

II. Pathobiology of pulmonary arterial hypertension

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Program in Translational Lung Research

Division of Pulmonary Sciences and Critical Care
Medicine, Department of Medicine

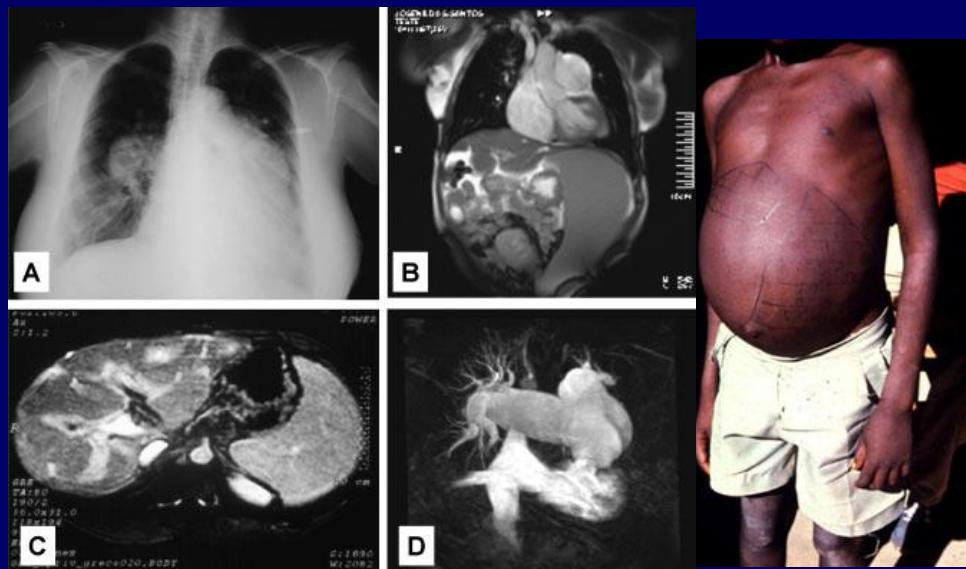
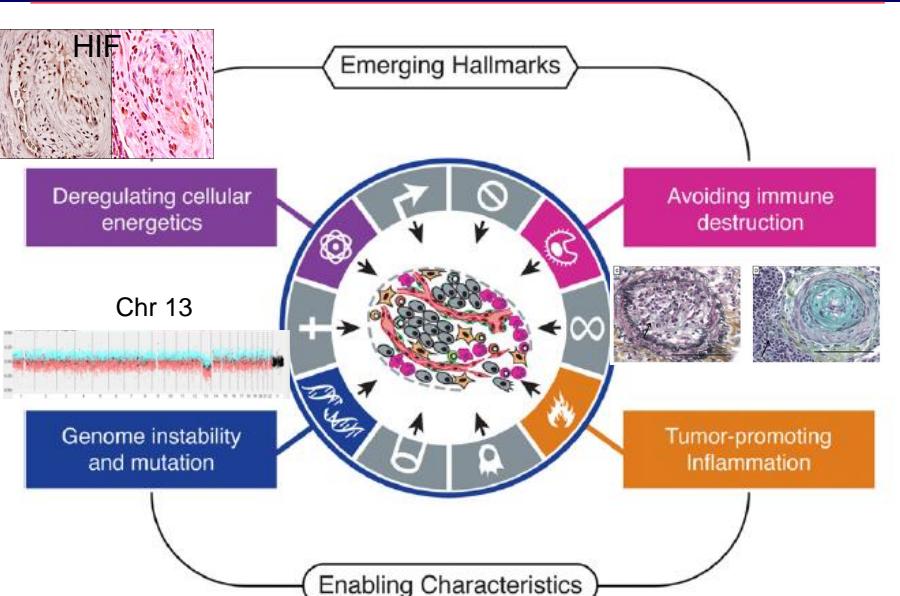
University of Colorado, School of Medicine

PVRI



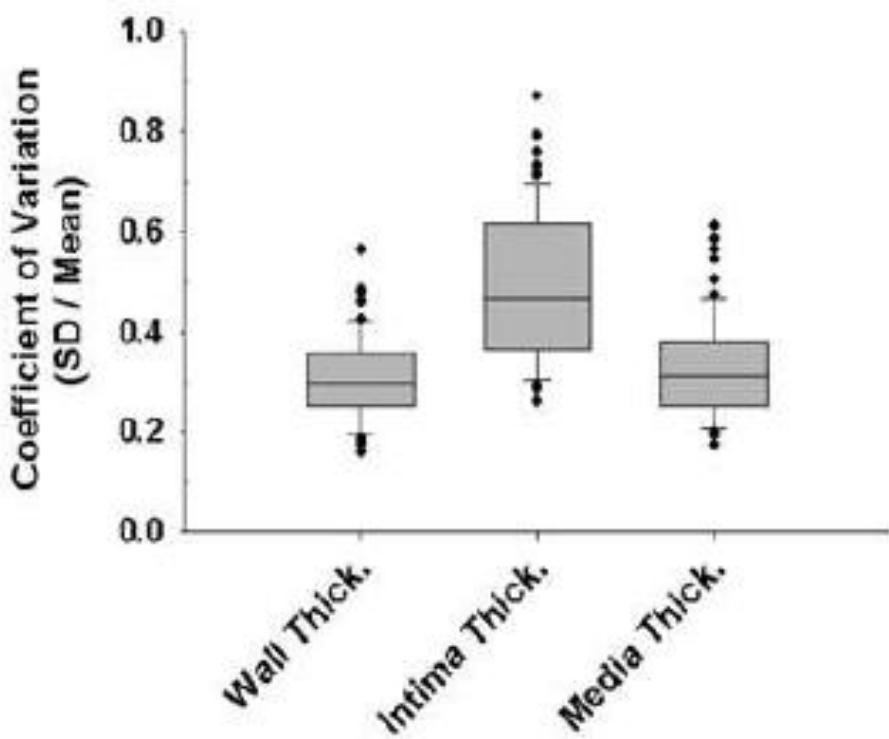
17 β estradiol → CYP1B1

(Revisited) Key features of cancer

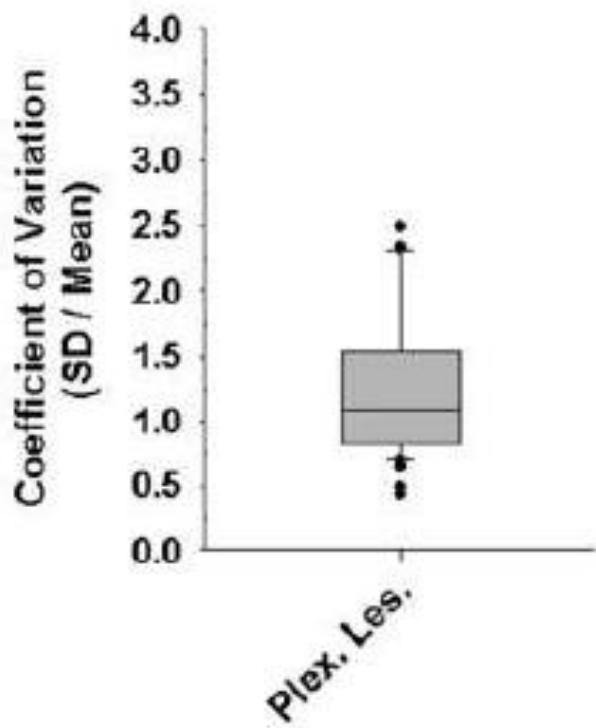


Variability of pulmonary vascular lesions

A

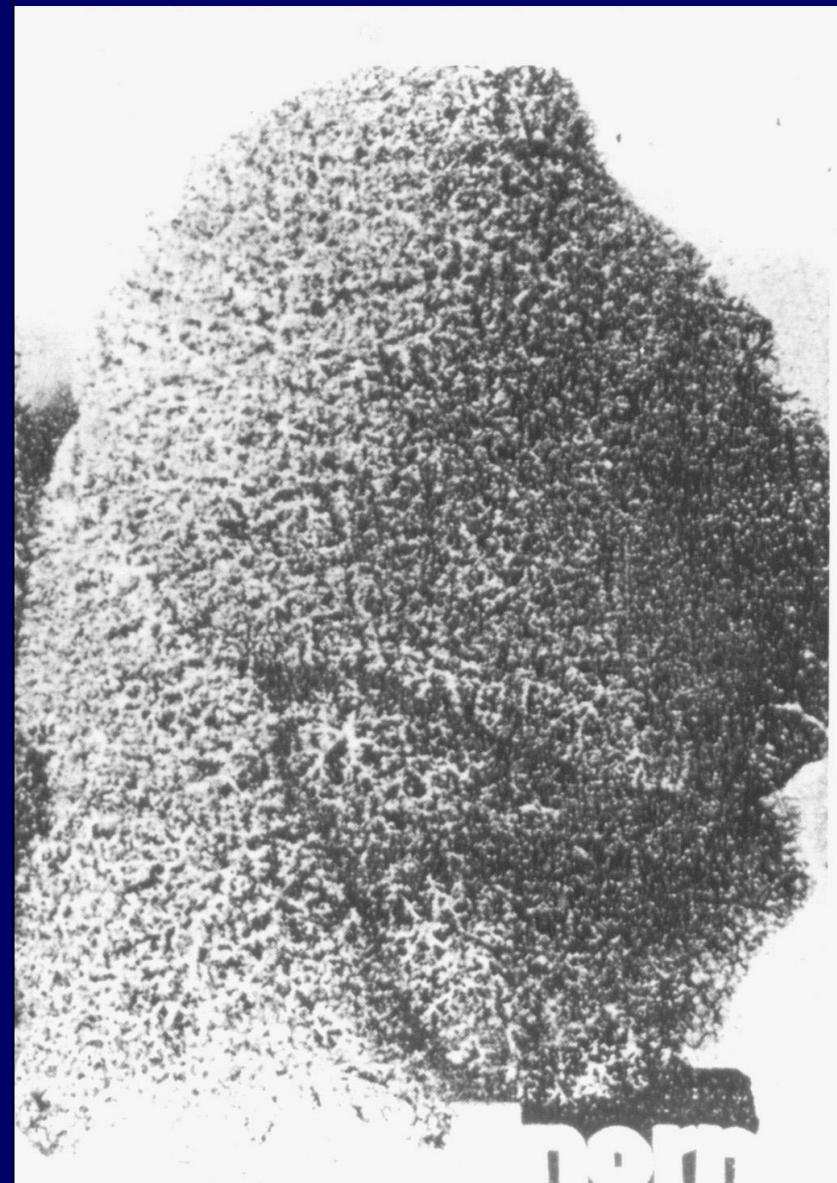


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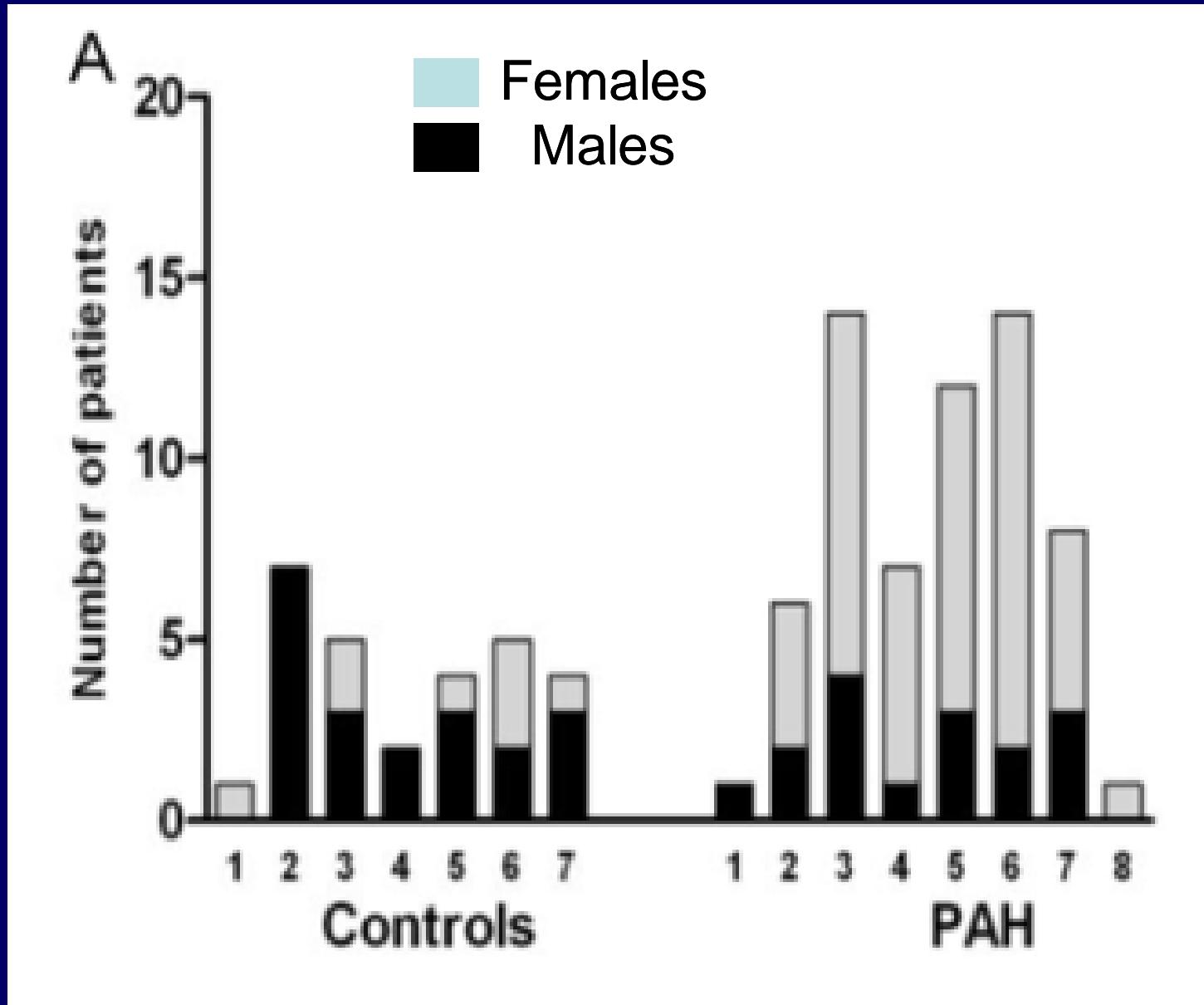


Where do pulmonary vascular lesions occur?

