

# **Cardiovascular Discussion Session**

**Biology of the Perimenopause: Impact on  
Health and Aging Workshop**

**Thursday, May 27<sup>th</sup>, 2004**

**7:30-8:30 AM**

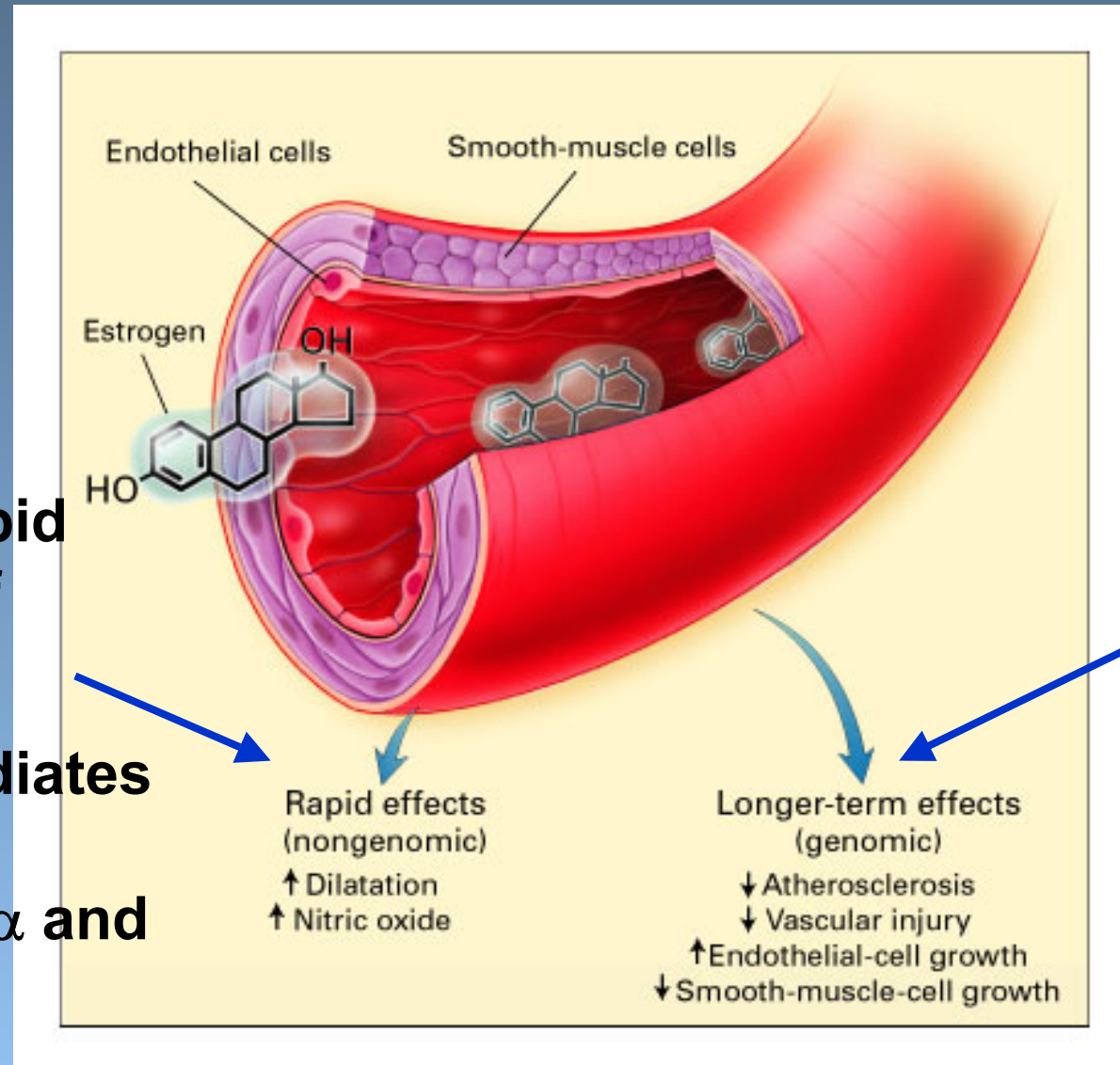
# Outline of the Session

- |   |        |       |
|---|--------|-------|
| • Introduction                          | 5 min  | MM    |
| • Epidemiology                          | 10 min | KS-T  |
| • Vascular Biology<br>& Atherosclerosis | 20 min | RK&PS |
| • Coagulation<br>& Fibrinolysis         | 20 min | BL&DG |
| • Summary                               | 5 min  | MM    |

# Themes for the Session

- ***Timing of Loss of Hormones Influences Biology and Experimental Models***
- ***Timing and Mode of HRT Influences Biology and Experimental Models***

