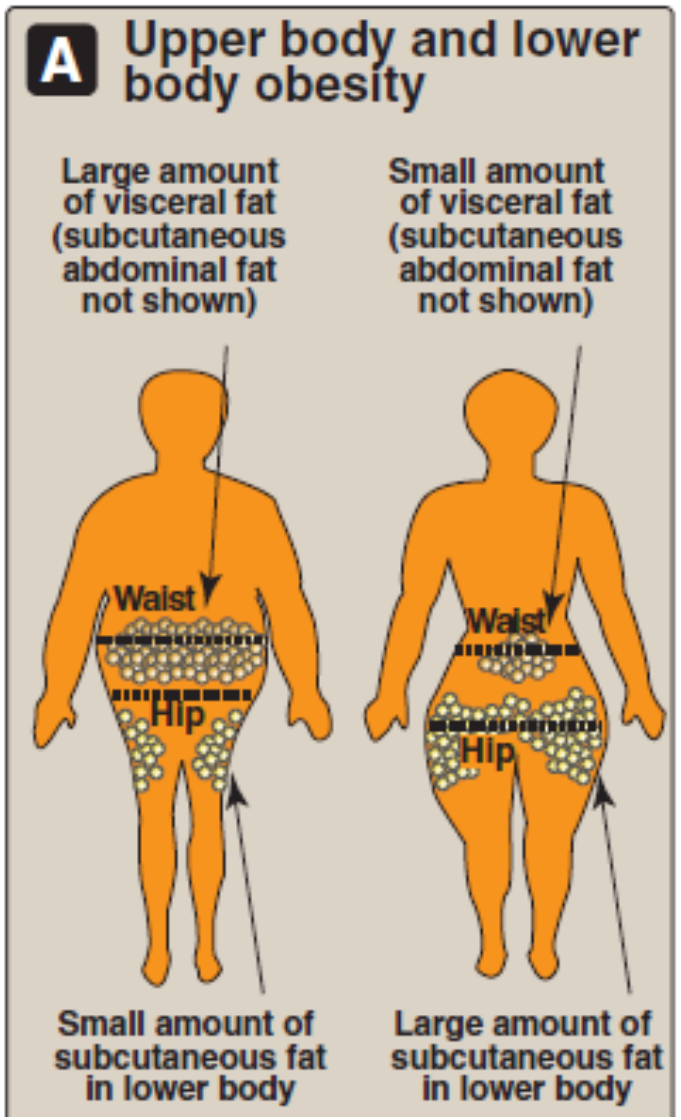
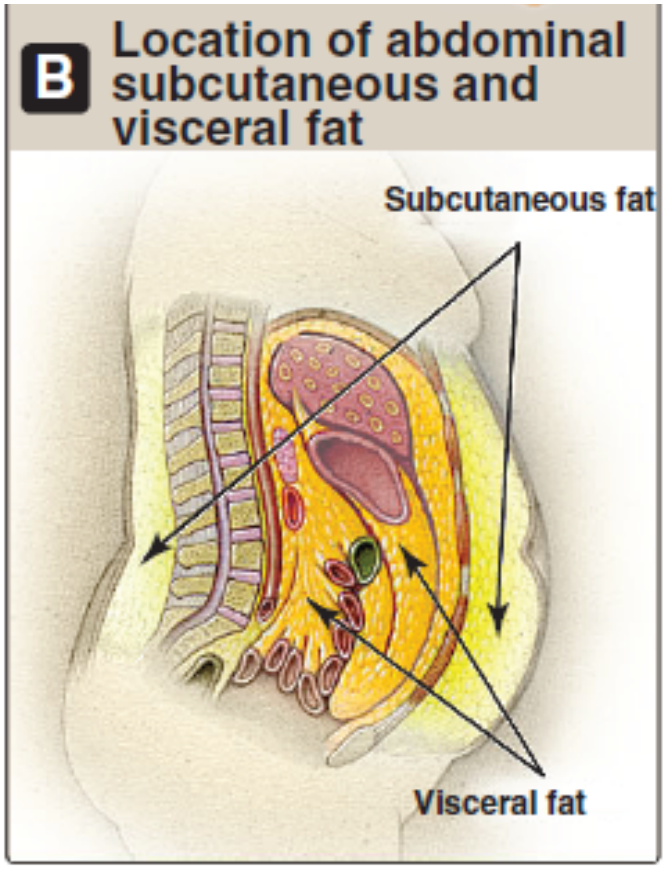
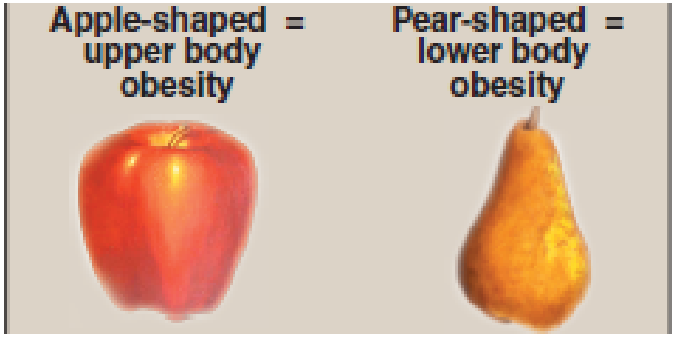
Sex differences in adipose tissue: *mechanisms and role in disease risk associated with obesity*

