VANDERBILT UNIVERSITY
MEDICAL CENTER

Defining the Role of Sex Hormones in PAH: Science and Career Development

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No relationships to disclose

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- I am still on this career development journey

Successful Physician-Scientist Dev't

- Be ***Proactive*** in carving out your career path
- ***Seek and Cultivate*** Mentors
- Establish an area of ***Expertise***
- Medical research is a ***Team Sport***
- Aggressively pursue ***Funding Opportunities***
- Navigate the diverse missions of academic medicine with ***Self-Discipline***

Adapted from Andrew I. Schafer, MD. Perspective: The Successful Physician-Scientist of the 21st Century. Clinical and Translational Science Network series. May 28, 2010.

Proactive & Mentorship

Focus on PH, specifically PAH

1. PULMONARY ARTERIAL HYPERTENSION (PAH)

- Idiopathic PAH
- Heritable PAH (Family and/or gene mutation)
- Drug- and toxin-induced
- Associated with:
  - Connective tissue diseases
  - Congenital heart diseases
  - HIV
  - Portal hypertension
  - Schistosomiasis

1'. PULMONARY VENO-OCCLUSIVE DZ (PVOD) AND/OR PULMONARY CAPILLARY HEMANGIOMATOSIS (PCH)

1". PPHN

2. PH DUE TO LEFT HEART DISEASE

- Systolic dysfunction
- Diastolic dysfunction
- Valvular disease

3. PH DUE TO LUNG DISEASES AND/OR HYPOXIA

- Bronchopulmonary dysplasia (BPD), COPD
- Interstitial Lung Disease (ILD)
- Other lung dz's w/ mixed restrictive/obstructive defects
- Sleep-disordered breathing
- Alveolar hypoventilation disorders
- Chronic exposure to high altitude
- Developmental lung abnormalities

4. CHRONIC THROMBOEMBOLIC PH (CTEPH)

5. PH UNCLEAR MULTIFACTORIAL MECHANISMS

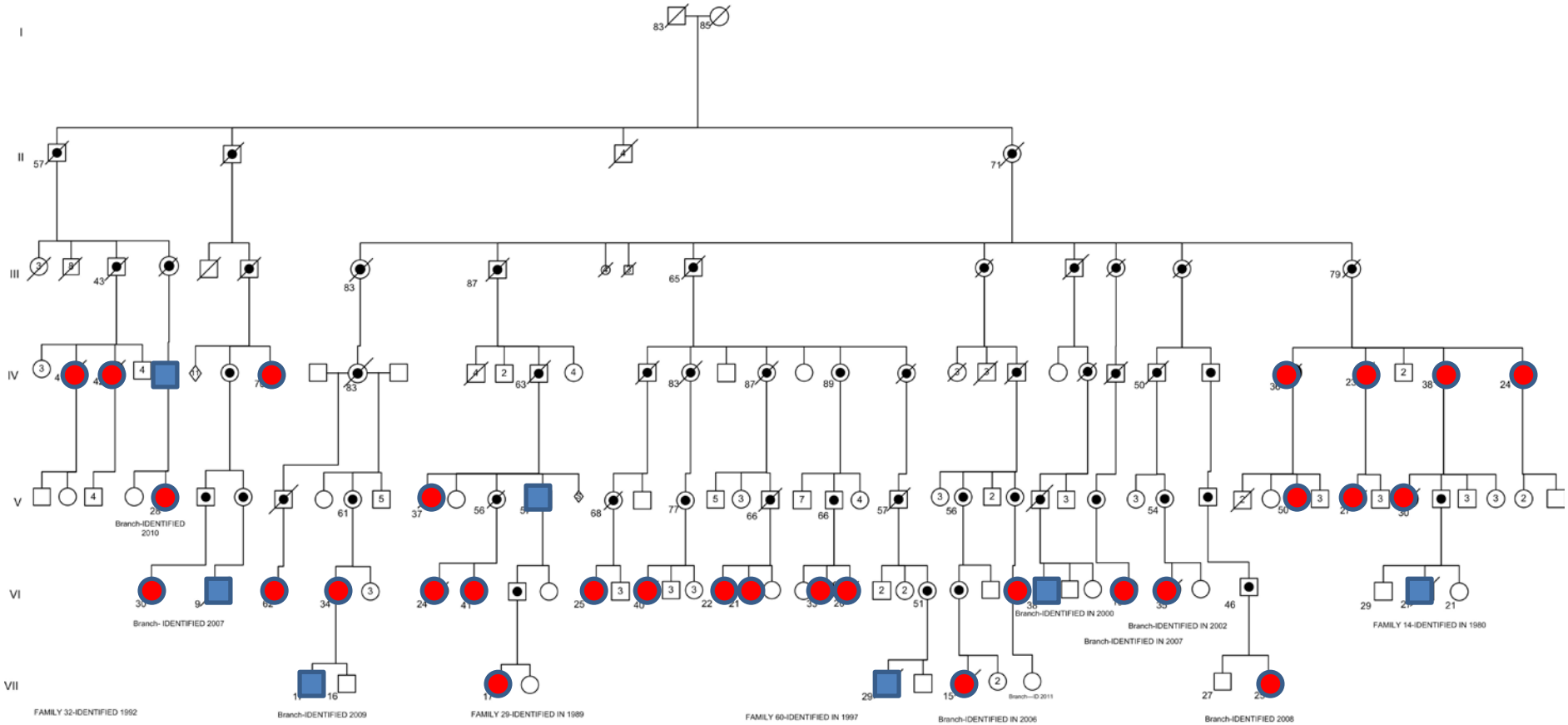
- Hematologic d/o's: hemolysis, myeloproliferative, splenectomy
- Systemic d/o's: sarcoidosis, LCH, LAM, NF, vasculitis
- Metabolic d/o's: glycogens storage dz, Gaucher's Thyroid
- Others: tumurol obstruction, fibrosing mediastinitis, CR