- Number of pulmonary Arteries (17 orders)
 10^8
- Elastic (orders 17-10):
3,000
- Muscular (orders 9-5):
800,000
- Precapillary (orders 4-1;
25 um):
70 million

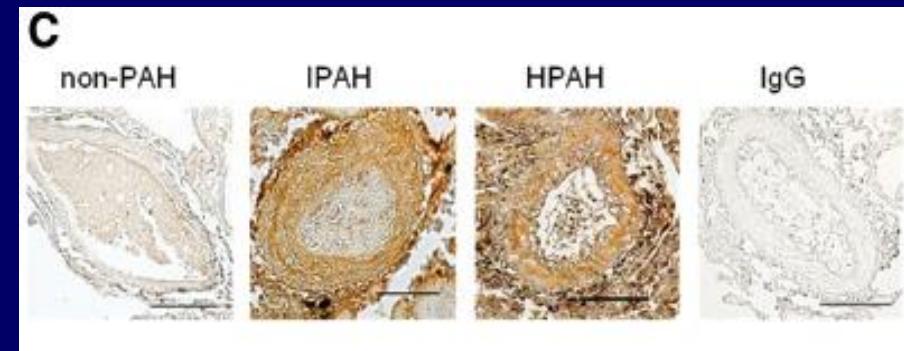
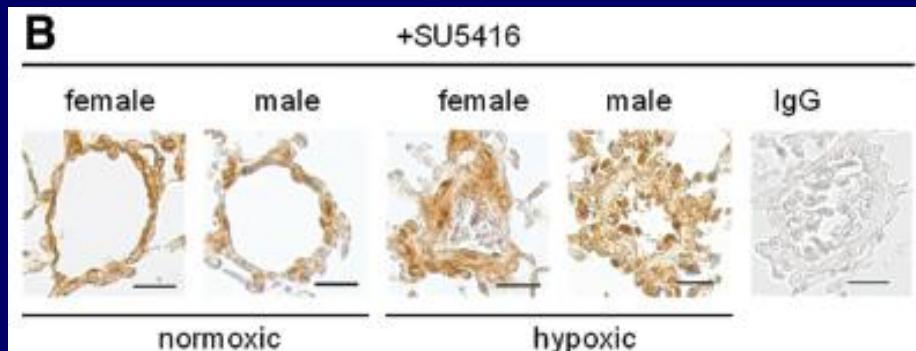
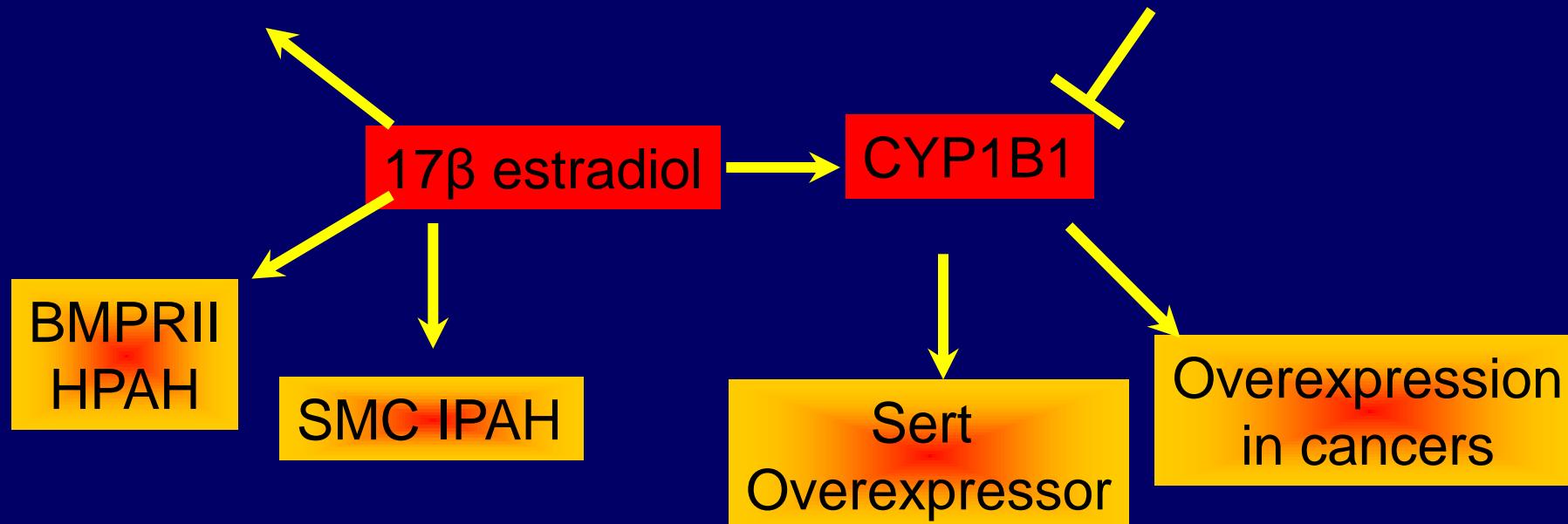


Predominance of PAH in women



4 and 16-hydroxylation of estrogen

Dehydro
epiandrosterone

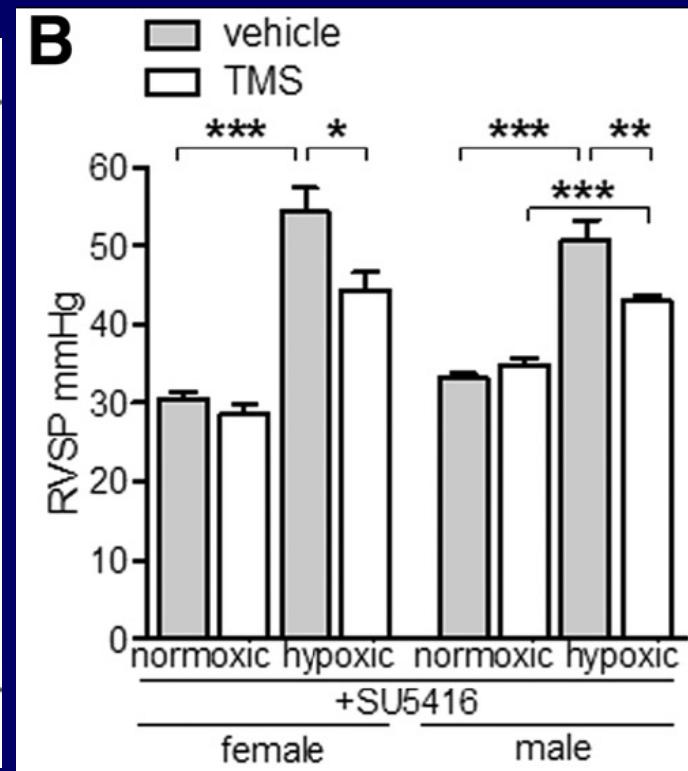
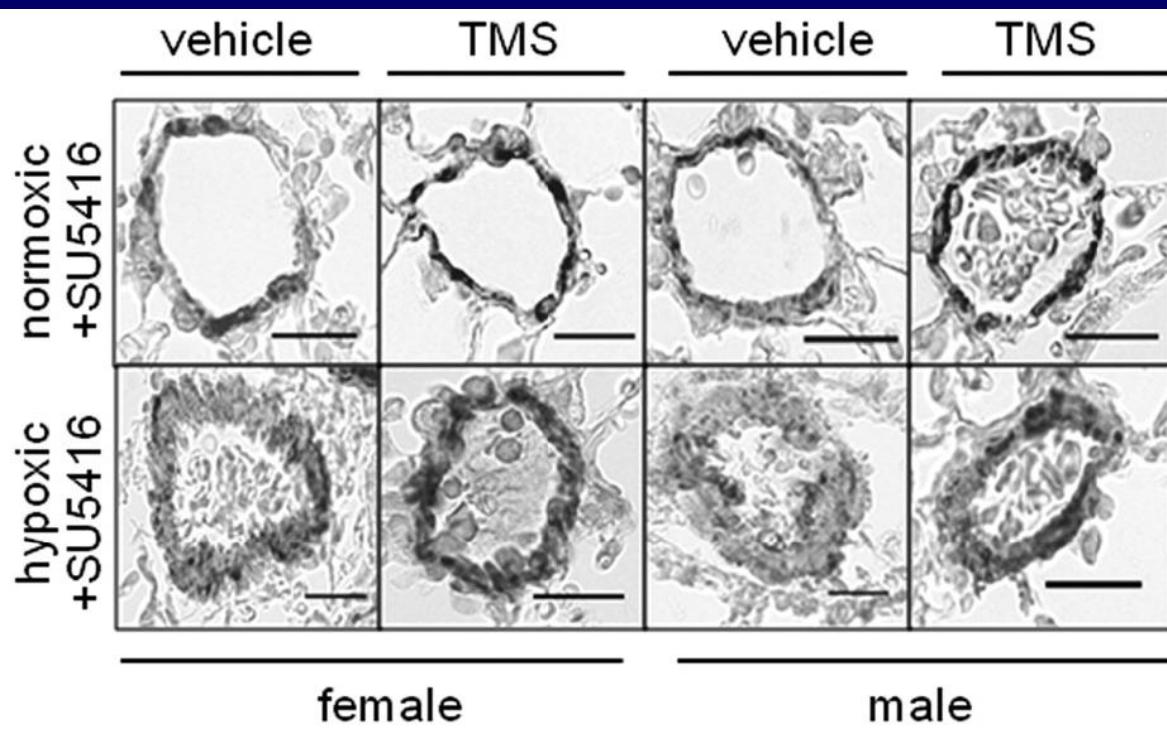


CYP1B1 causes pulmonary hypertension

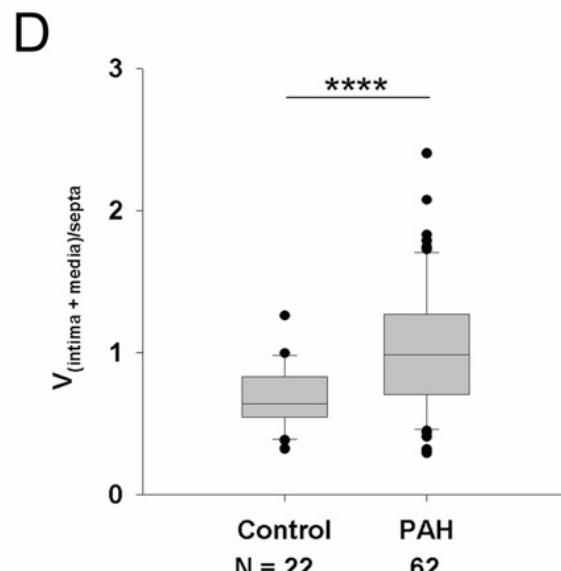
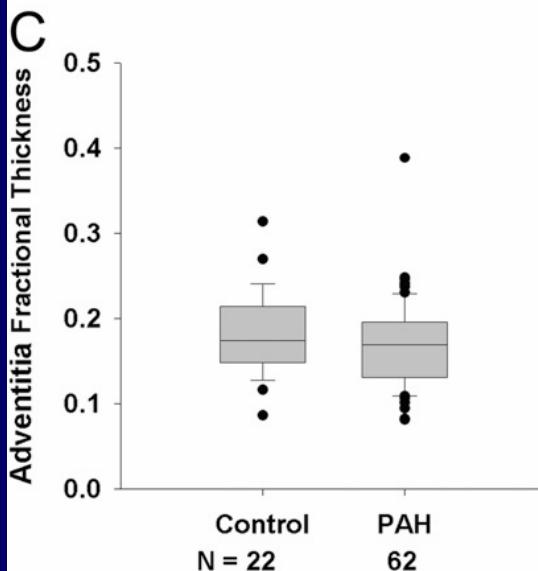
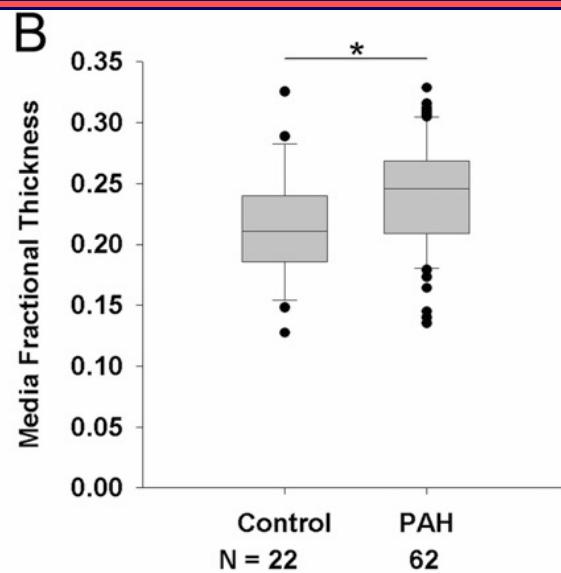
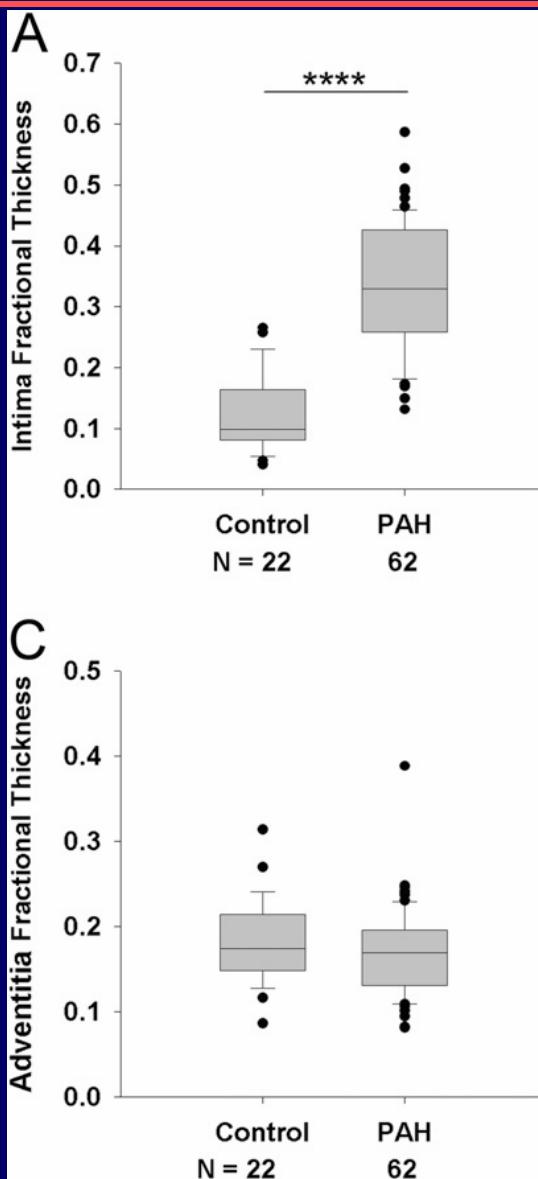
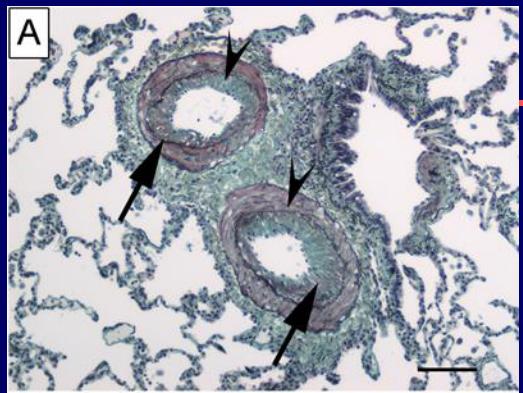
2,3,4,5-tetramethoxystilbene (TMS)