Director: Susan K. Fried, Ph.D.

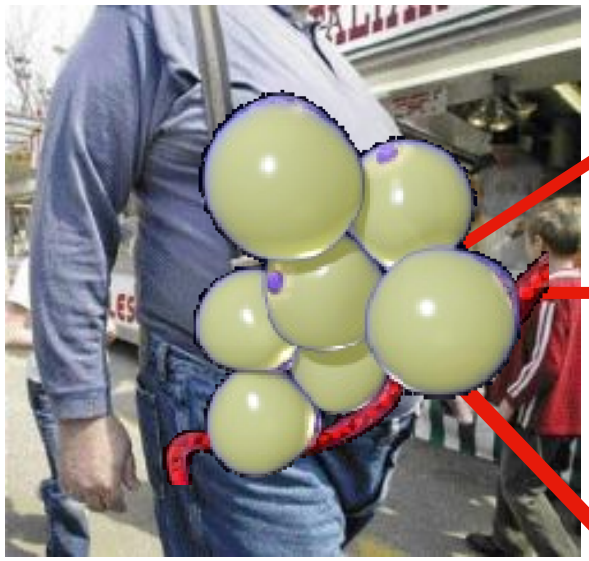
Co-Director: Paul Pilch, Ph.D.

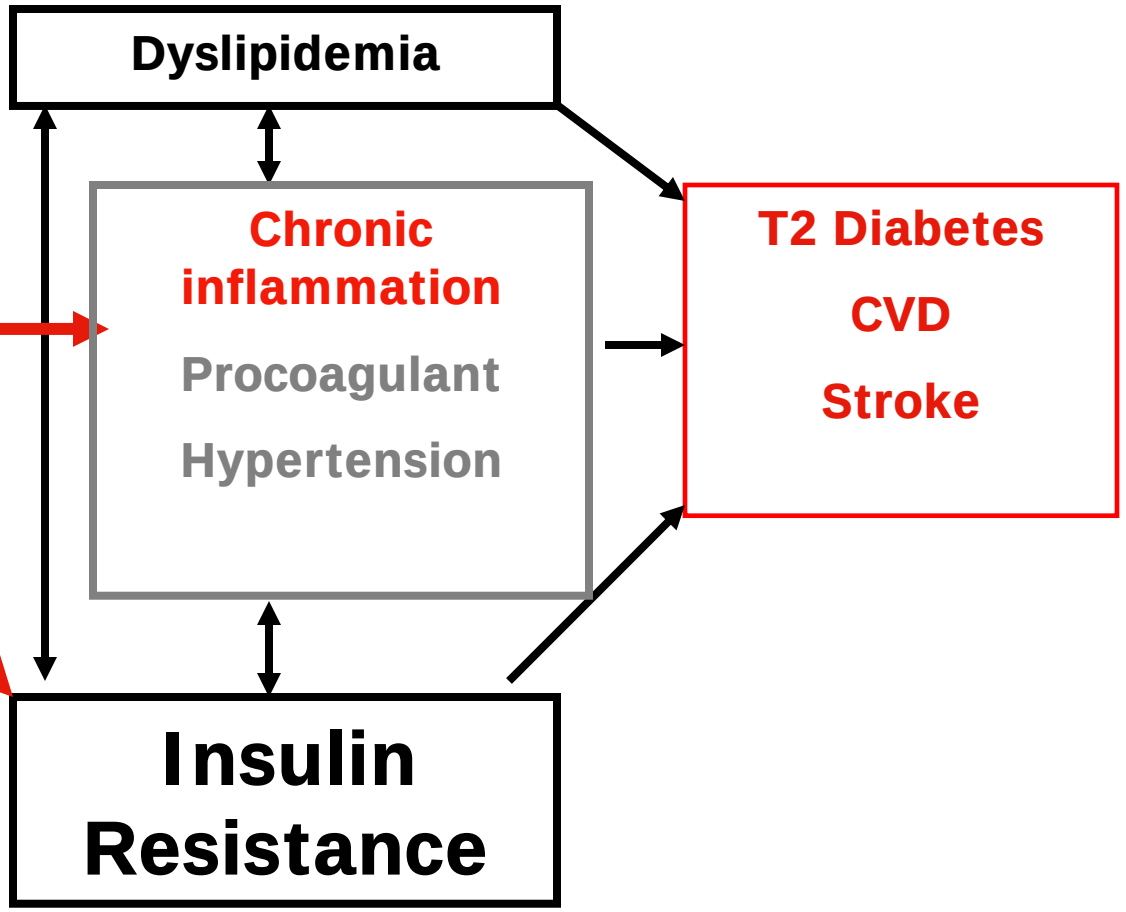

A
Upper body and lower body obesity
Large amount of visceral fat (subcutaneous abdominal fat not shown)
Small amount of visceral fat (subcutaneous abdominal fat not shown)
Waist
Hip
Waist
Hip
Small amount of subcutaneous fat in lower body
Large amount of subcutaneous fat in lower body