Simonneau et al, *JACC* 2013

Established Risk Factors for PAH

- Genetic susceptibility
  - *BMPR2* gene mutation (TGFβ genes, *CAV1*, *KCNK3*)
- Female
- Connective tissue disease
- Hereditary hemorrhagic telangiectasia (HHT)
  - *ALK1* & *ENG* gene mutations
- Portal Hypertension
- Drug & toxin exposures
  - aminorex, fenfluramine, dexfenfluramine

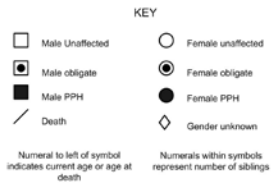
BMPR2 HPAH:
reduced penetrance and variable expressivity



A Large HPAH Family: 36 Confirmed PAH

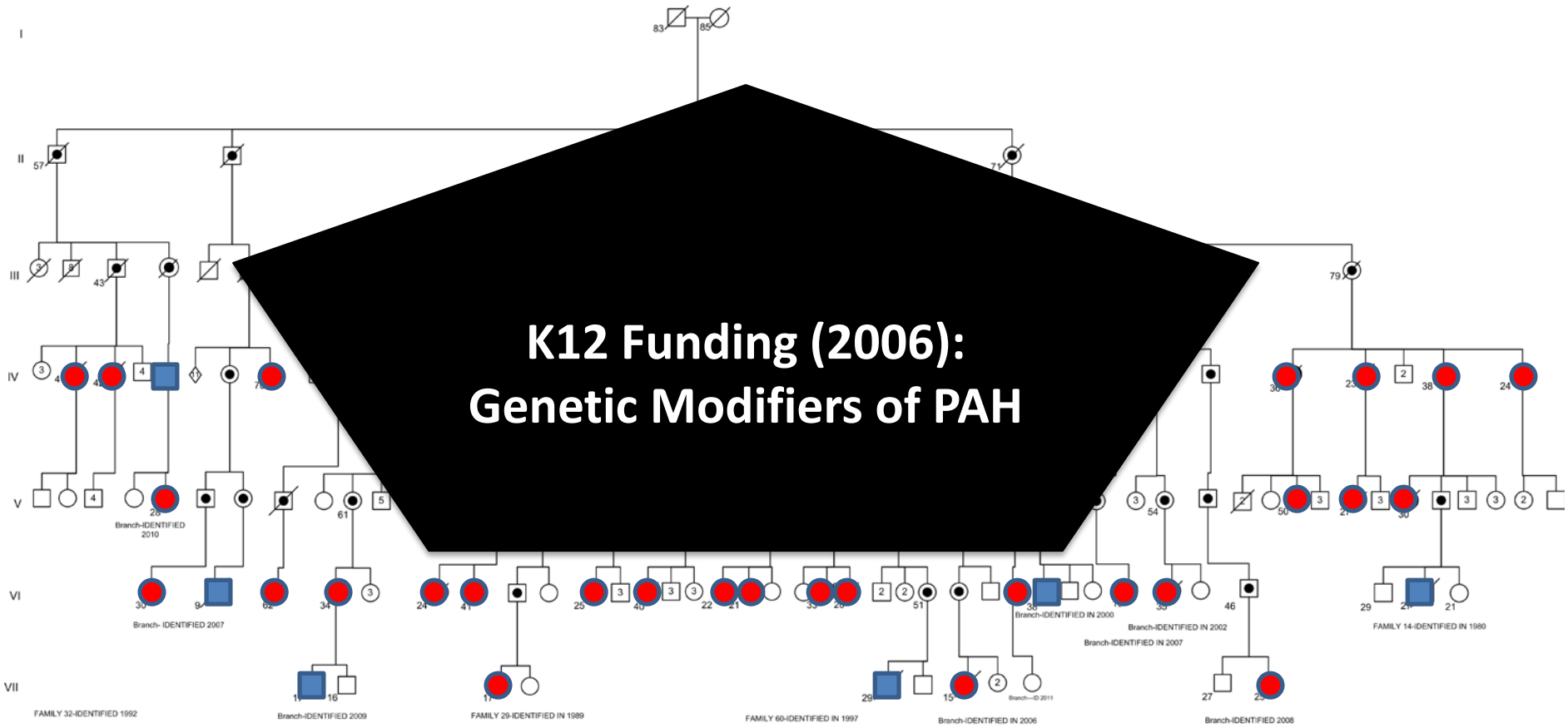
29 Female

7 Male



Updated Summer 2011 (*Pulm Circ*)—initial pub by Loyd, Primm, Newman *Am Rev Resp Diseases* 1984

