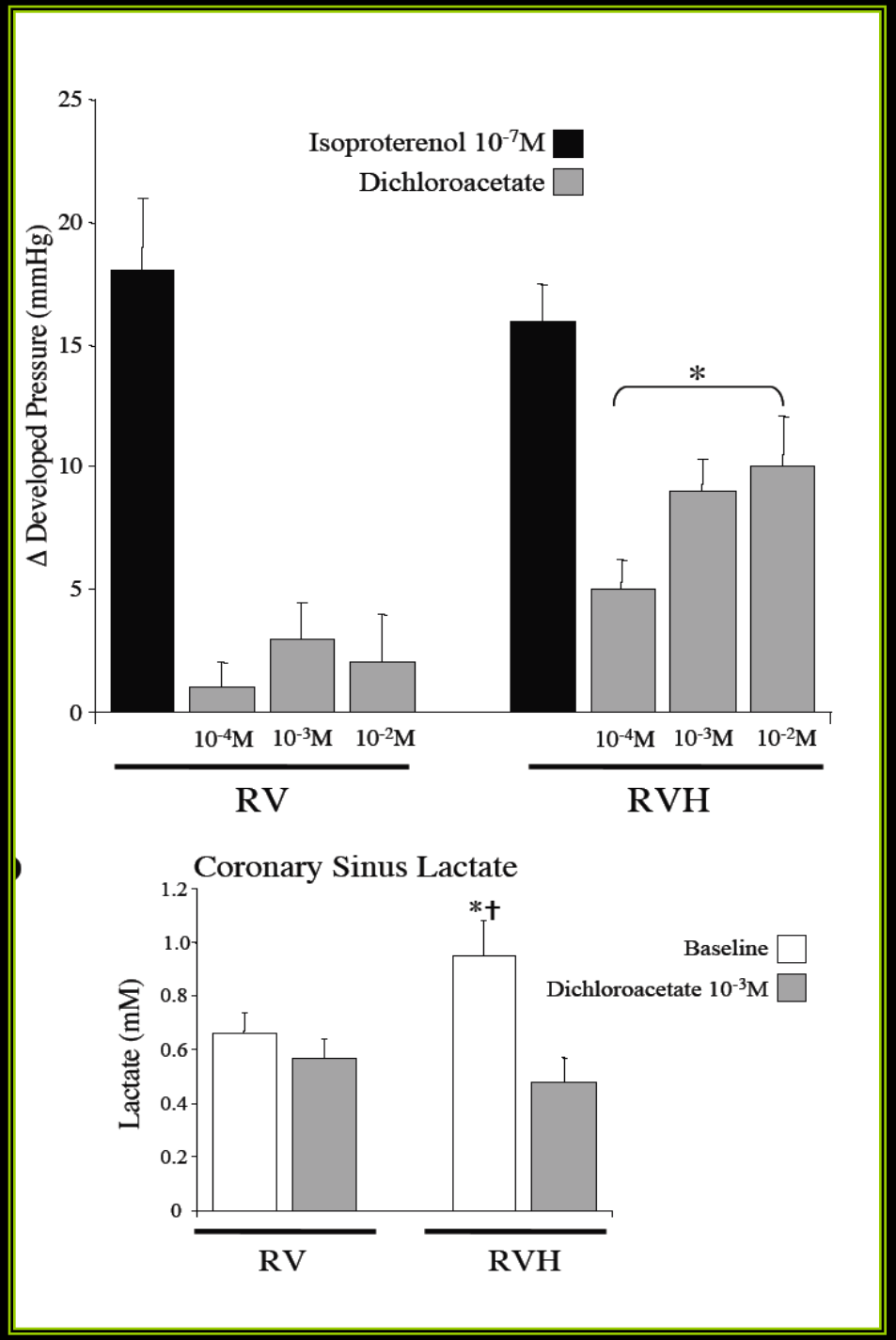
FDG-18/PET IMAGING

Modified Langendorff isolated perfused heart



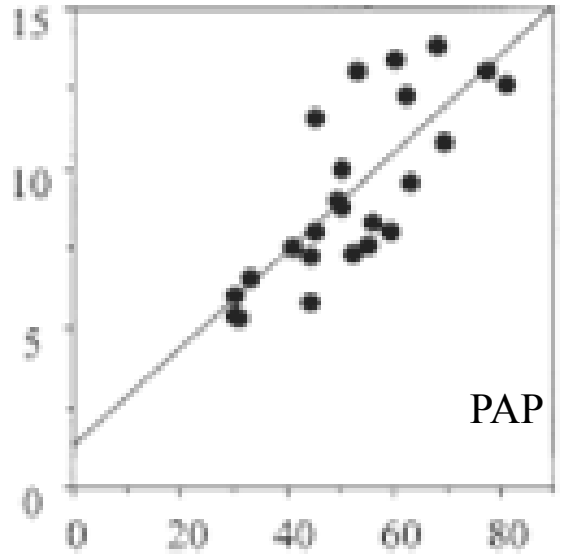
DCA: a positive RVH inotrope





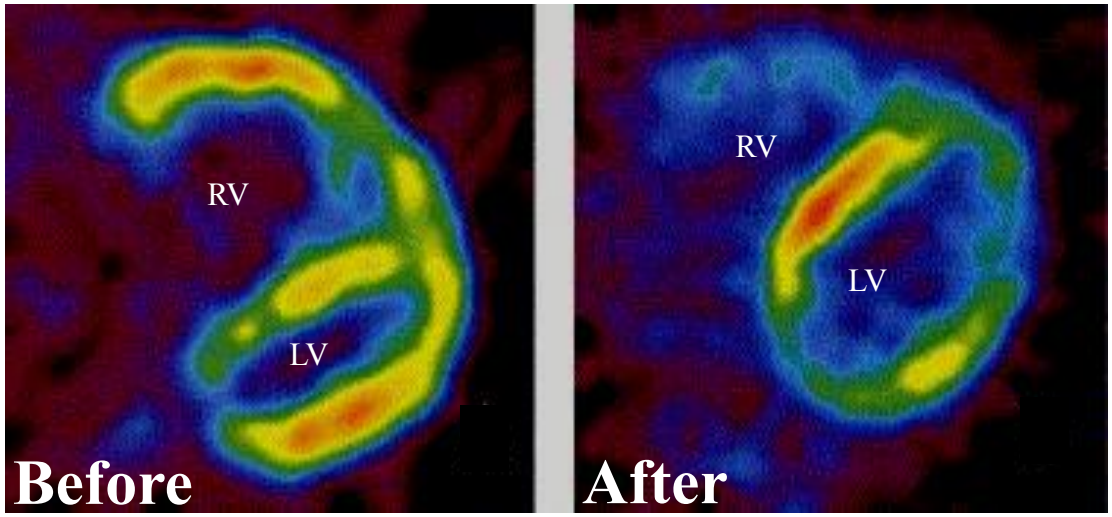