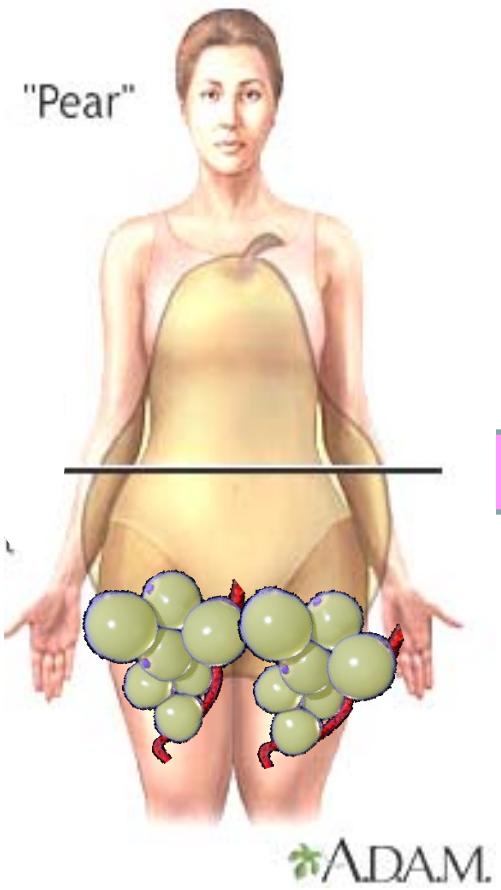

B
Location of abdominal subcutaneous and visceral fat
Subcutaneous fat
Visceral fat


Apple-shaped = upper body obesity
Pear-shaped = lower body obesity

Hazardous waists:







INSULIN SENSITIVE

LOW TG
High HDL

Normotensive

Long (and happy) life free from chronic disease

J Appl Physiol 104: 700–707, 2008.
First published December 13, 2007; doi:10.1152/japplphysiol.01035.2007.