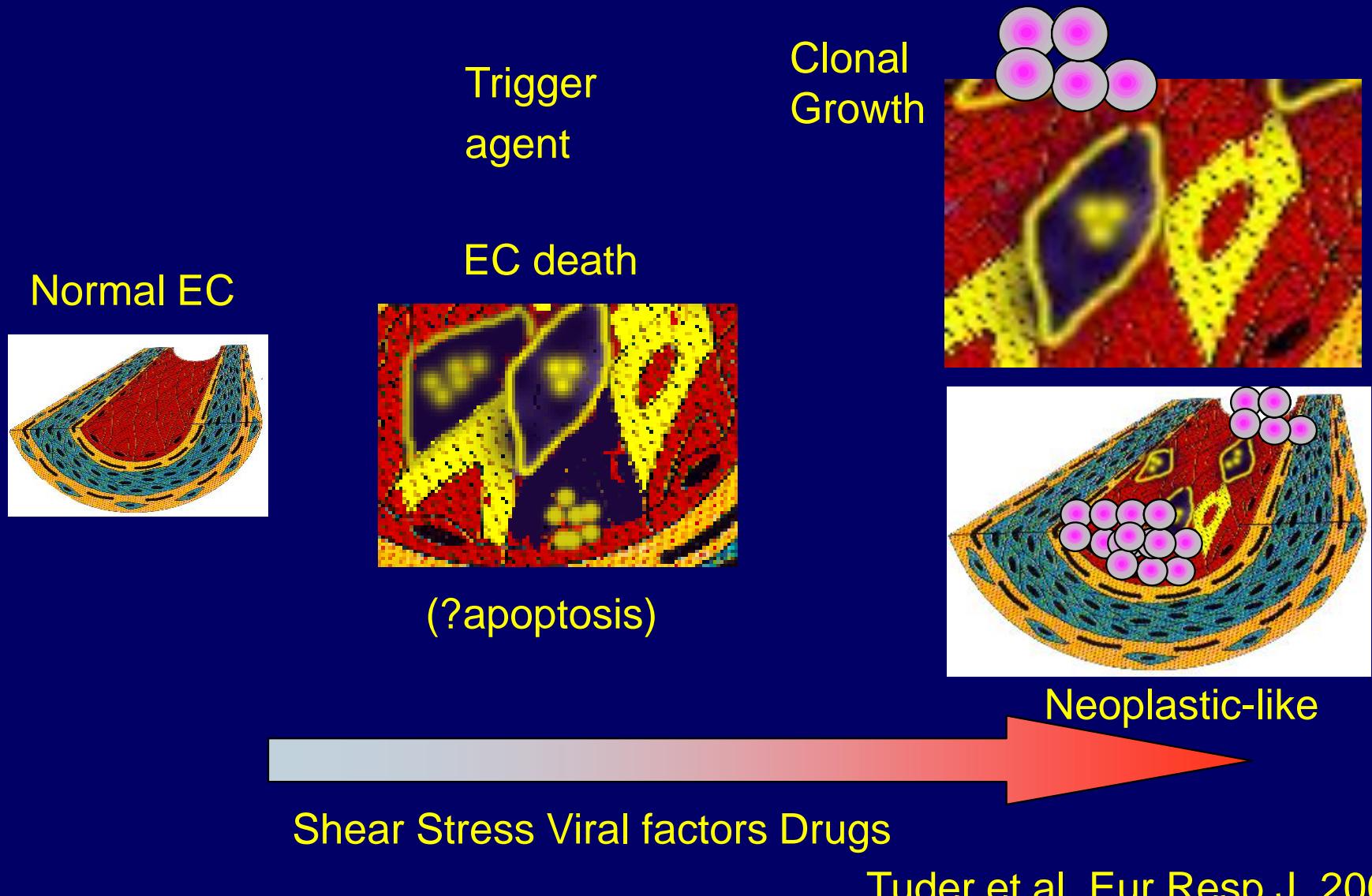
16-OH estrogen ← CYP1B1



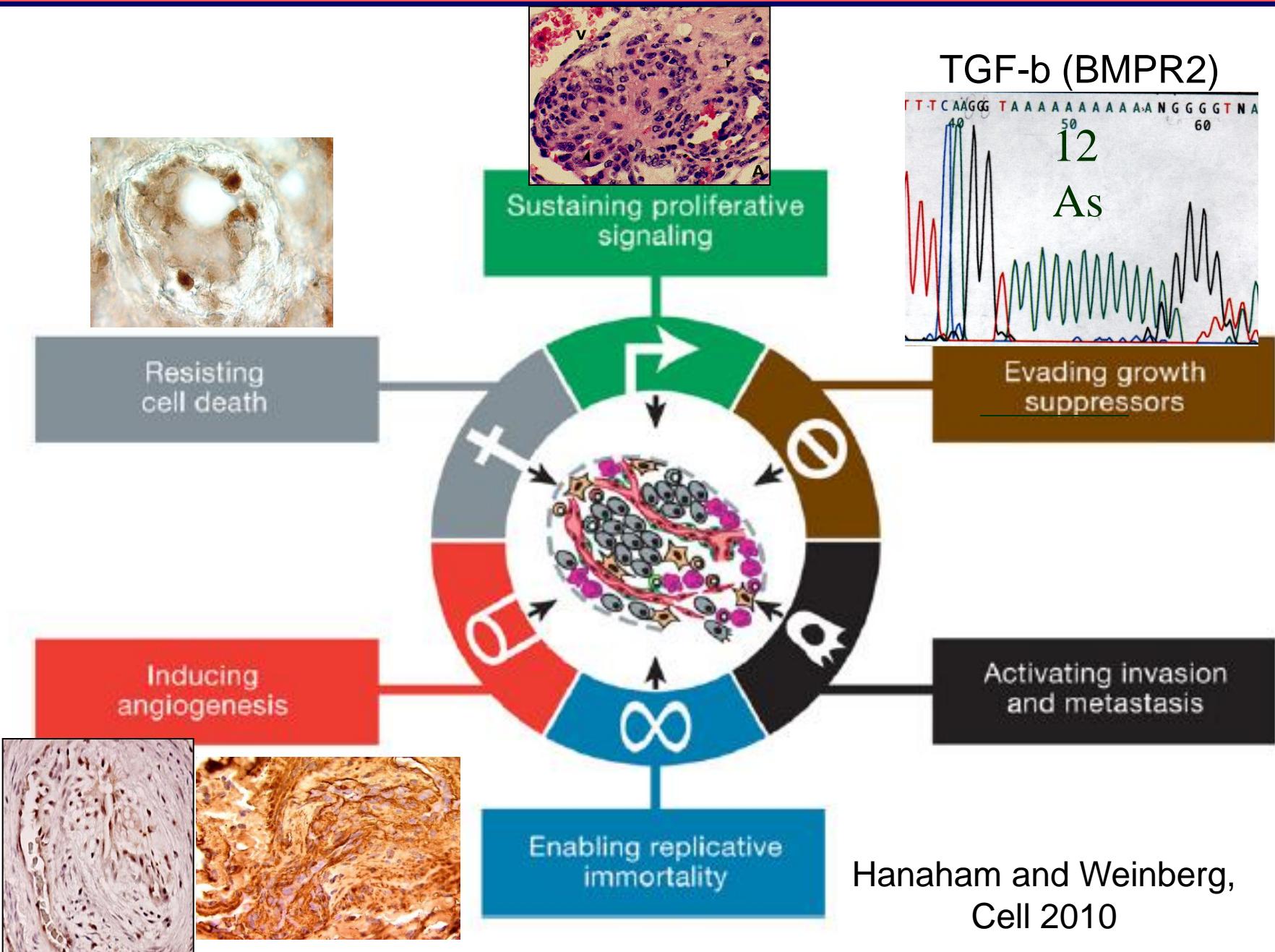
Morphometric parameters: control vs. PAH