Nagendran et al, JTCS, 2008

Increased RV Glu uptake in iPAH

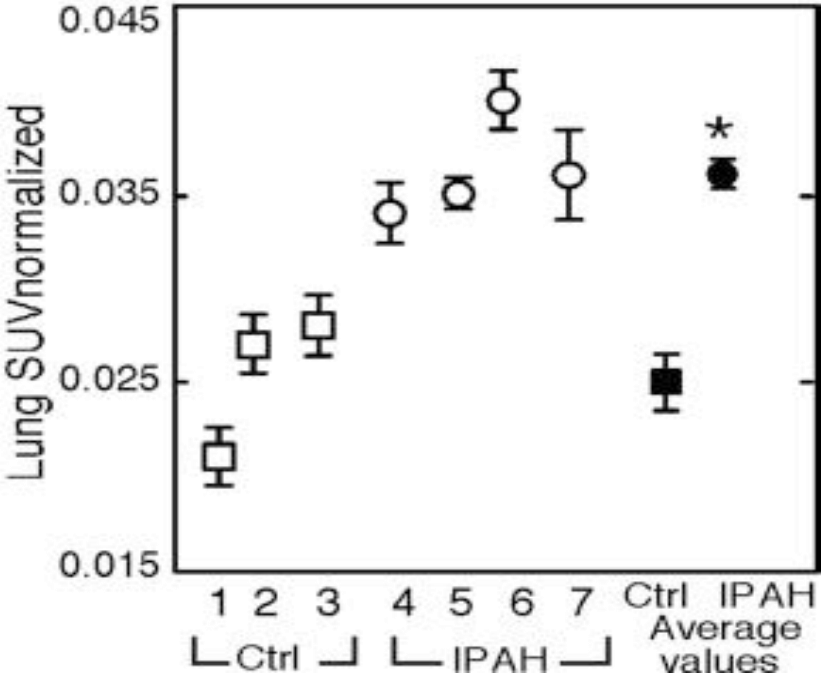


Oikawa et al, JACC 2005

Flolan decreases RV Glu uptake



Increased lung glucose uptake in iPAH patients



Xu et al, PNAS, 2007