Femoral-gluteal subcutaneous and intermuscular adipose tissues have independent and opposing relationships with CVD risk

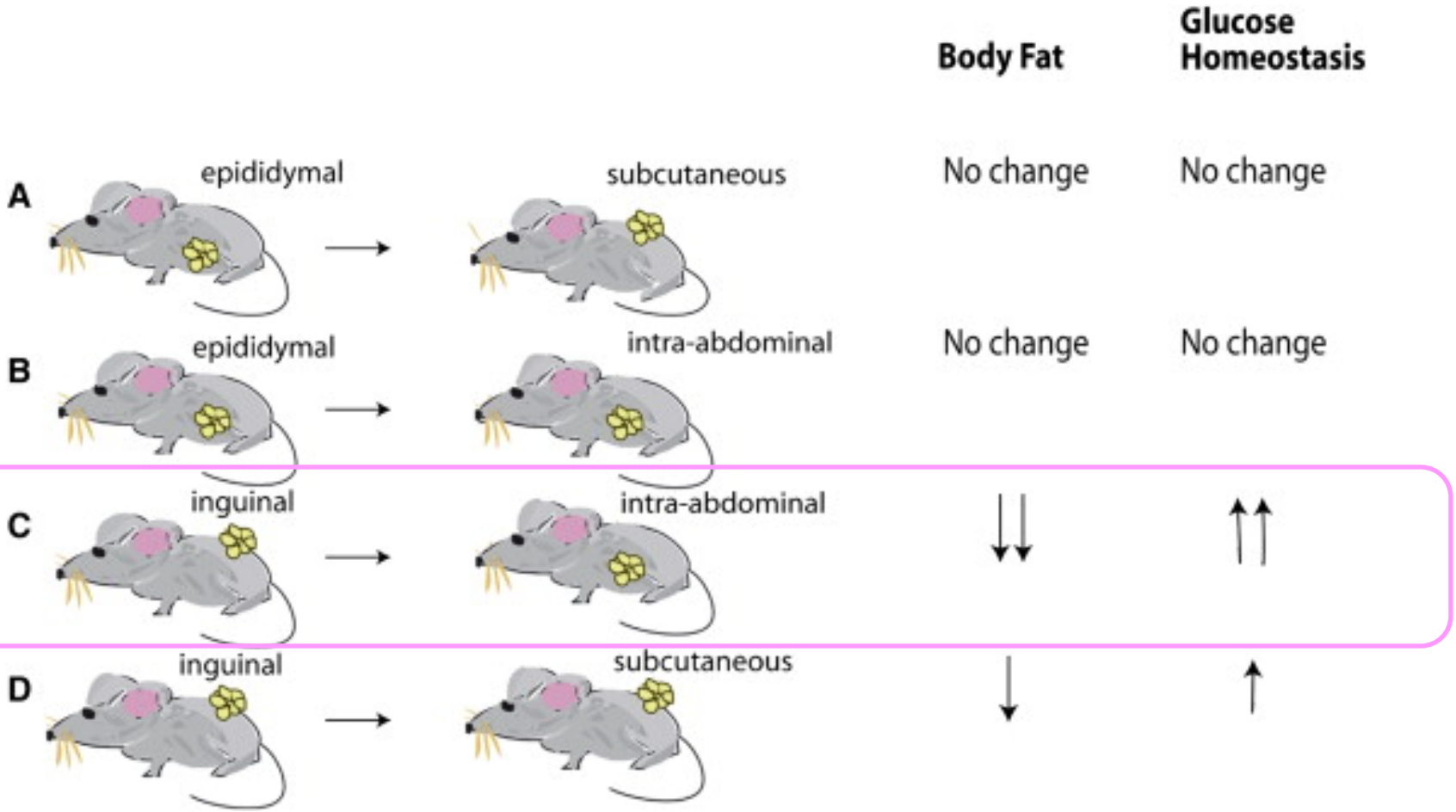
Jung-Eun Yim,[1] Stanley Heshka,[1] Jeanine B. Albu,[1] Steven Heymsfield,[1] and Dympna Gallagher[1,2]
[1]*Department of Medicine, Obesity Research Center, St. Luke's-Roosevelt Hospital;* [2]*Institute of Human Nutrition, Columbia University, New York*