Conceptual framework for severe PAH: selection of apoptosis resistance

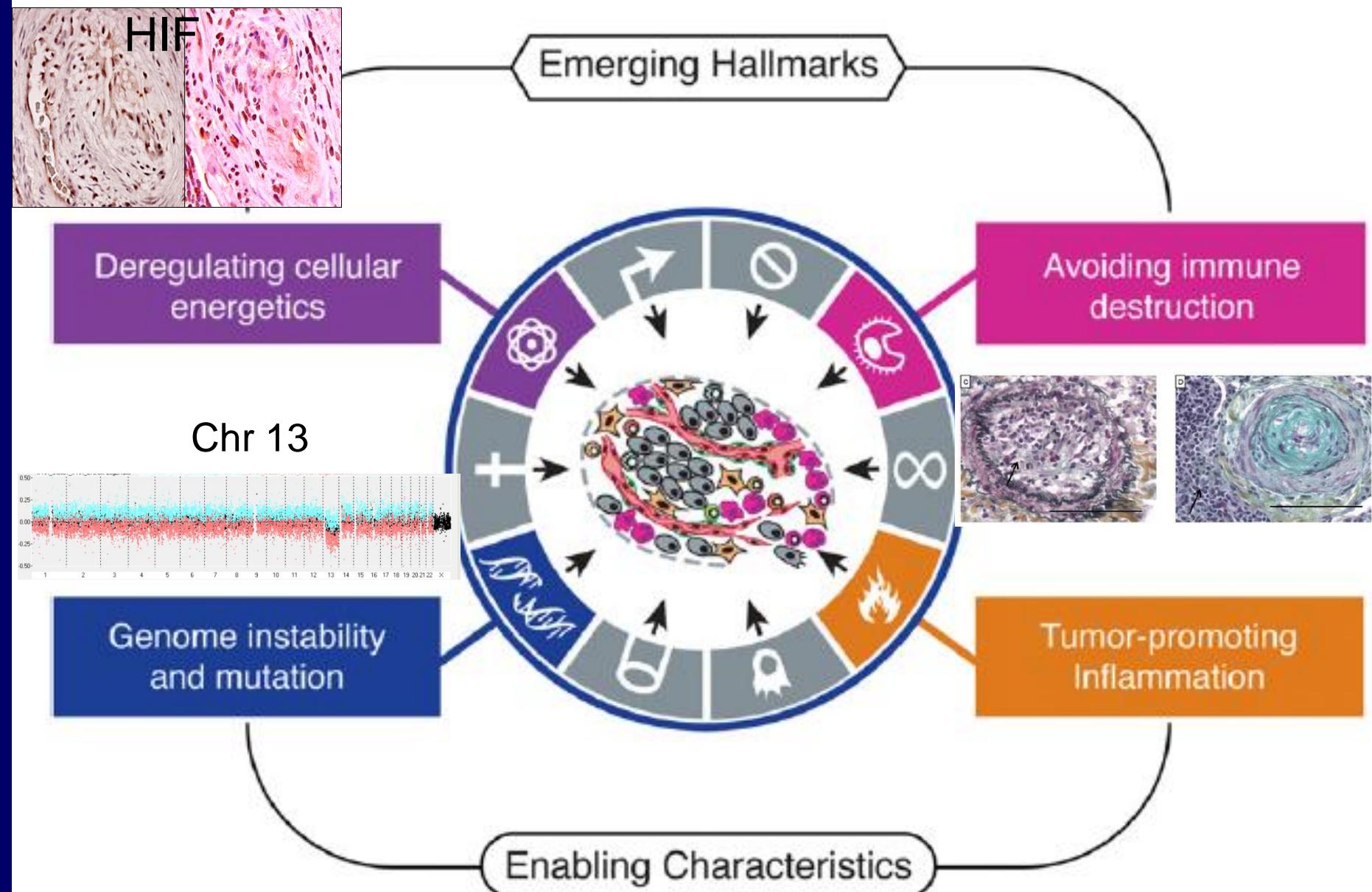


Key features of cancer

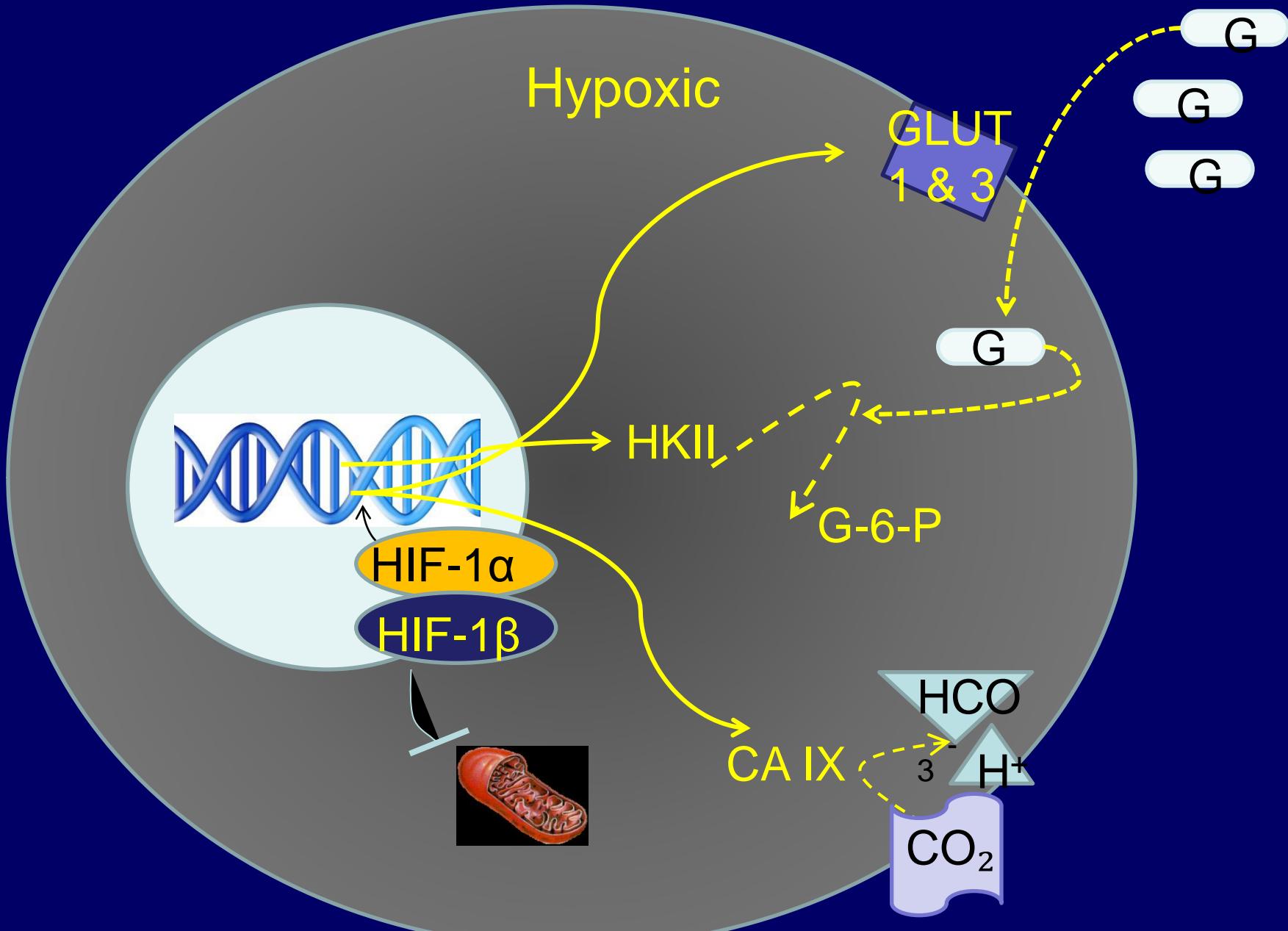


Hanahan and Weinberg,
Cell 2010

(Revisited) Key features of cancer

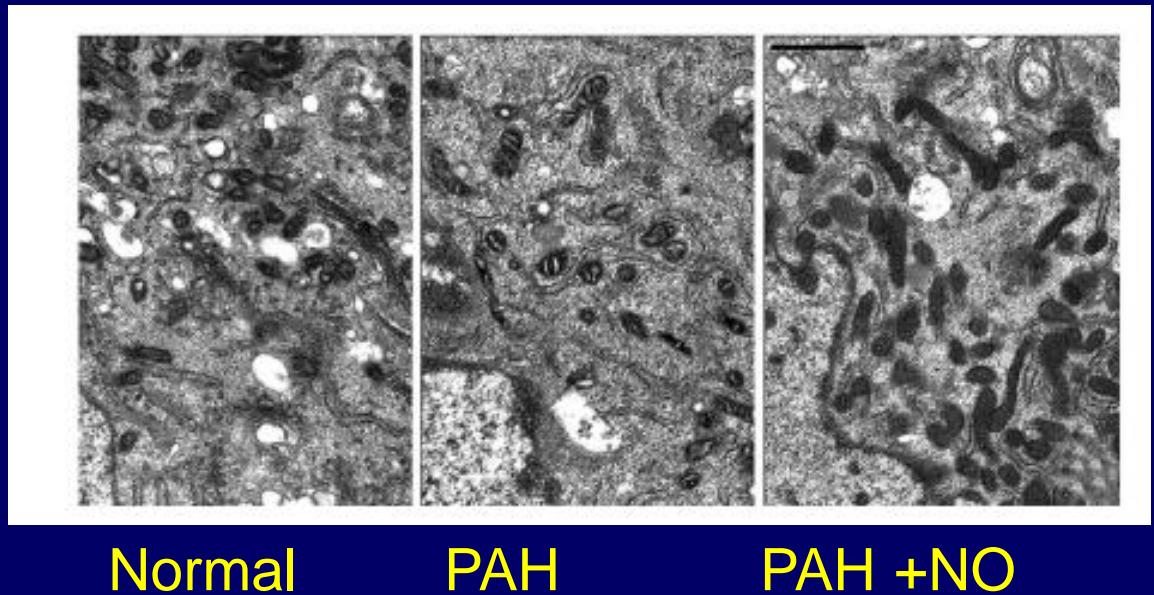
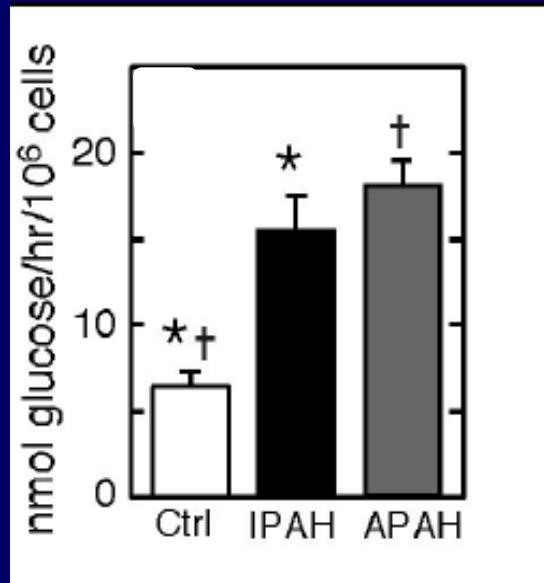


HIFs and Pulmonary Hypertension



PH Endothelial Cells: Shift to a Glycolytic Pathway

PH ECs have less mitochondria

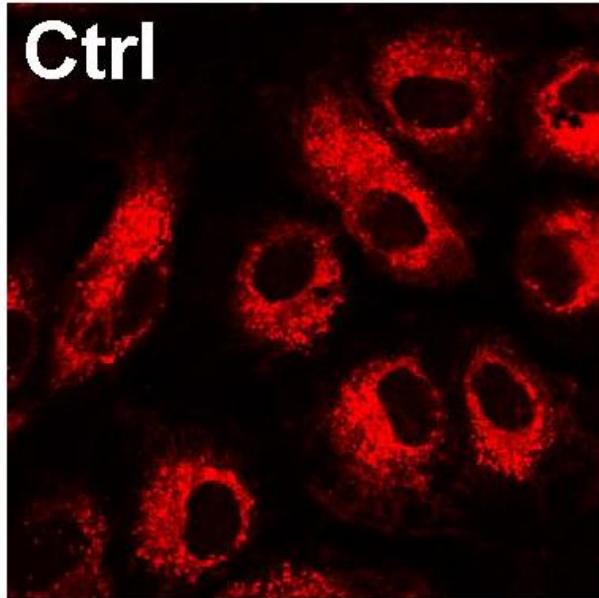


Cleveland Clinic: Serpil Erzurum, Weiling Xu, Suzy Comhair,
Raed Dweik, Kewal Asosingh

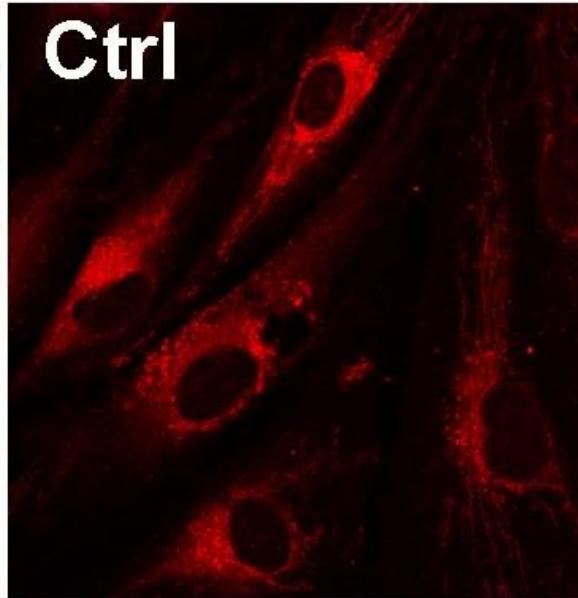
IPAH-ECs energetic switch:

a No DNA Anti-HIF miRNA Neg miRNA

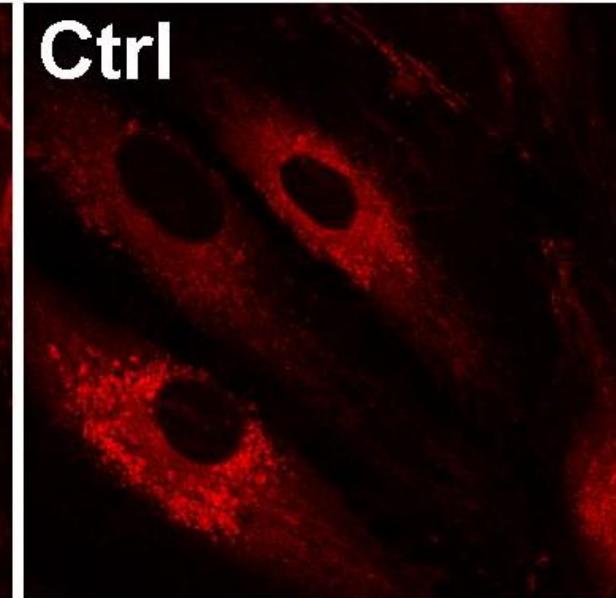
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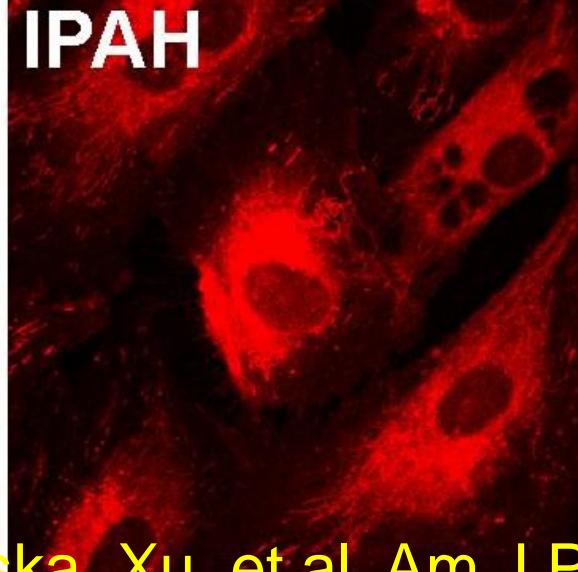
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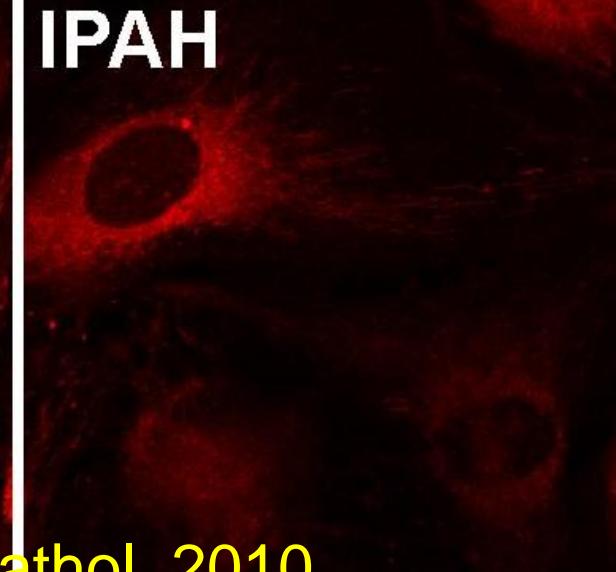
IPAH



IPAH

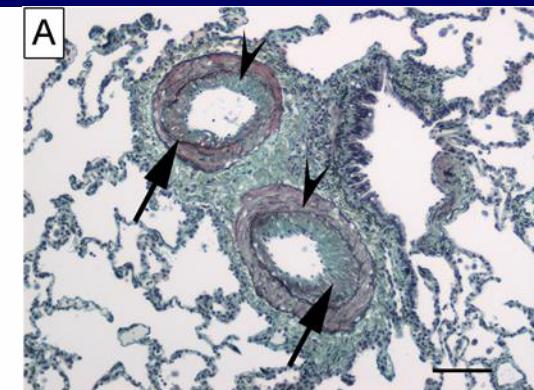
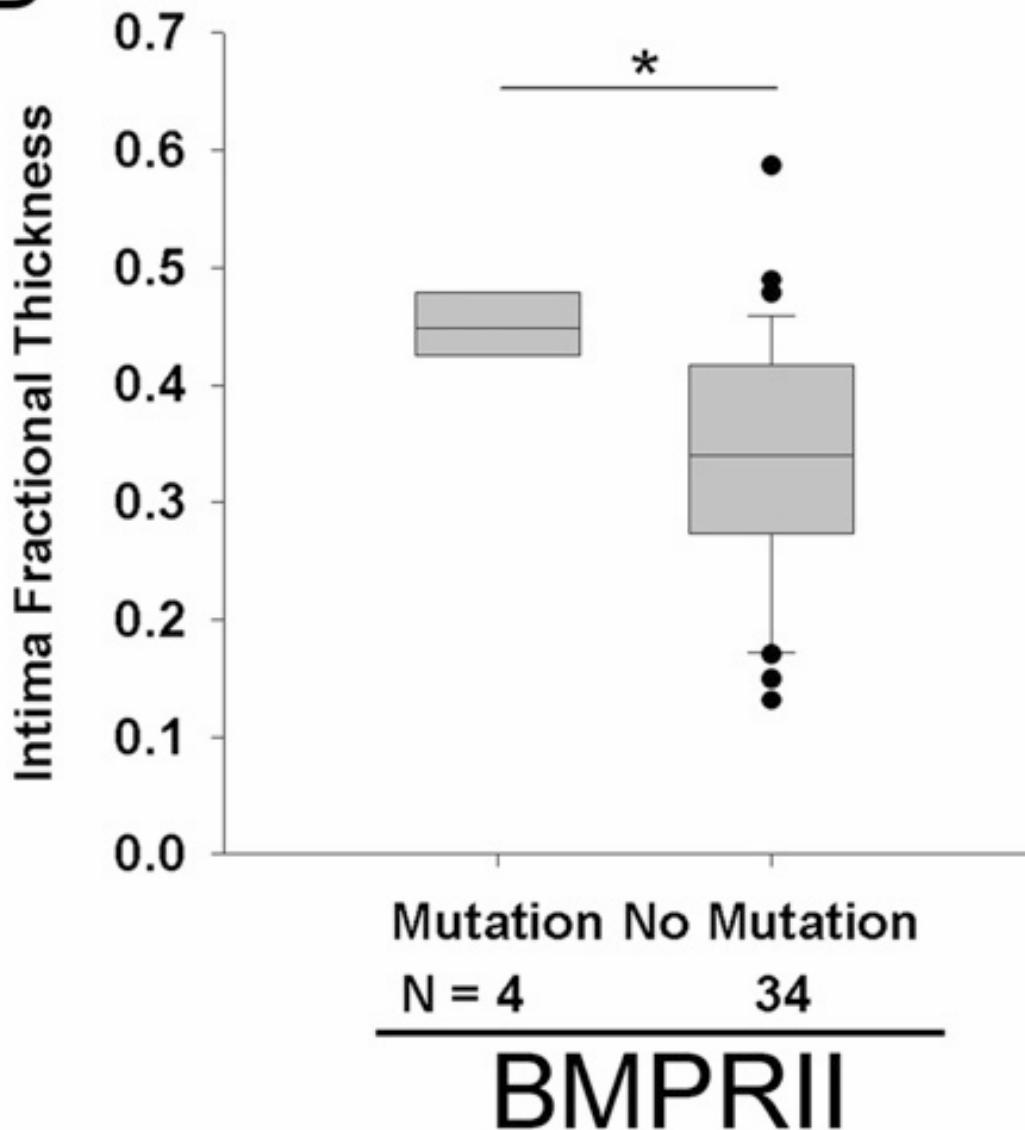