# Direct Effects of Estrogen on the Blood Vessel



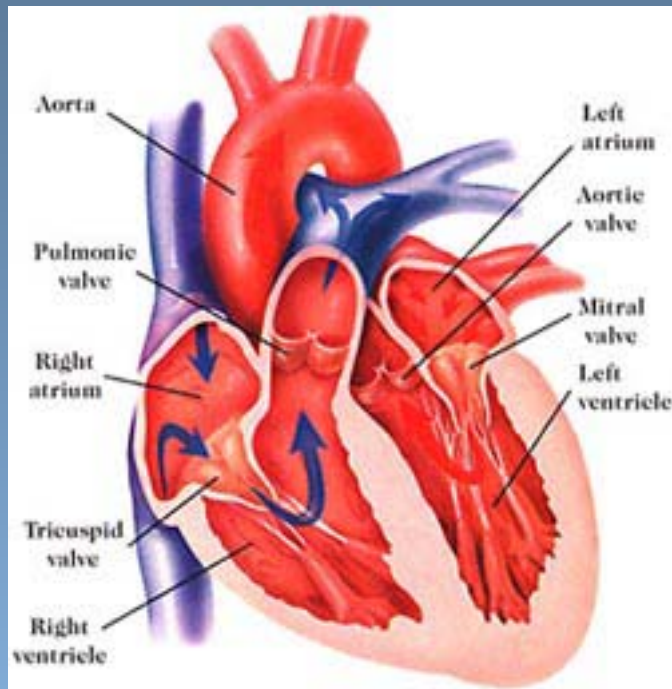
- $ER_{\alpha}$ , [ $ER_{\beta}$ ] Mediates rapid activation of eNOS

- **Striatin** mediates interaction between  $ER_{\alpha}$  and eNOS

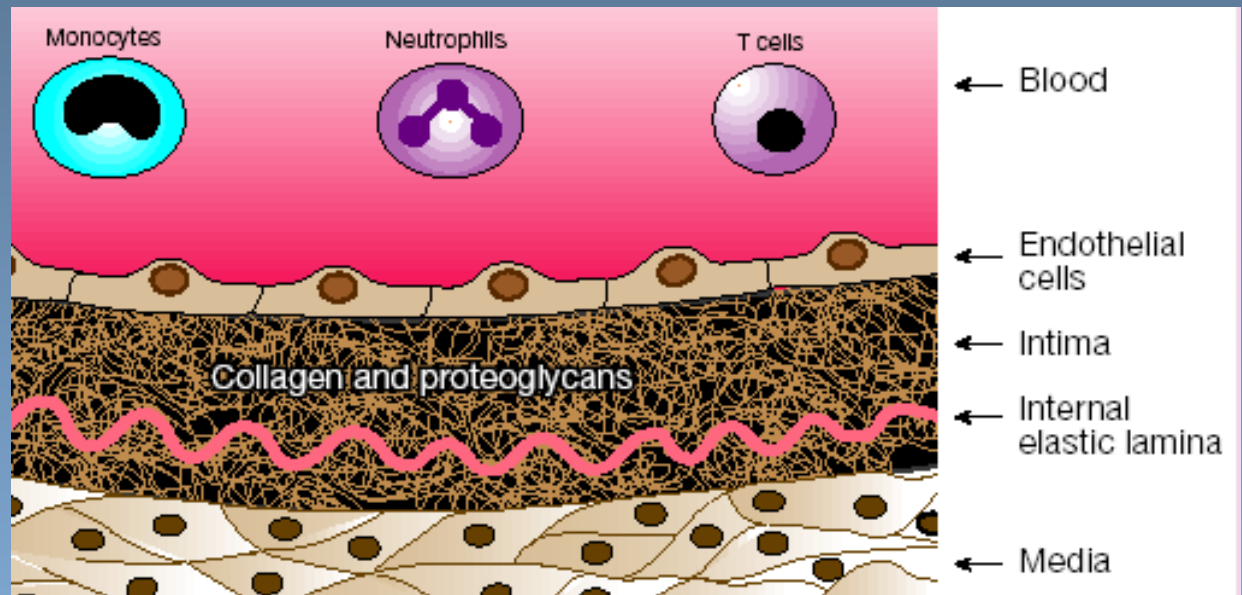
- $ER_{\alpha}$  mediates E2 Inhibition of Vascular Injury