Associations of hip and thigh circumferences independent of waist circumference with the incidence of type 2 diabetes: the Hoorn Study[1–3]

Marieke B Snijder, Jacqueline M Dekker, Marjolein Visser, Lex M Bouter, Coen DA Stehouwer, Piet J Kostense, John S Yudkin, Robert J Heine, Giel Nijpels, and Jacob C Seidell

Conclusion: Large hip and thigh circumferences are associated with a lower risk of type 2 diabetes, independently of BMI, age, and waist circumference, whereas a larger waist circumference is associated with a higher risk. *Am J Clin Nutr* 2003;77:1192–7.

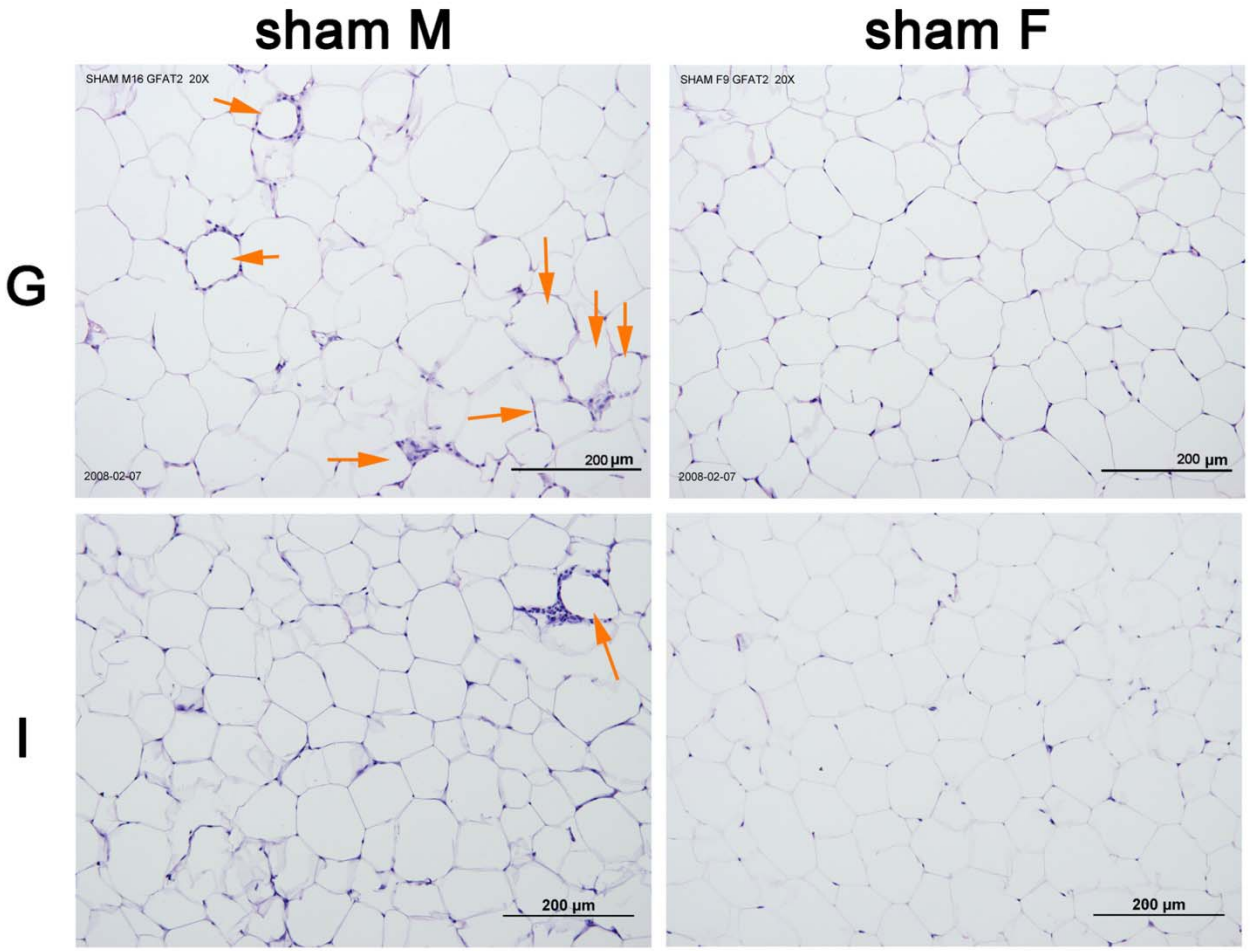
What is magic about gluteo-femoral fat?