IPAH

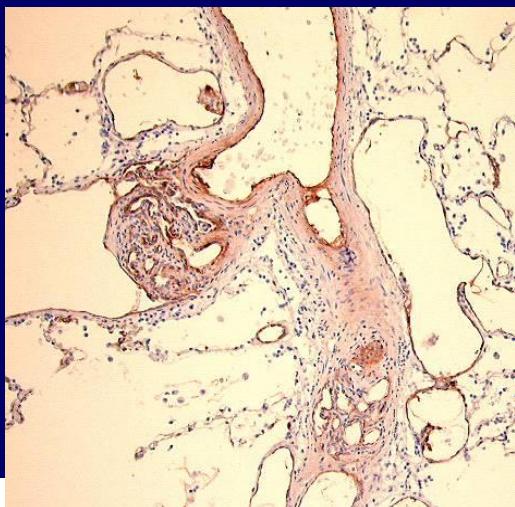


BMPRII: worse pulmonary vascular remodeling

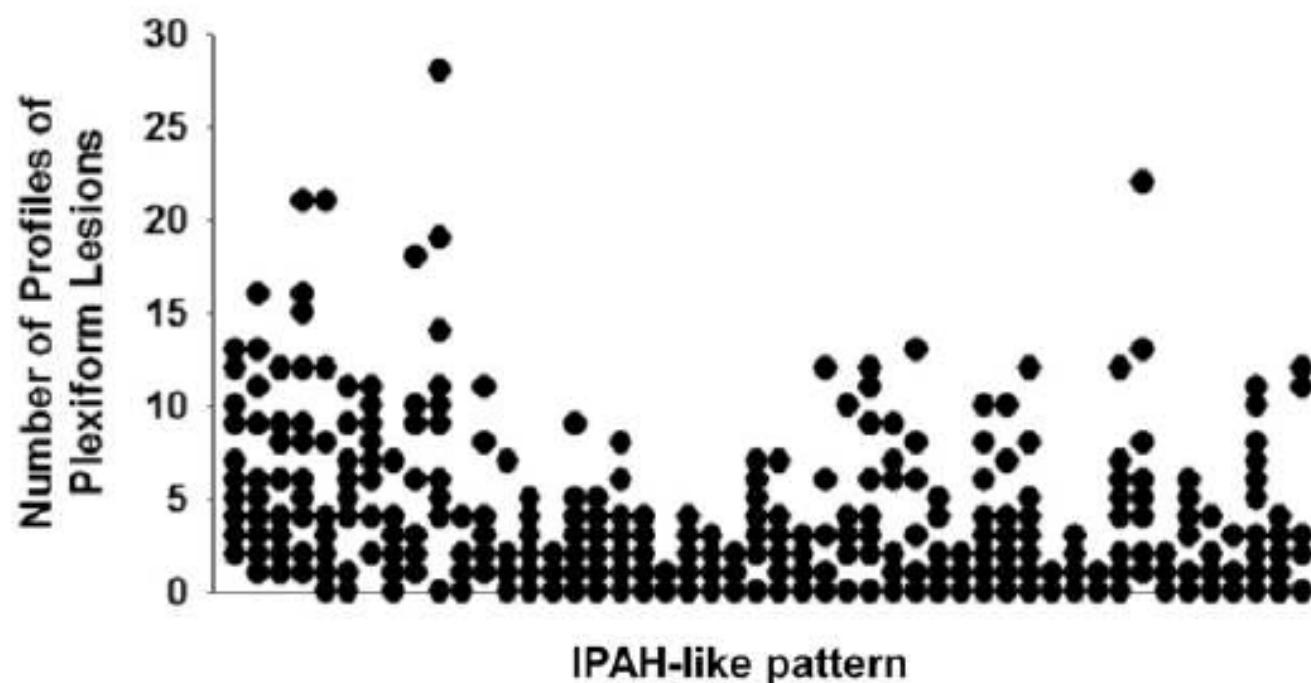
D



Plexiform lesions

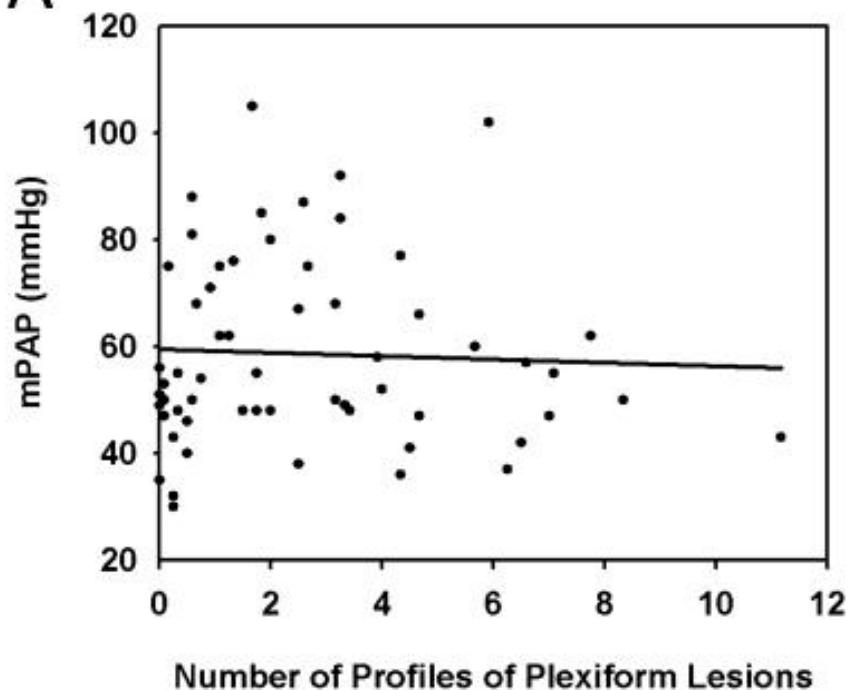


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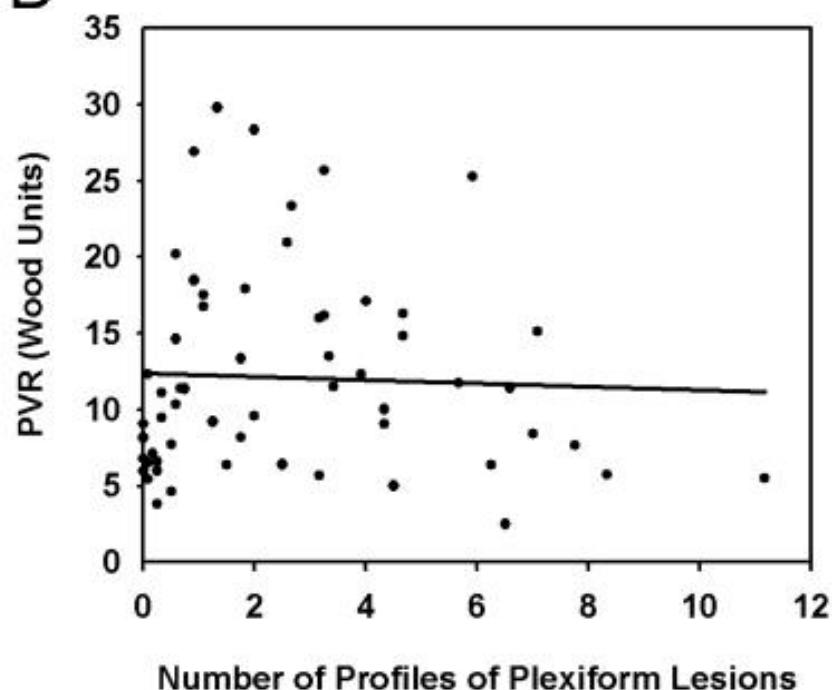


Morphometric parameters and pathological PAH subphenotypes: plx lesions

A

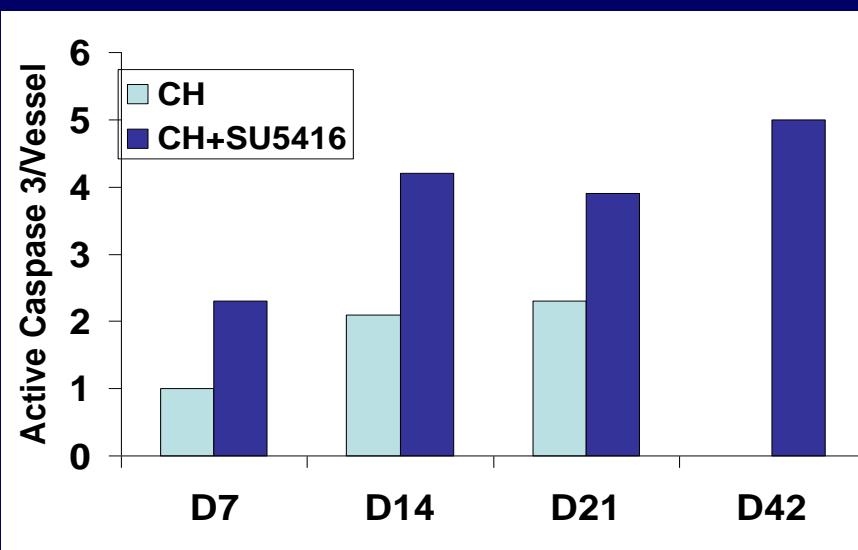
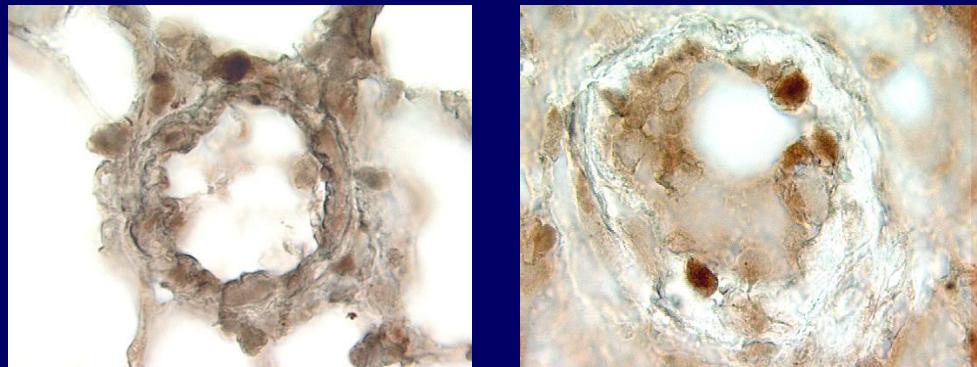


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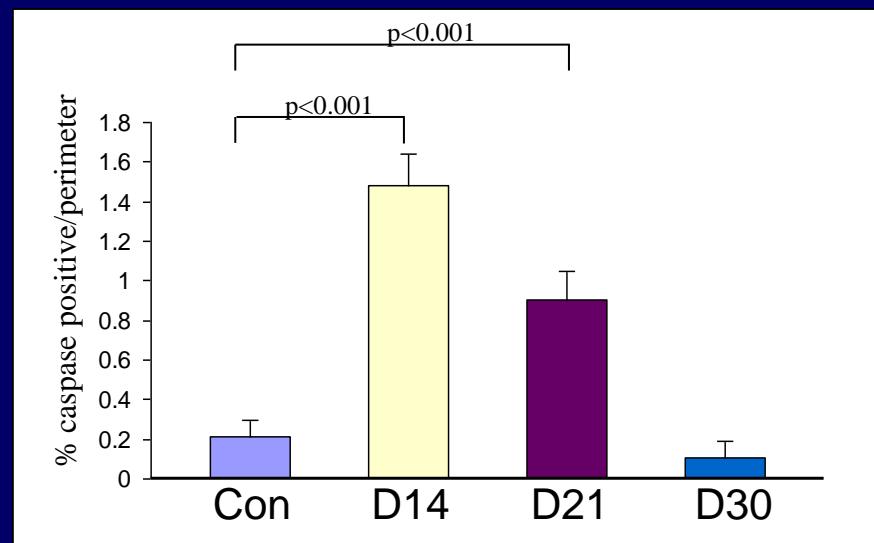
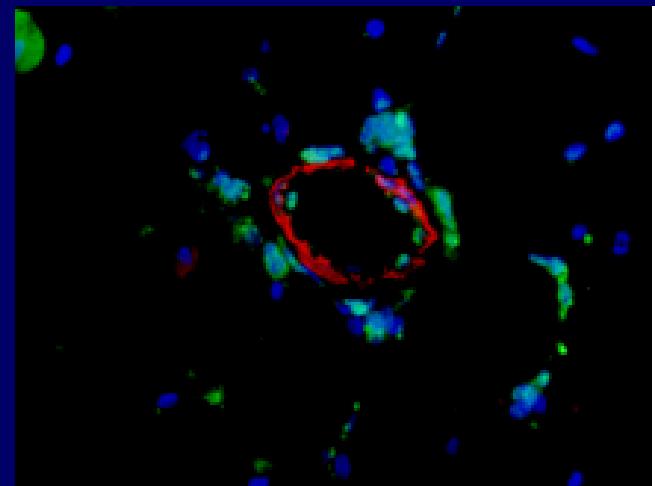