BMPR2 HPAH: penetrance higher females



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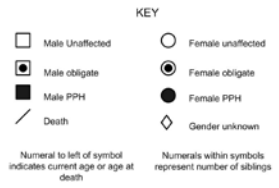
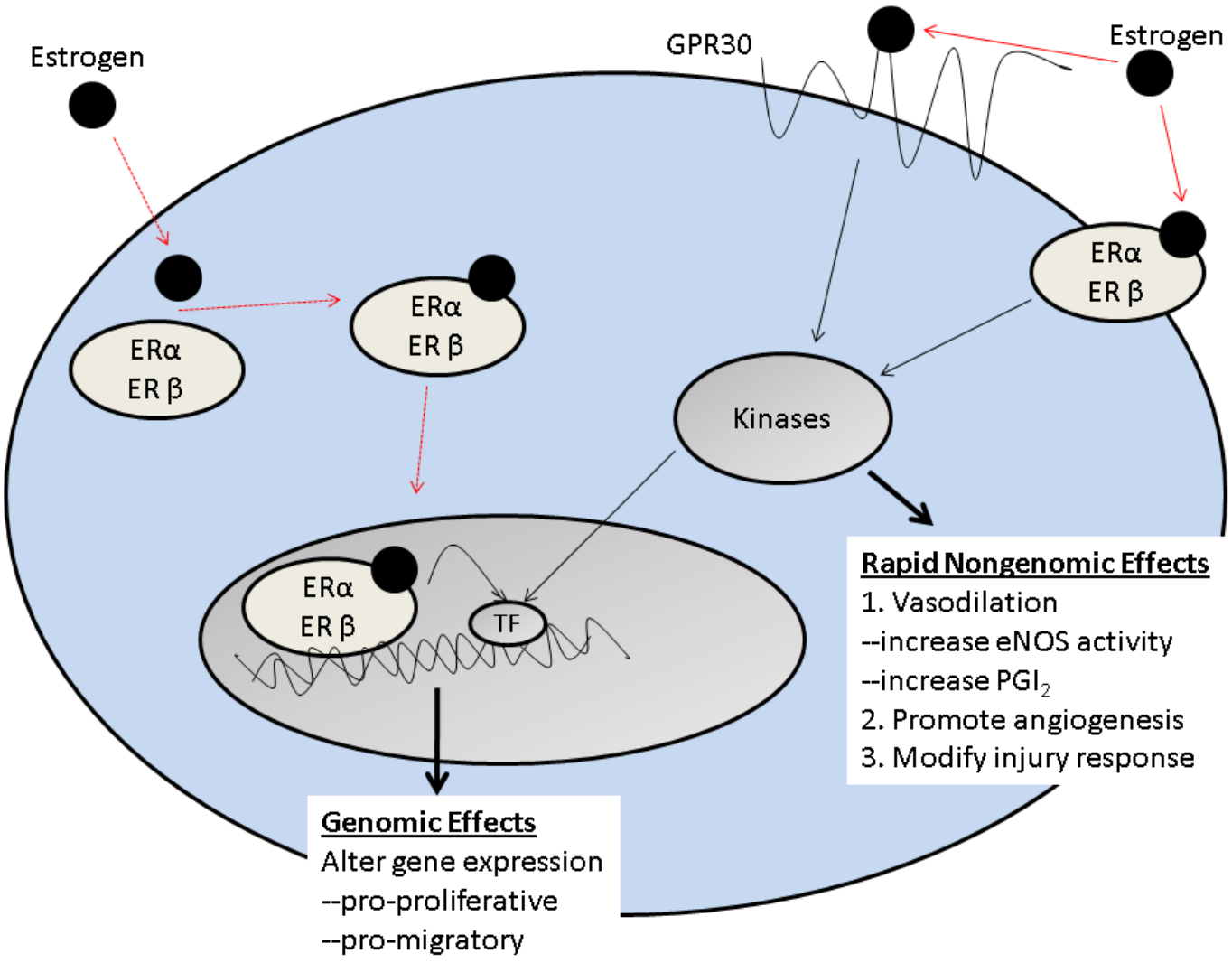


Updated Summer 2011 (*Pulm Circ*)—initial pub by Loyd, Primm, Newman *Am Rev Resp Diseases* 1984

Female predominance suggests a role for Sex Hormones

- Penetrance of *BMPR2* mutations not equal for females (higher) and males
- Most forms of PAH are female predominant
- Gene expression data suggestive that Sex Hormone Metabolism is different in PAH patients
  - *CYP1B1* expression
- Conflicting data about estrogens and PH in animal models
- Survival