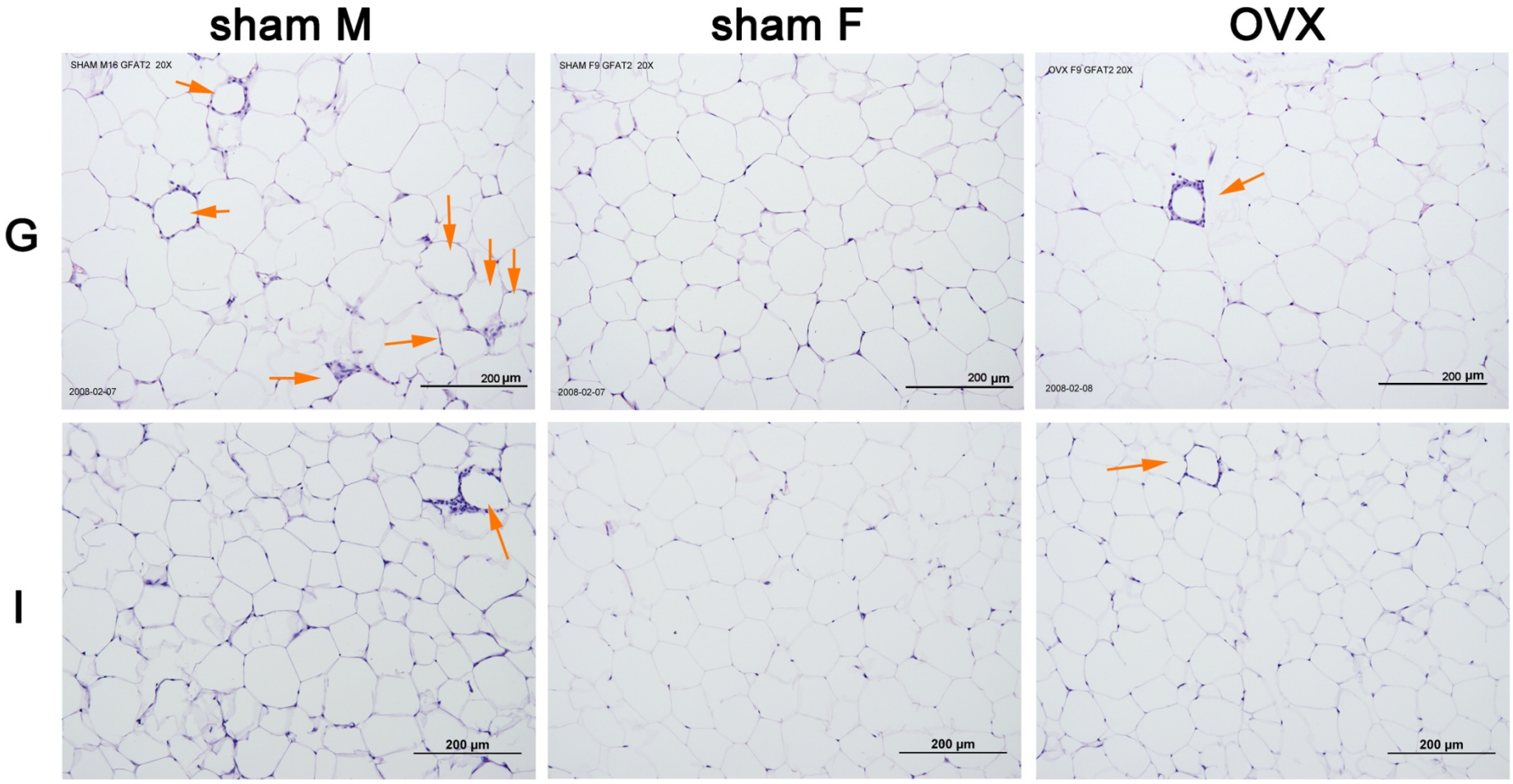
Male C57/BL6 Tran et al, Cell Metabolism , 2008