Role of EC APOPTOSIS in the genesis of severe PH SU5416+CH and MCT Models

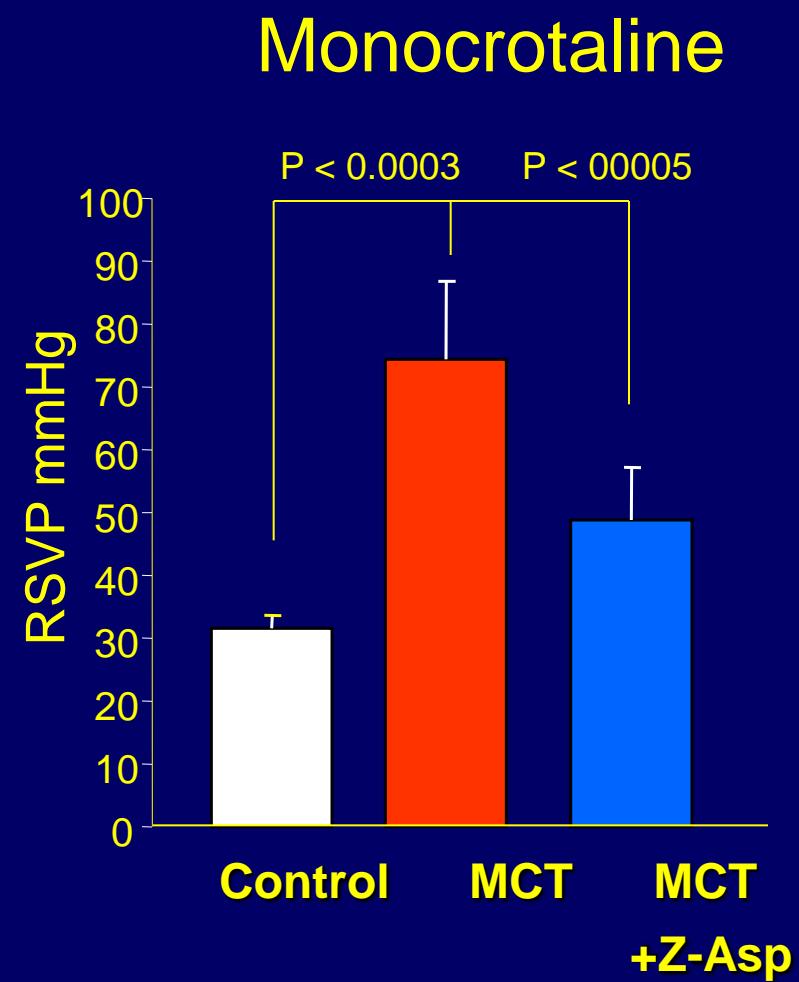
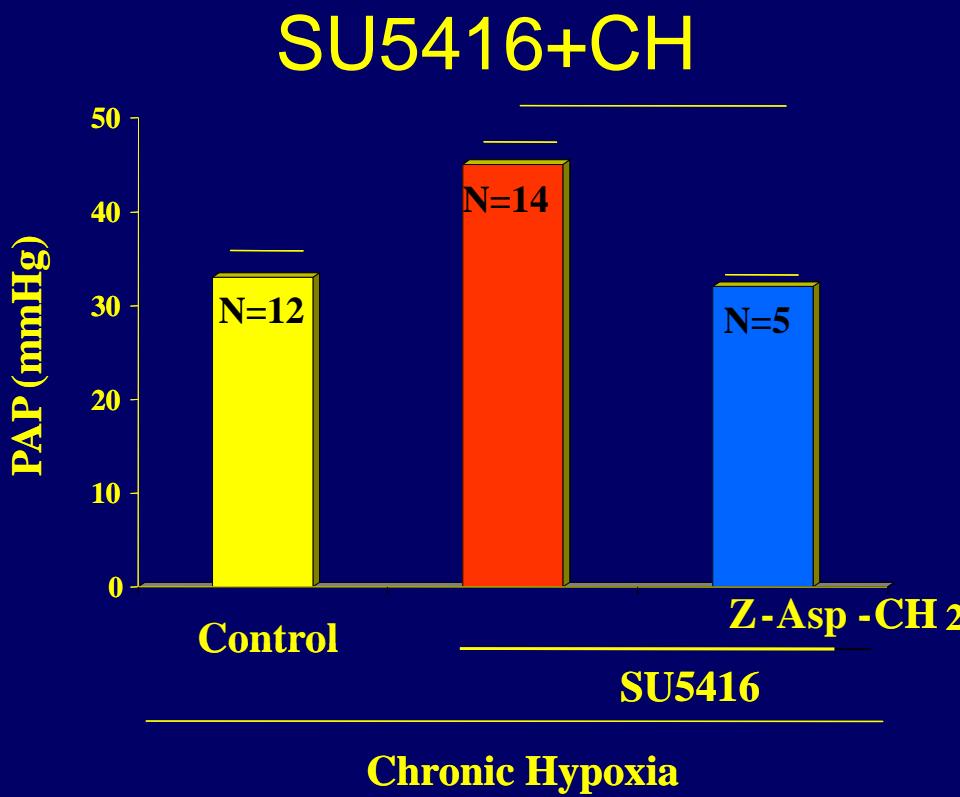
Chronic hypoxia CH+ SU5416



Monocrotaline

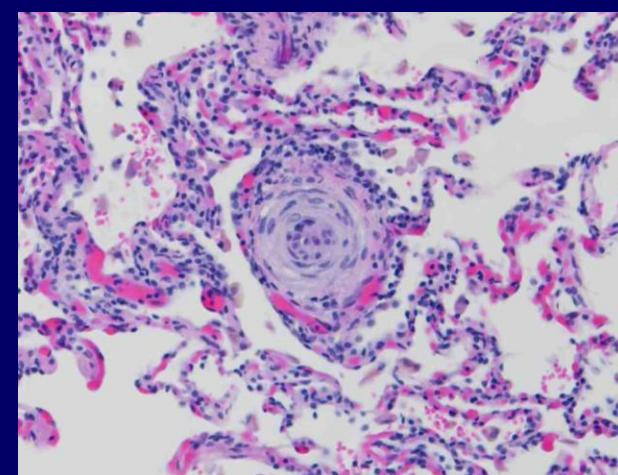
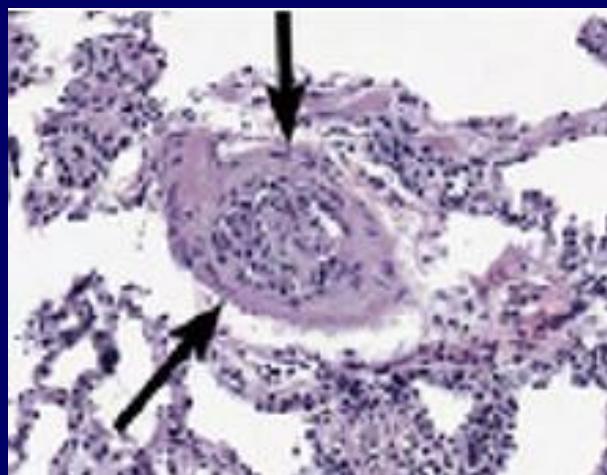
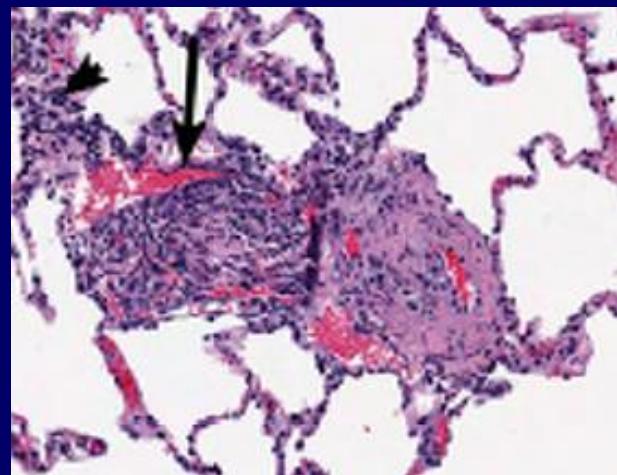


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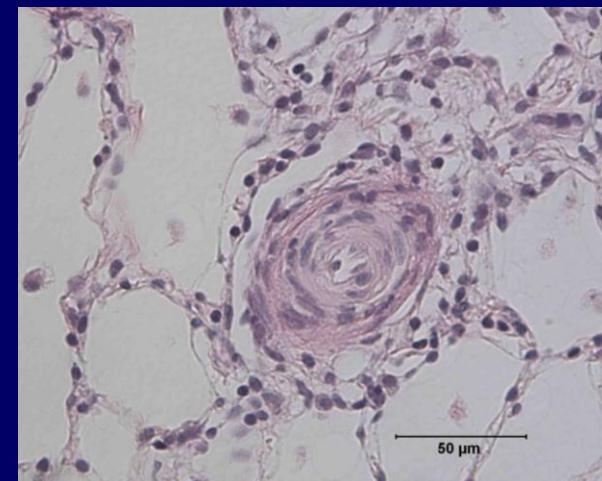
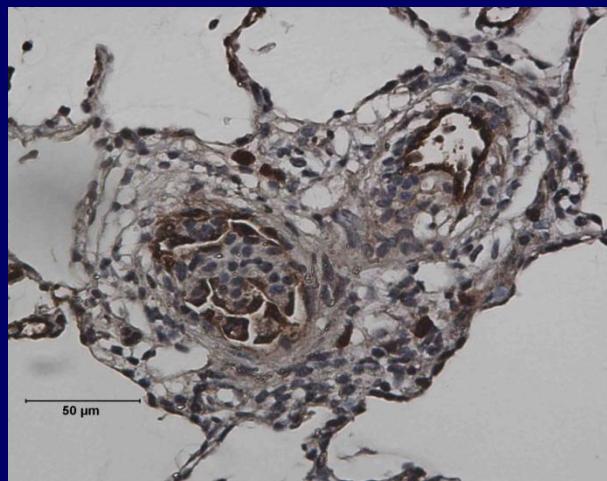
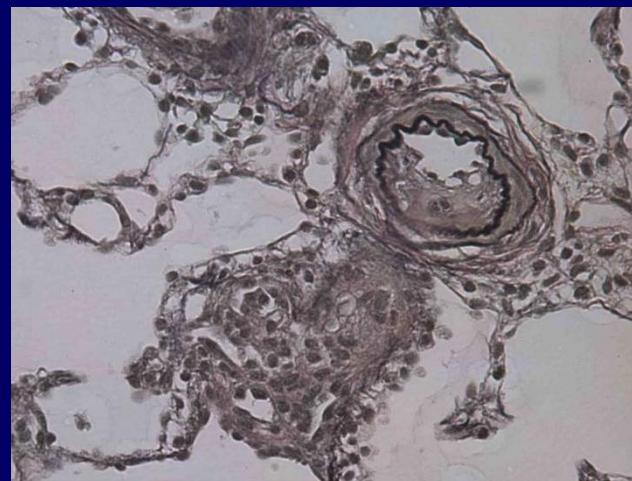


VEGF receptor blockade: SU5416+CH rat model of human PAH with endothelial cell proliferation

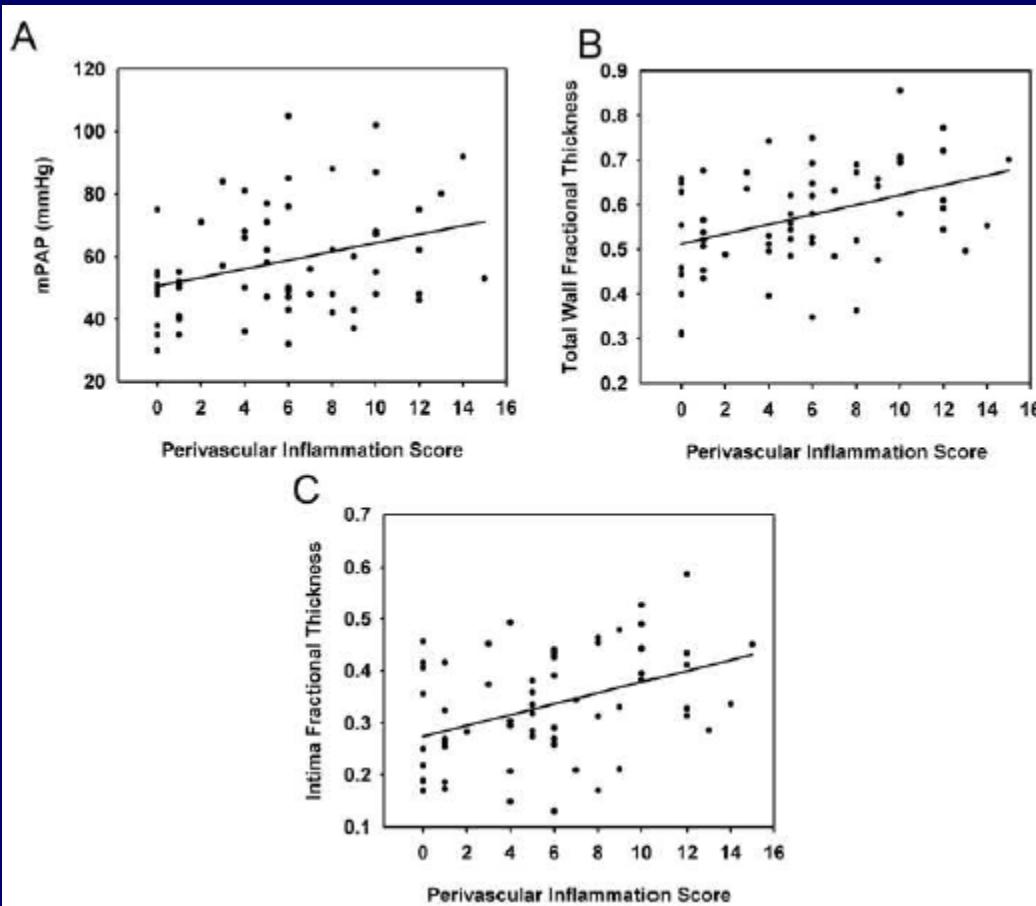
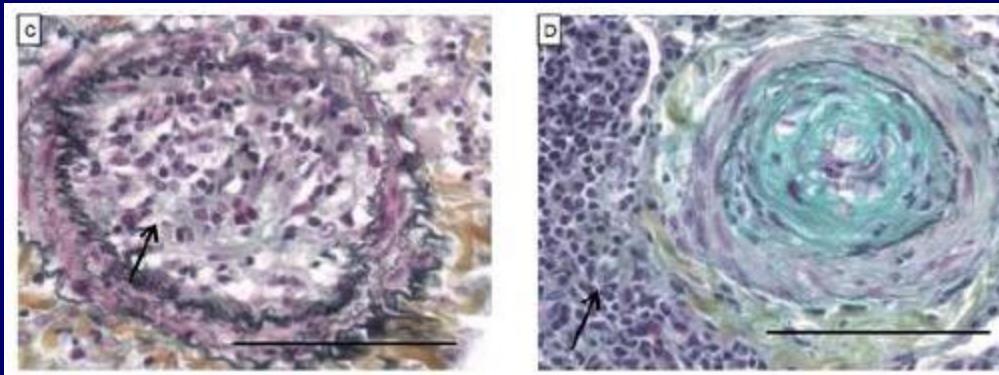
Human IPAH



Rat IPAH-like



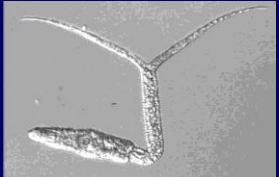
Impact of perivascular inflammation



Stacher et al.,
AJRCCM,
2012

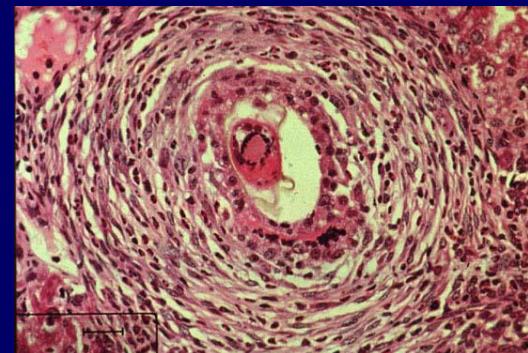
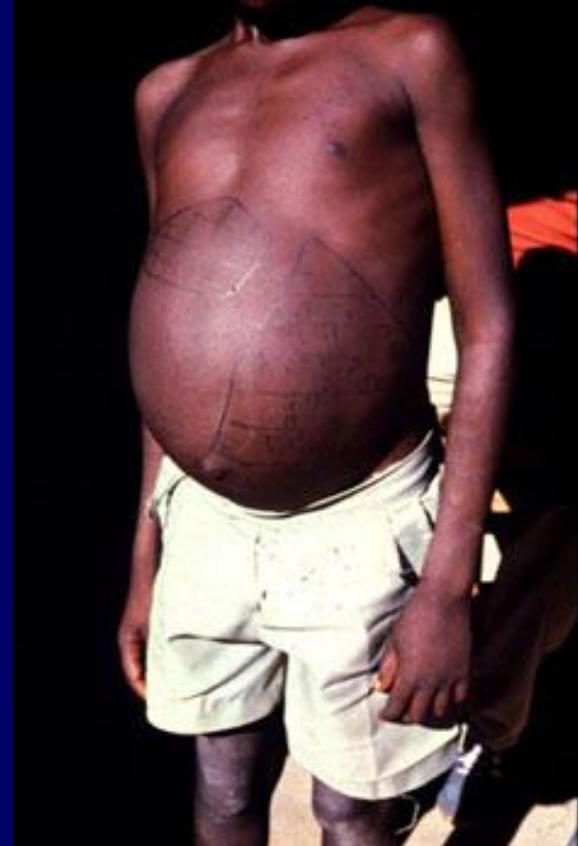
Schistosomiasis