- $ER_{\beta}$  required for normal vascular function, BP

# Cardiovascular Hormones and Receptors



Myocardial Cells:  $ER\alpha$ ,  $ER\beta$ , Aromatase



Vascular Endothelial Cells:  $ER\alpha$ ,  $ER\beta$ , Aromatase, Activin

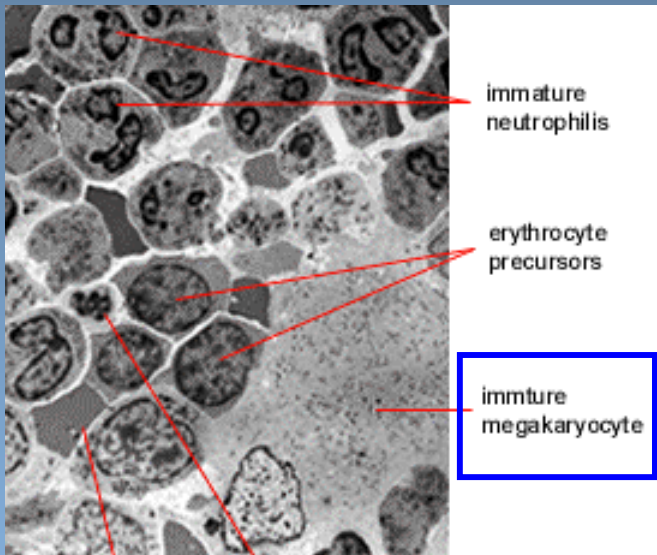
Vascular Smooth Muscle Cells:  $ER\alpha$ ,  $ER\beta$ , PR, AR, Aromatase, Activin

Monocytes/Macrophages:  $ER\alpha$ ,  $ER\beta$ , AR

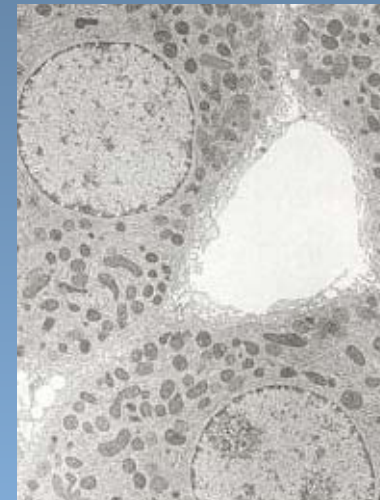
Neutrophils:  $ER\alpha$ ,  $ER\beta$ , AR

T Cells:  $ER\alpha$ ,  $ER\beta$ , AR

# Liver and Megakaryocyte Hormones and Receptors



Megakaryocytes:  $ER\beta^*$ , AR



Hepatocytes:  $ER\alpha^*$   
AR, Aromatase

# HRT Timing and CAD

## OVARIECTOMY

Plaque Area Reduction

Premenopause



Postmenopause

Healthy Diet

CEE + Atherogenic Diet

70 %<sup>1</sup>

Healthy Diet

Atherogenic Diet

Healthy Diet + CEE

0 %<sup>2</sup>

TIME

Human Studies

KEEPS

WHI (62) HERS (67)

<sup>1</sup> Clarkson et al. J Clin Endocrinol Metab. 1998; Adams et al. Arterioscler Thromb Vasc Biol, 1997.

<sup>2</sup> Williams et al. Arterioscler Thromb Vase Biol. 1995.

# **Part 1: Epidemiology of Vascular Dysfunction (Kim Sutton-Tyrrell)**

- ***What epidemiological data or clues exist to explain changes in vascular disease frequency as a function of perimenopausal change?***
- ***What epidemiological data exist regarding changes in the H-P-O axis hormones across the menopausal transition?***



# **Part 2: Biology of Vascular Dysfunction & Atherosclerosis**

## **(Richard Karas and Philip Shaul)**

- **What is the evidence that alterations in *vascular dysfunction and/or atherosclerotic progression occur across the menopausal transition? are influenced by changes in H-P-O axis hormones?***
- **What are the *potential underlying mechanisms* by which the heart and vasculature are altered across the menopausal transition?**

# **Part 3: Coagulation and Fibrinolytic Systems (Barbara Konkle and David Ginsburg)**

- **What is the evidence that *the coagulation and fibrinolytic systems and susceptibility to thrombosis* are altered:**
  - (a) across the menopausal transition?**
  - (b) from initiation and/or maintenance of HRT?**
- **What are the *potential underlying biologic mechanisms* by which *the coagulation and fibrinolytic systems and susceptibility to thrombosis* are altered in each case?**

# Research Questions

- **General Issues:**
  - Prog, Androgens, SHBG, FSH, LH, Activins, Inhibins & CV function
  - Balance between hormones: think beyond estrogen and progesterone
  - Different vascular beds may differ
  - Genetics of CVD and specific coagulation- and hormone-related genes: Studies in Clinical DNA Databases (SWAN, e.g.)
- **Thrombosis:**
  - What are the key hemostatic components regulated by estrogens/progestins? How are they regulated?
  - Differences for natural vs. exogenous hormones?
  - Etiology of increased arterial thrombosis in HRT?
  - What are the interactions between genetic, hormonal and other thrombosis risk factors?
- **Cardiovascular Diseases:**
  - New Models: Use “Perimenopause Models”; “Cyclic Hormone Models”
  - Study Old vs Young Animals
  - Systemic versus local hormone production?
  - Oxysterols?