Female fat is resistant to high fat diet induced inflammation in C57/BL6 mice

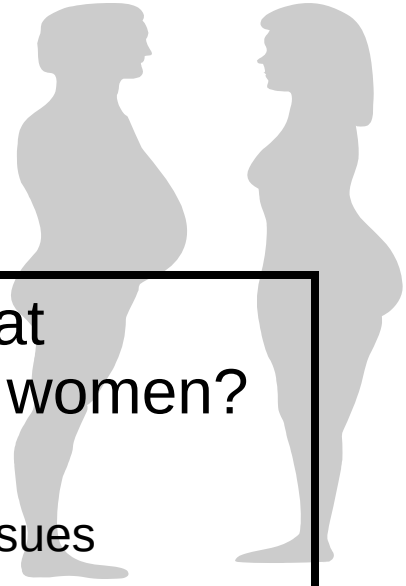
(Clegg et al., in press)



OVX only partially reverses:
more than sex steroids factor



Key questions



- What are the mechanistic links between fat distribution and metabolic risk in men and women?
  - endocrine vs. metabolic effectors
    - importance of different sc & visceral adipose tissues
- Physiological and molecular mechanisms regulating regional fat accumulation
  - males/females (sex specificity)
  - menopause
  - role of sex steroids and their receptors

Cell autonomous, sex-biased intrinsic differences in adipocytes from different depots?

ARC Objectives

- Establish a mouse model to determine cell autonomous, sex-related differences in adipocyte and adipose tissue biology
  - focus on mechanisms underlying the protection of females from adipose tissue inflammation/remodeling and insulin sensitivity.

- Identify sex-biased and depot-specific differences in gene expression networks that are common in mouse and human *(bioinformatic analysis of existing datasets).*

- Determine if preadipocytes and mesenchymal stem cells derived from male and females retain distinct metabolic characteristics and investigate the key genes involved and possible differential responses to sex steroids*(cell culture studies).*

Group expertise

- Adipose tissue metabolic and endocrine function
  - Various cell and tissue culture systems
  - hormone and nutrient signaling
  - Cell biology/imaging
- Adipose tissue birth and death
  - adipogenesis
  - remodeling
    - histology/immunohistochemistry,
    - immunology/FACS
- angiogenesis & vascular function
- Bioinformatics
  - nuclear receptors and gene networks
- Clinical Investigation
- Epidemiology