Cercariae

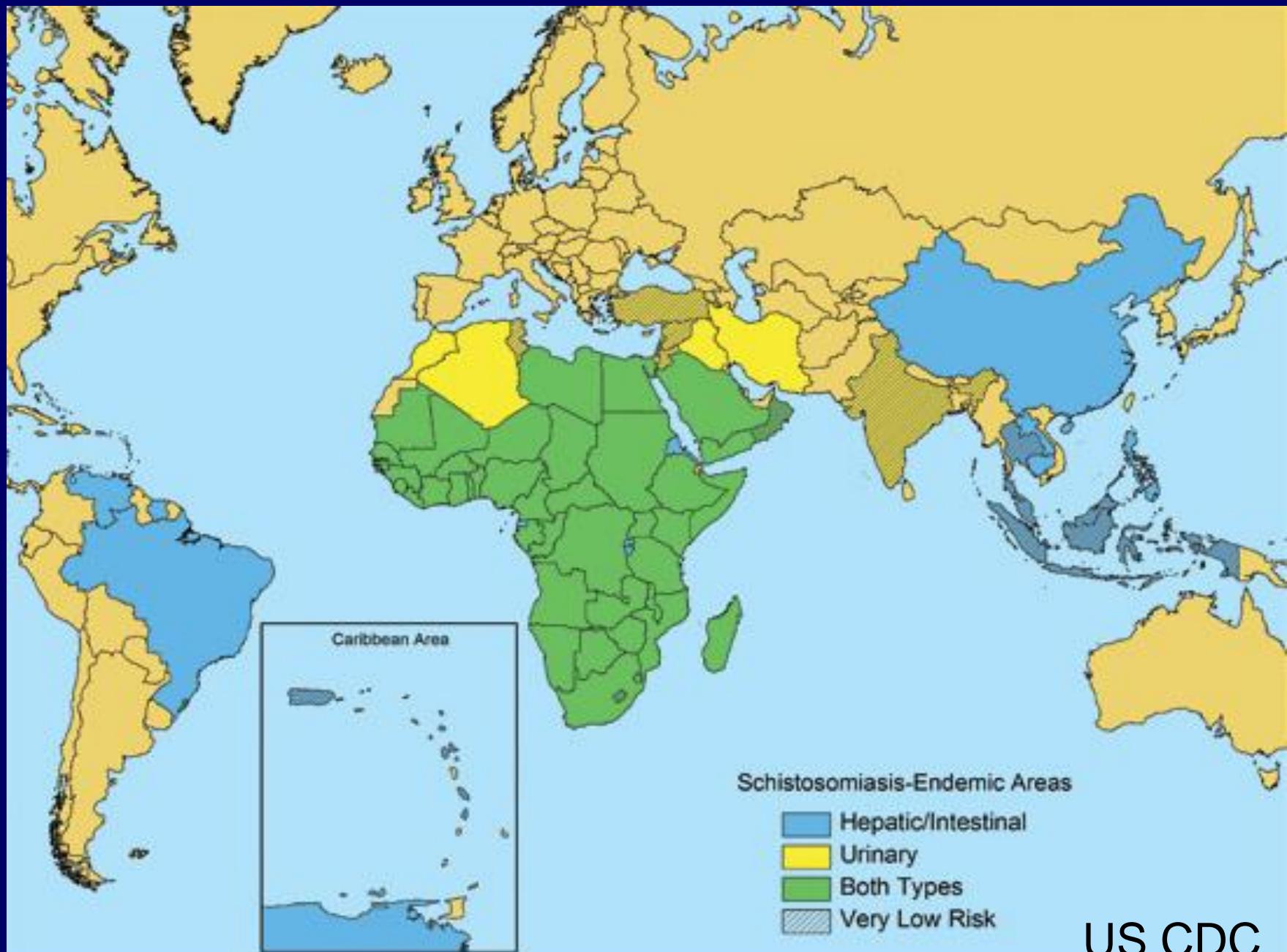


Egg

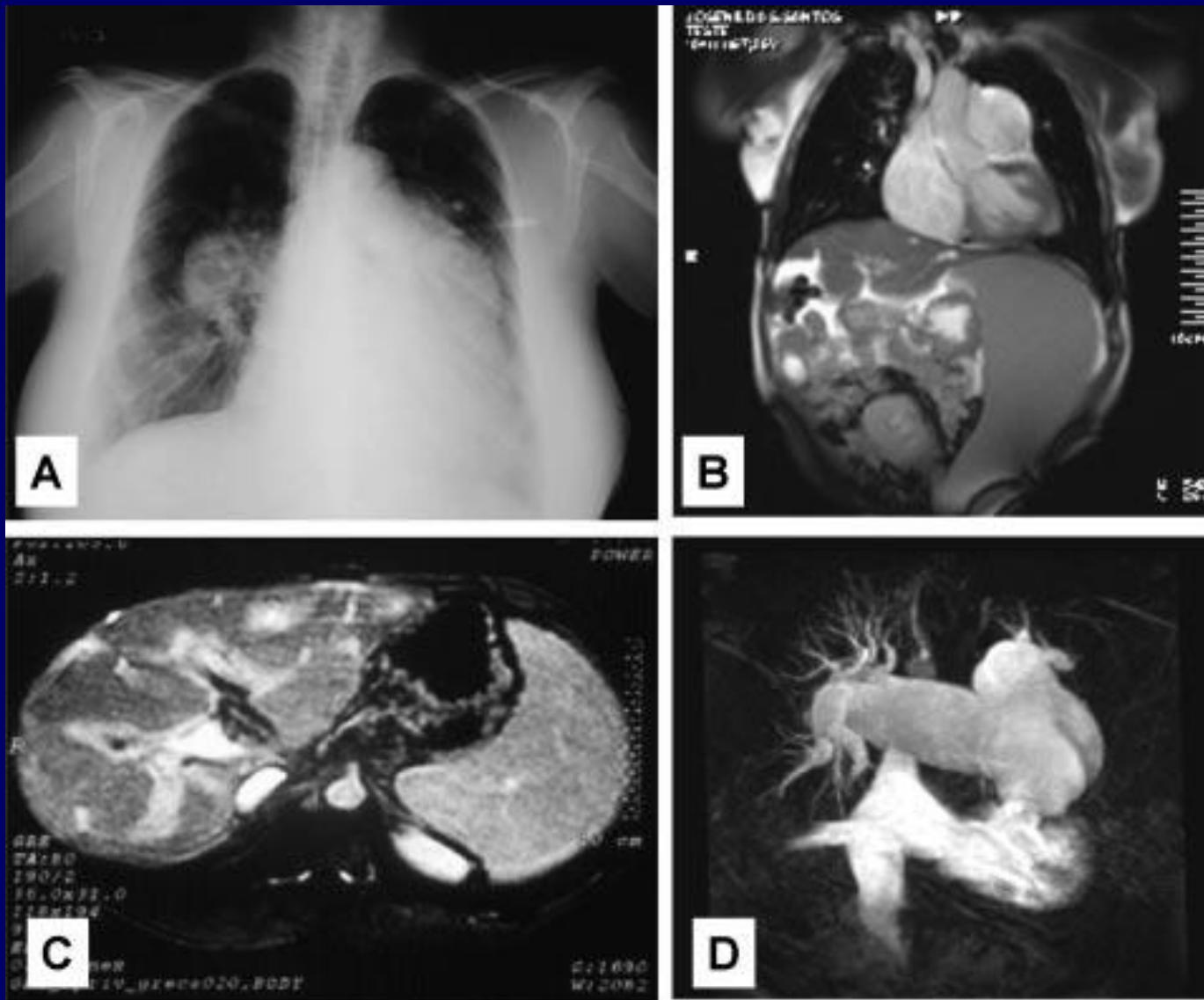
S mansoni and
S japonicum



200 million people affected by Schistosomiasis

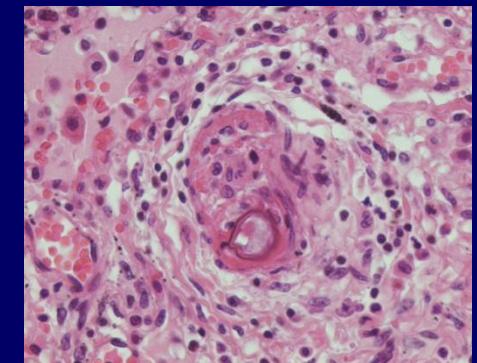
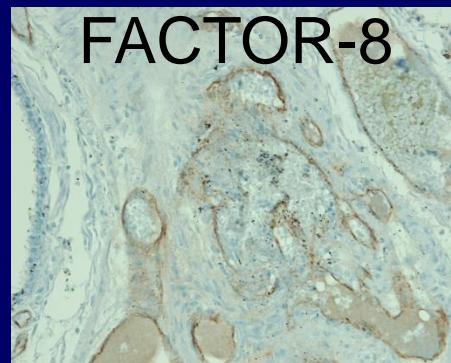


Schistosomiasis-PAH



Butrous et al. Circulation, 2008; courtesy of Dr. Angela Bandeira

Schistosomiasis-PAH: Pathology



Courtesy Prof. Zilton Andrade

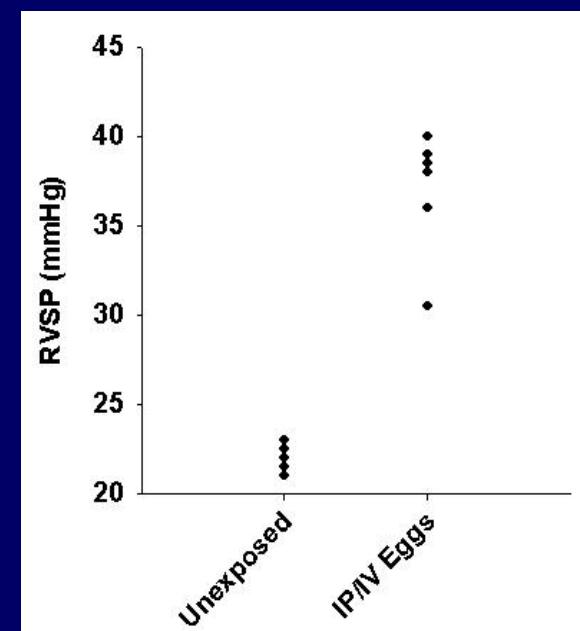
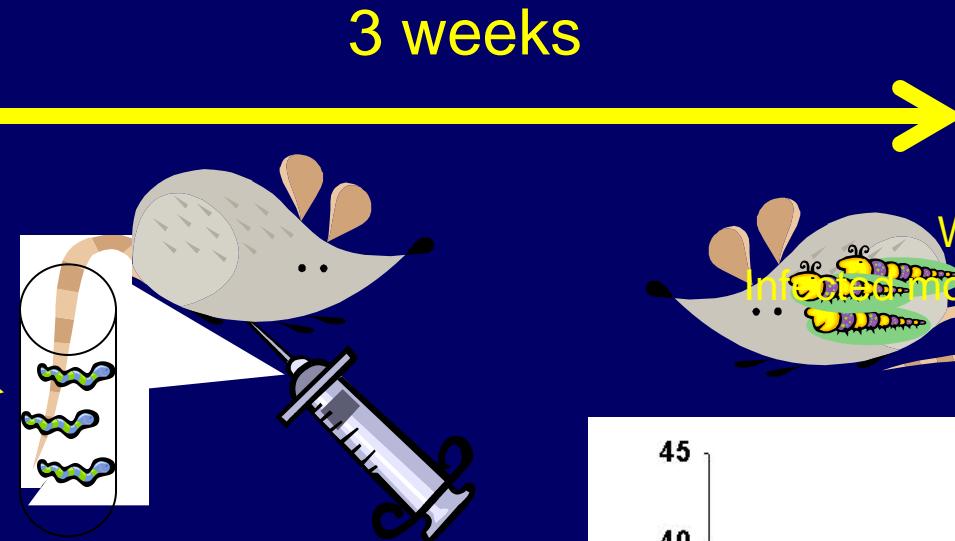
Mouse model of Schisto-PH