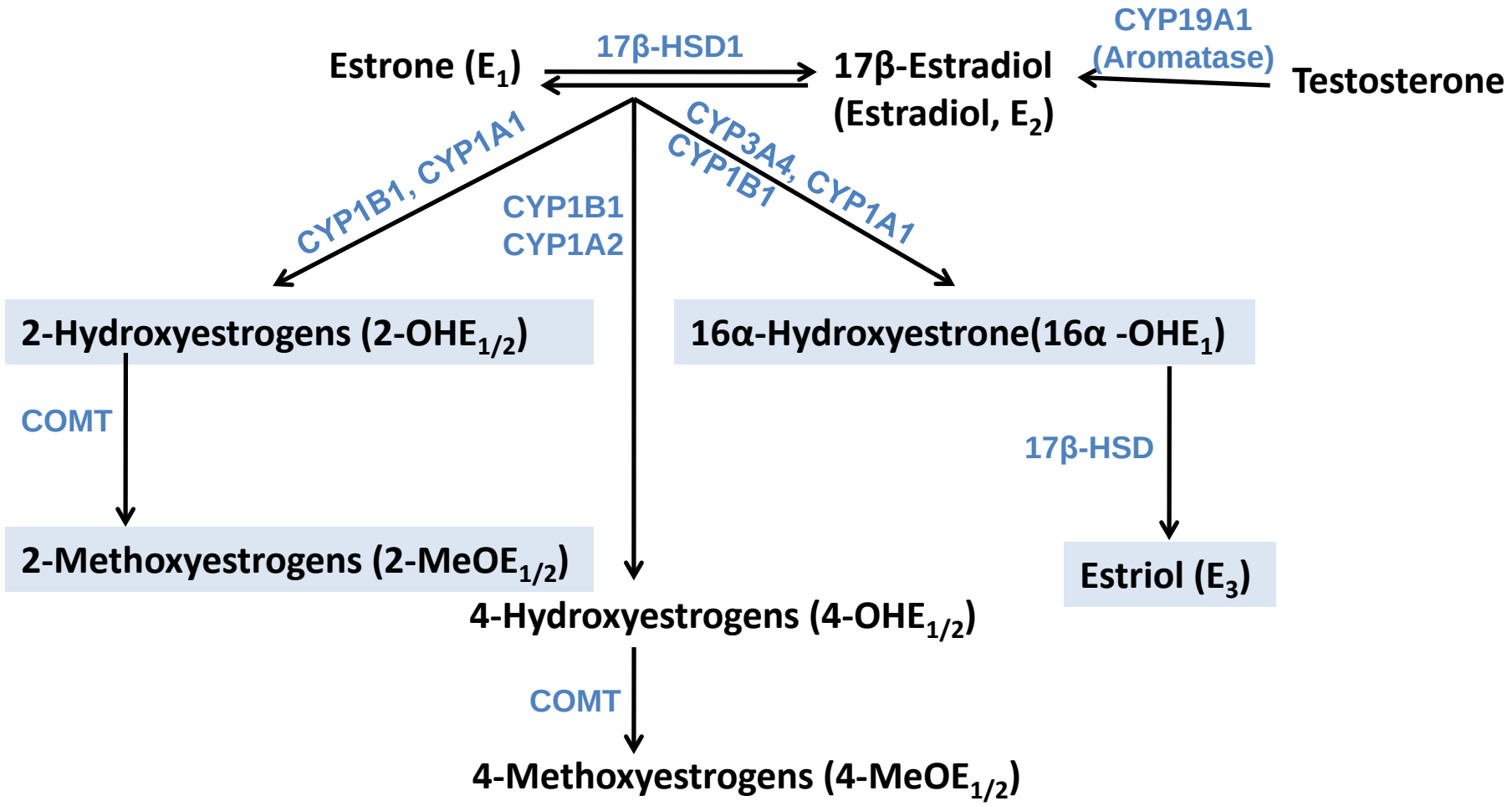
Pursuit: Estrogens



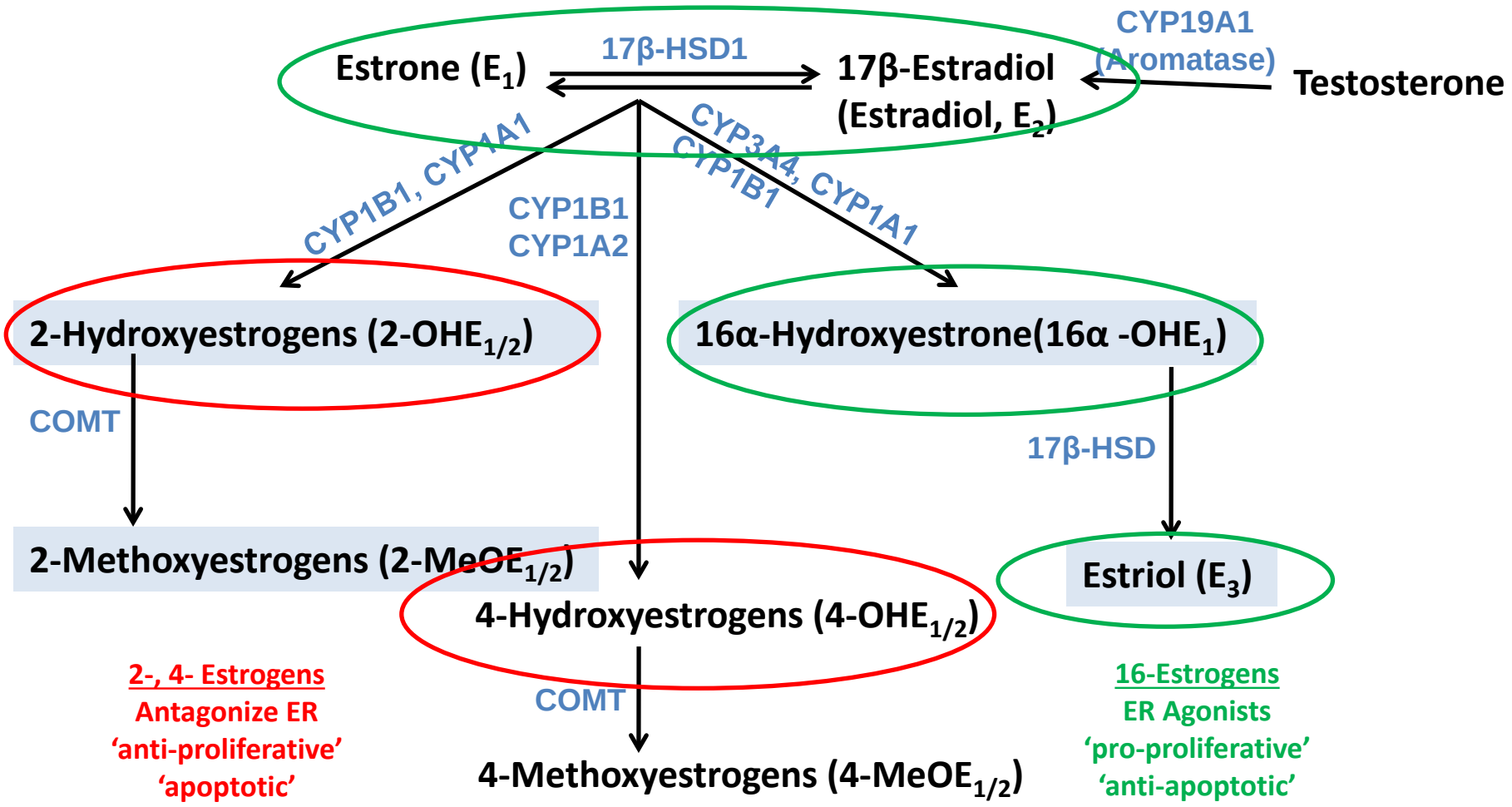
SERMs modify these effects, as do certain Estrogen Metabolites

Adapted from: Lahm et al *Crit Care Med*. 2008;36(7):2174-83.

Sex Hormone Metabolism



Sex Hormone Metabolism



CYP1B1 N453S : N/N genotype associated with lower CYP1B1 activity*

Females	*BMPR2*-PAH n (%)	*BMPR2*-Healthy n (%)	*P* value
N/N	46 (74%)	10 (42%)	0.005
N/S or S/S	16 (26%)	14 (58%)	
Males	***BMPR2*-PAH n (%)**	***BMPR2*-Healthy n (%)**	***P* value**
N/N	18 (60%)	17 (71%)	0.407
N/S or S/S	12 (40%)	7(29%)	

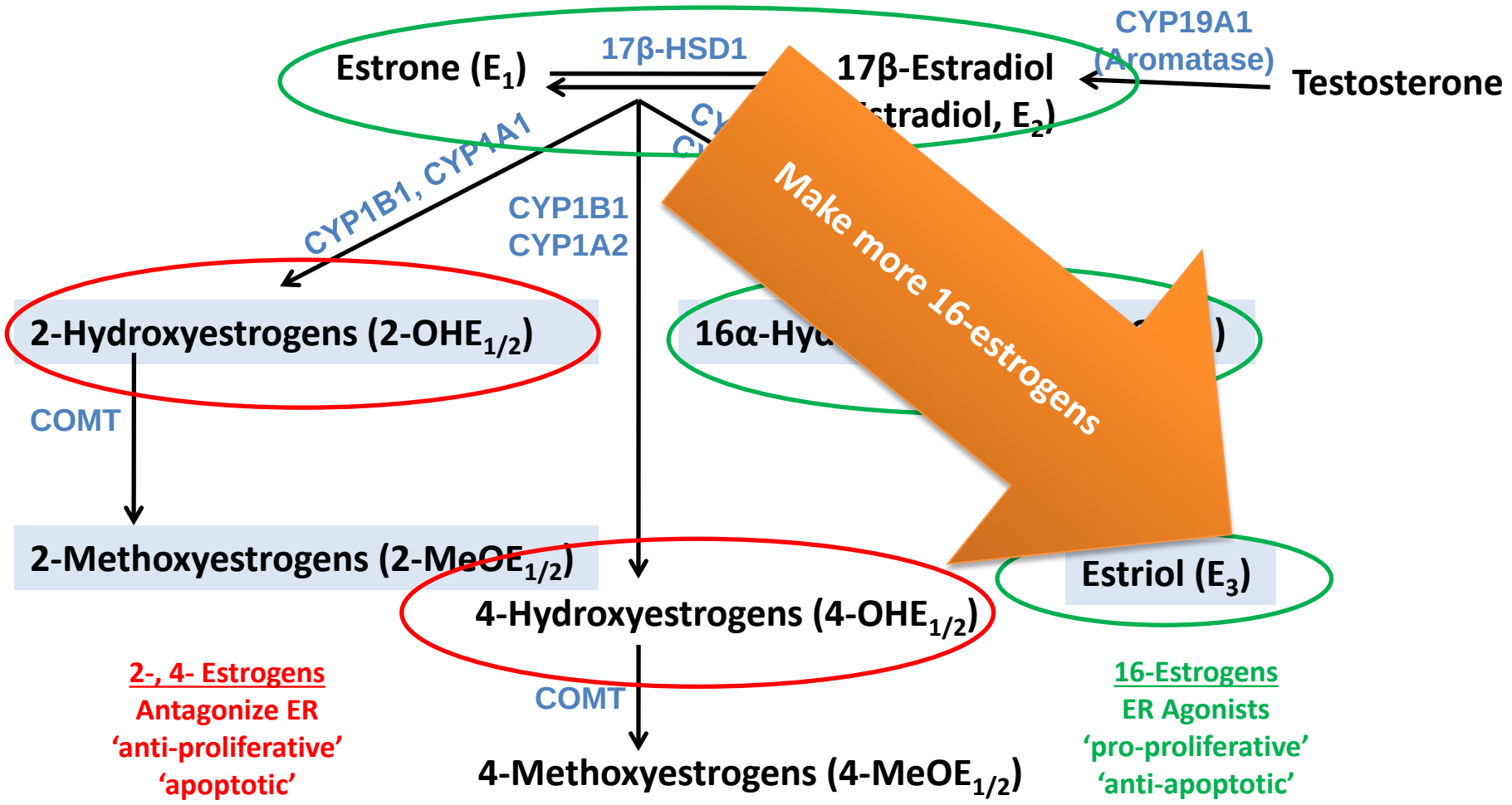
Females with N/N genotype:

Unadjusted OR = 4.1

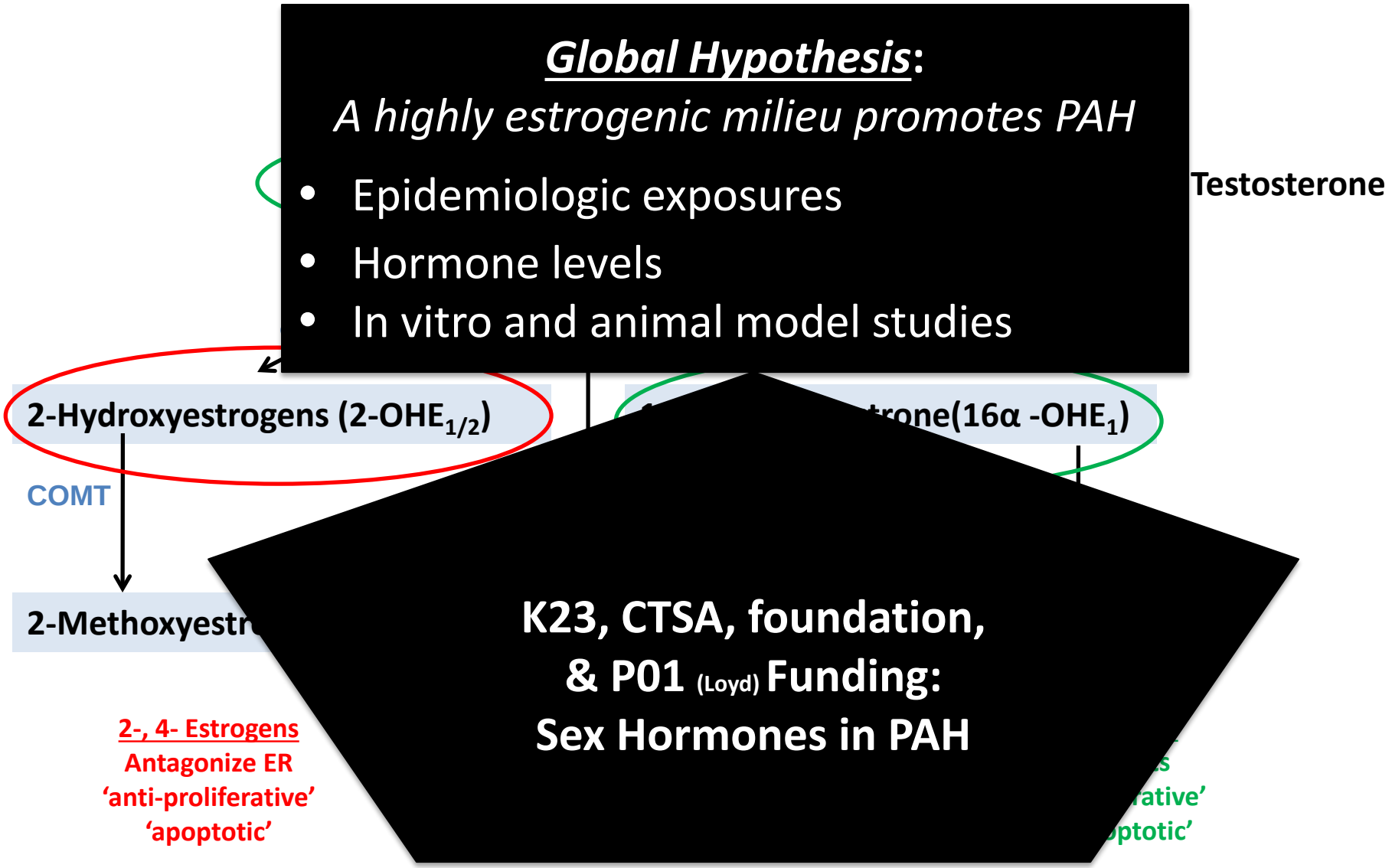
* Hannah, *Cancer Res* 2000

Austin, *Eur Resp J* 2009

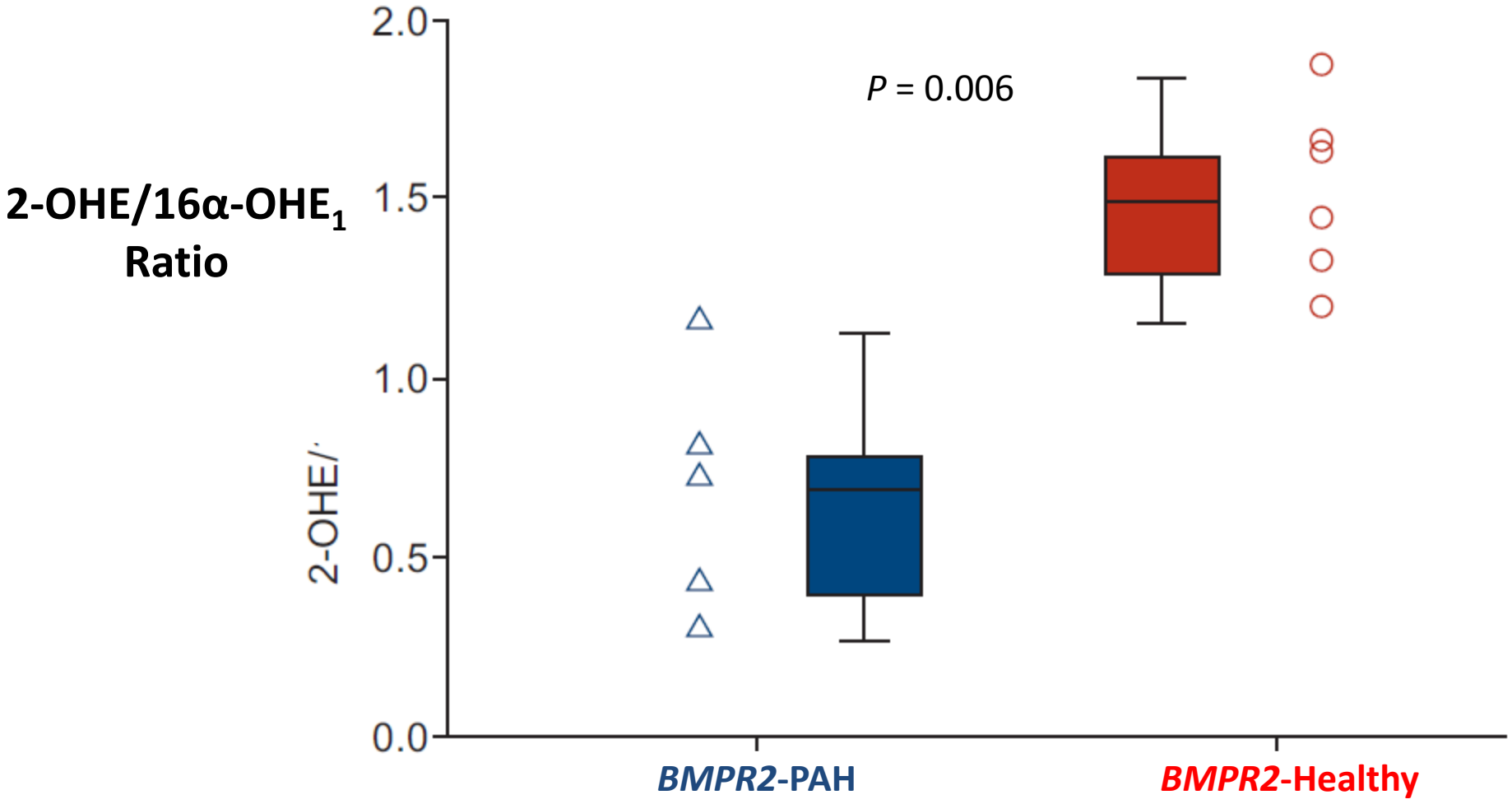
Sex Hormone Metabolism



Sex Hormone Metabolism



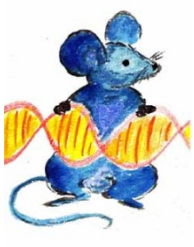