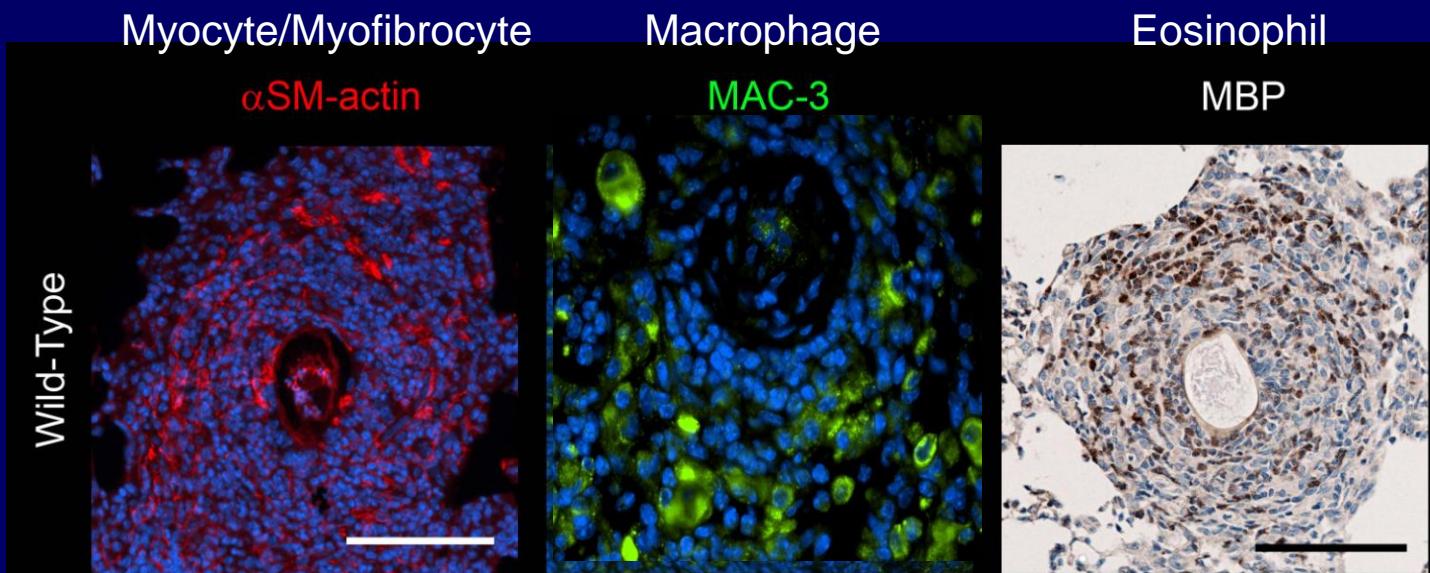
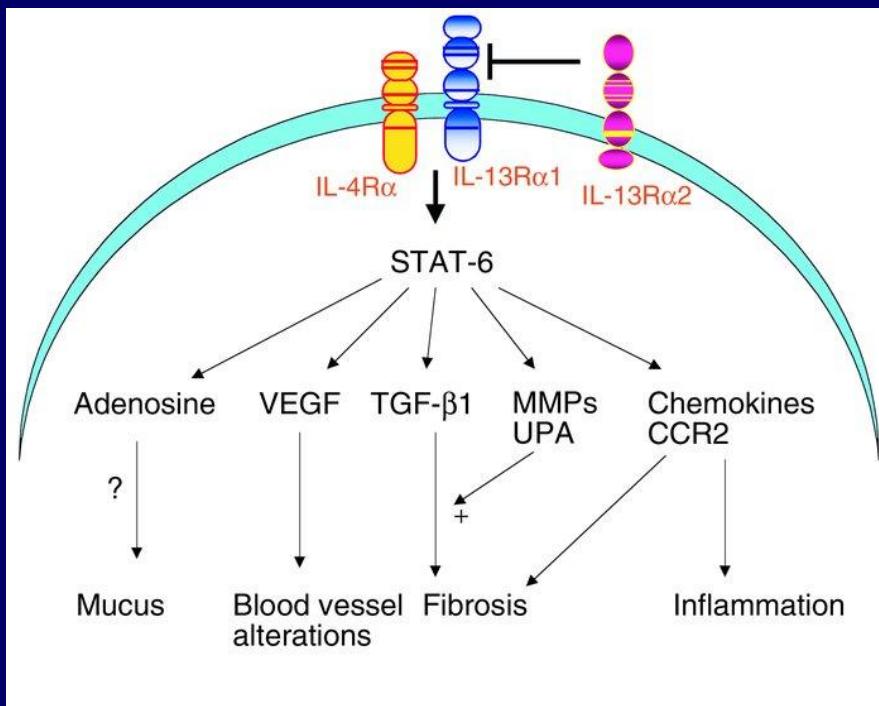
Purified ova



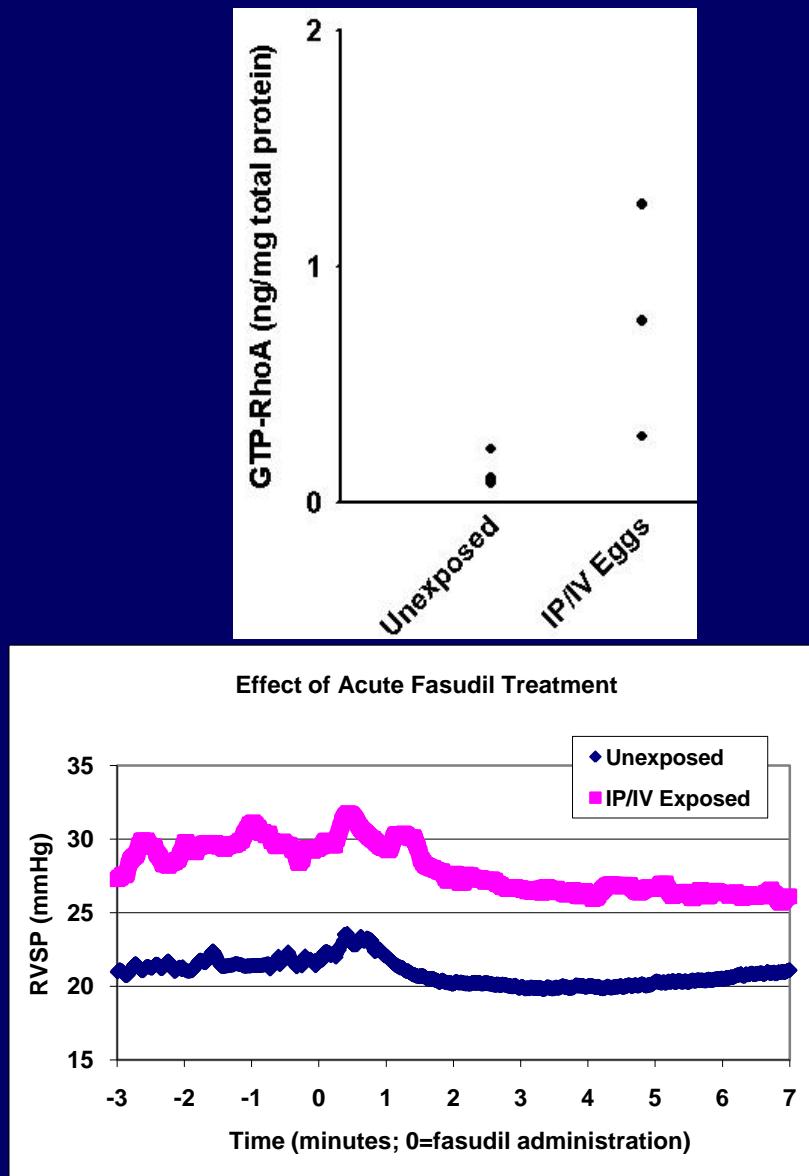
Cercariae



Th2 Peri-Egg Granulomas



Schisto-PH: combined remodeling and vasoconstriction (Rho kinase)



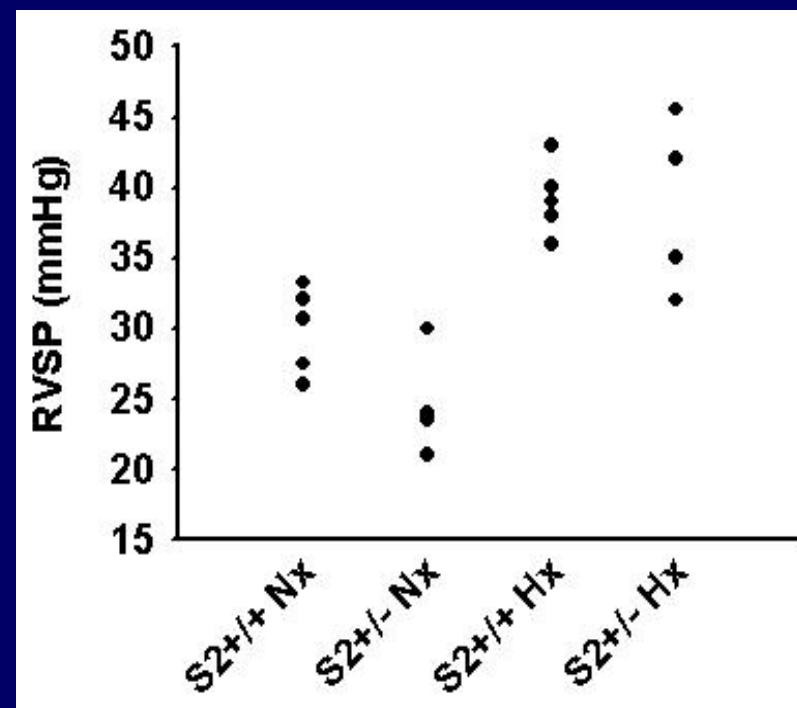
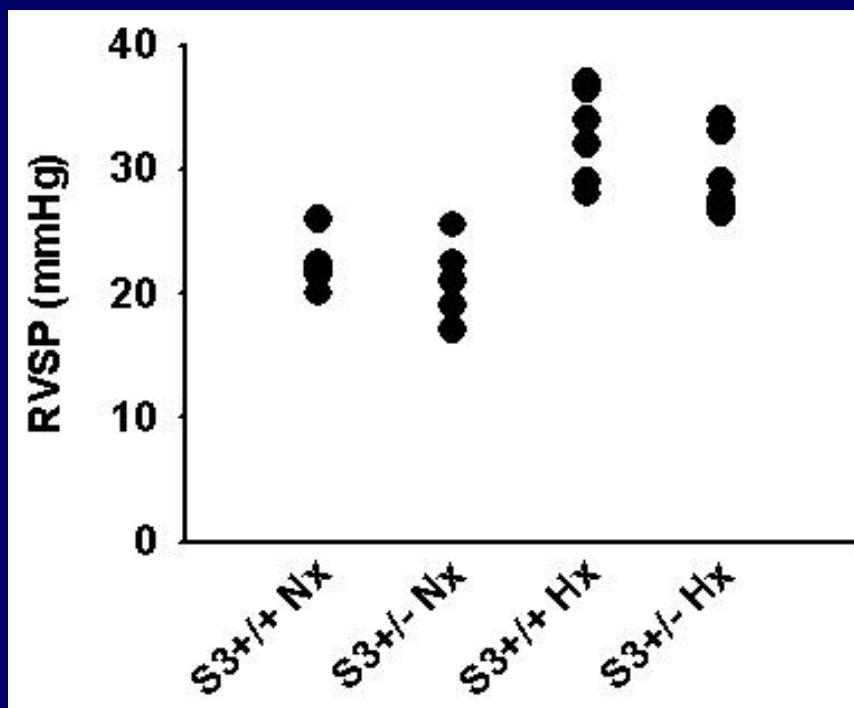
Lack of role for selective loss of either Smad2 or Smad 3 in hypoxic PH

Hypoxia:
50% 3 weeks

TGF- β

\rightarrow RII \rightarrow

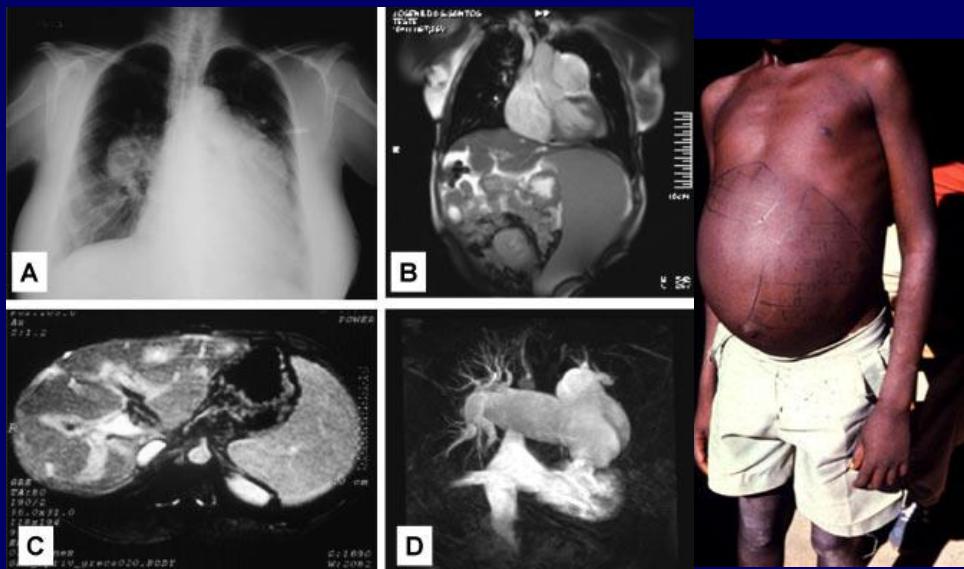
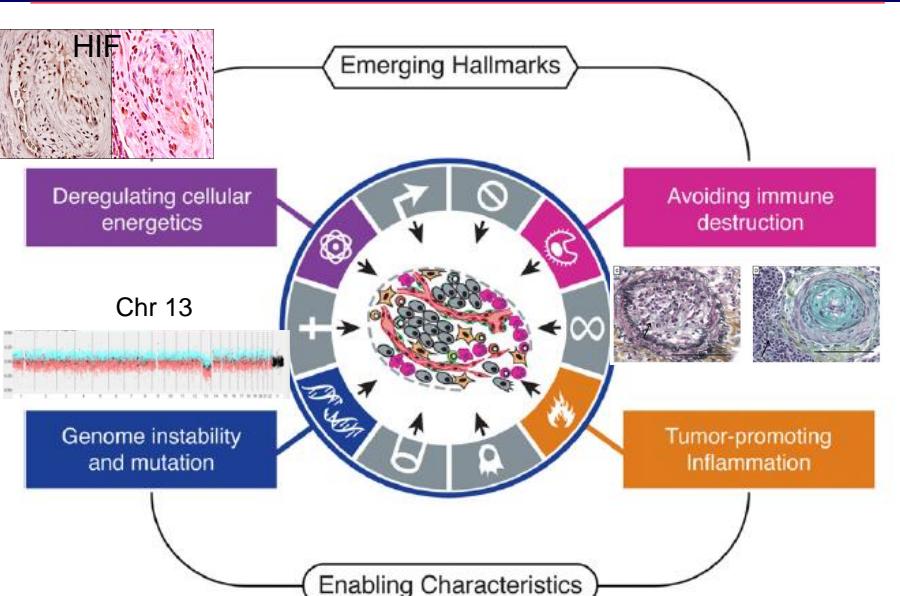
Smad3
Smad2
 T
 $+/-$





17 β estradiol → CYP1B1

(Revisited) Key features of cancer



Acknowledgments

Univ. Colorado: Elvira Stacher (Univ. of Graz), Brian Graham, James Hunt, Aneta Gandjeva, Carlyne Cool, Steve Groshong

University of Michigan (DTC): Valerie McLaughlin, Marsha Jessep

Univ. Alabama: William Grizzle

PHBI:

Transplant sites: Alleghene University of Medical Sciences (PI: Raymond L. Benza, M.D.); Baylor College of Medicine (George Noon, M.D.); Cleveland Clinic (PI: Serpil Erzurum, M.D.); Duke University (PI: Pang-Chieh Jerry Eu, M.D.); Stanford University-UCSF (PI:: Marlene Rabinovitch, M.D.); University of Alabama (PI: Keith Wille, M.D.; prior PI: Raymond L. Benza, M.D.); University of California, San Diego (PI: Patricia Thistlethwaite, M.D., Ph.D.); Vanderbilt University (Barbara Meyrick, Ph.D..