Ratio of '2-estrogens' / '16-estrogens': Lower in PAH Patients



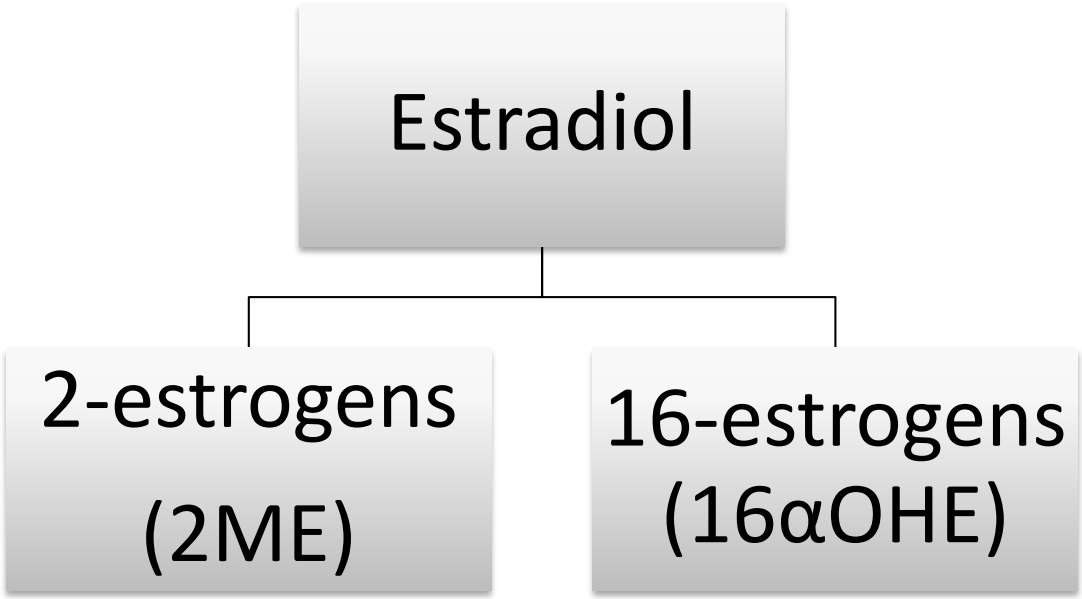
Female Data Shown, but similar in males and IPAH cases (P = 0.05)

Austin ED et al. *Eur Respir J*. 2009;34(5):1093-9.

Team Sport: James West's Bmpr2^{R899x} transgenic murine model: 2ME versus 16αOHE



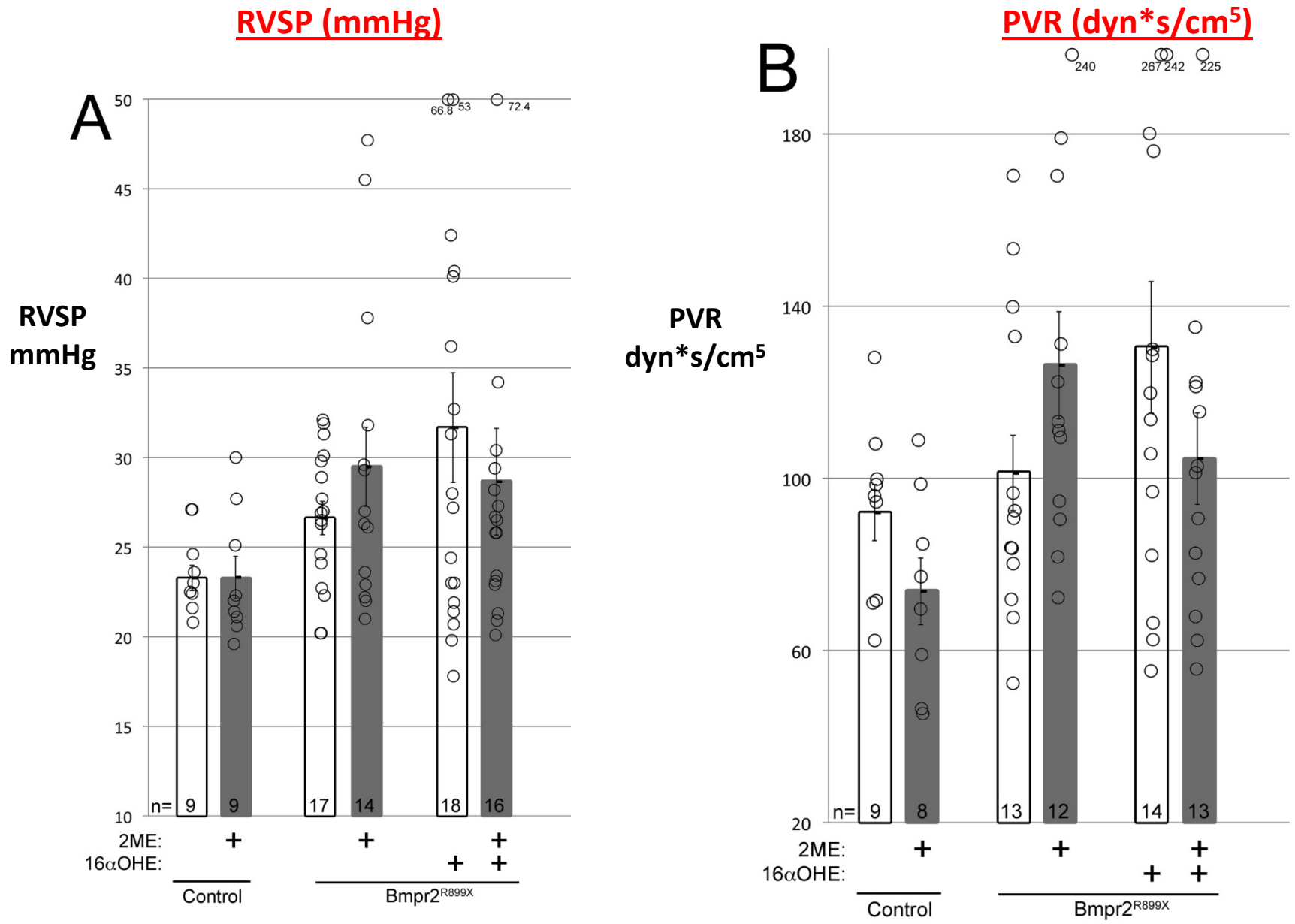
- Male mice
  - 1.25 mg/hr x 4 weeks
  1. vehicle
  2. 2ME
  3. 16αOHE
  4. 2ME + 16αOHE



Hypothesis: 2-estrogens (2ME) protective while 16-estrogens (16αOHE) detrimental

Fessel JP et al. *Pulm Circ.* 2013;3(3):564-77.

16αOHE increases penetrance



Fessel JP et al. *Pulm Circ.* 2013;3(3):564-77.

Conclusions

- ***Proactive*** & ***Mentored*** pursuit of a pressing question in the PAH field w/ ***Team*** approach
- Sex Hormone contributes to PAH
  - Skew toward '16-estrogens' in humans
- '16-estrogens' amplify Bmpr2 murine model penetrance
- Estrogen antagonism may be protective
  - Long term effects unknown, incl. RV function
- Precise mechanisms active area investigation
  - Pulmonary vasculature
  - RV
- R01 application exploring the interplay between Sex Hormones, Cellular Metabolic Defects, and PAH

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