Adipocyte Biology

Barbara Corkey (Mol Med/Medicine)
Gerald Denis (Pharm/Medicine)
Steve Farmer (Biochem)
Susan Fried (Endo/Medicine)
Paul Pilch (Biochem)
Kostya Kandor (Biochem)
Vishwajeet Puri, Ph.D. Endo/Medicine
Andrew Greenberg, HNRC Tufts
Martin Obin, HNRC Tufts

Clinical Investigation

Steven Smith, (Burham Inst, FL)
Shalender Bhasin,M.D. (Endo)
CarolineApovian,M.D. (Endo)
Susan K.Fried,Ph.D. (Endo)
Noyan Goyce, M.D. (Cardiology)
Andrea Coviello,M.D (Endo)

Other Basic

James Hamilton (Phys/Biophys)
Sabeji Sarker (Epigenetics)

StephanieTauber Schneider
Graduate Student BU, Bioinformatics,

Yuanyuan Wu
Post-doc, BUSM

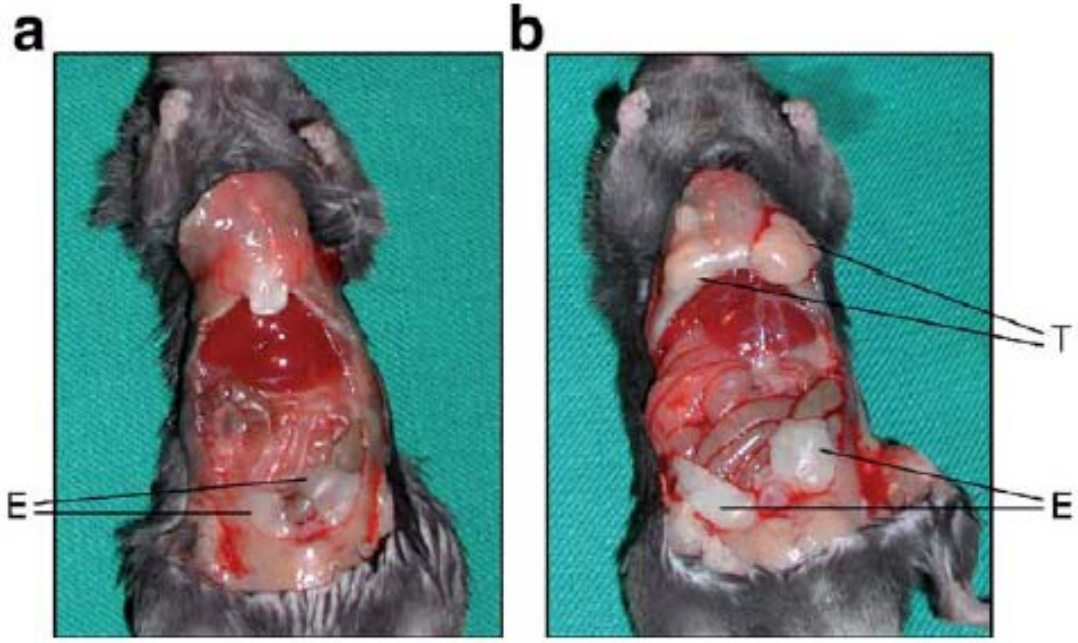
Uree Cho, Ph.D.
Research Associate.BUSM & Tufts

Experimental approach: transplantation studies

Expt 1: Transplant intra-abdominal (gonadal) and sc adipose tissue to the visceral vs. sc cavities of control and dietary obese female C57/BL6 mice.

Expt 2: Transplant female vs. male sc adipose tissue to the visceral or sc compartment of male mice challenged with low or high fat diets.

Expt 3: Transplantation of preadipocytes (stromal-vascular cells) originating from intra-abdominal or sc depots of females *vs.* males into males.



Konrad et al., Diabetologia (2007) 50:833–839

Guo et al. (2009) Am. J. Physiol *Regulatory Integrative Comp Physiol* 296, R1339-R1347

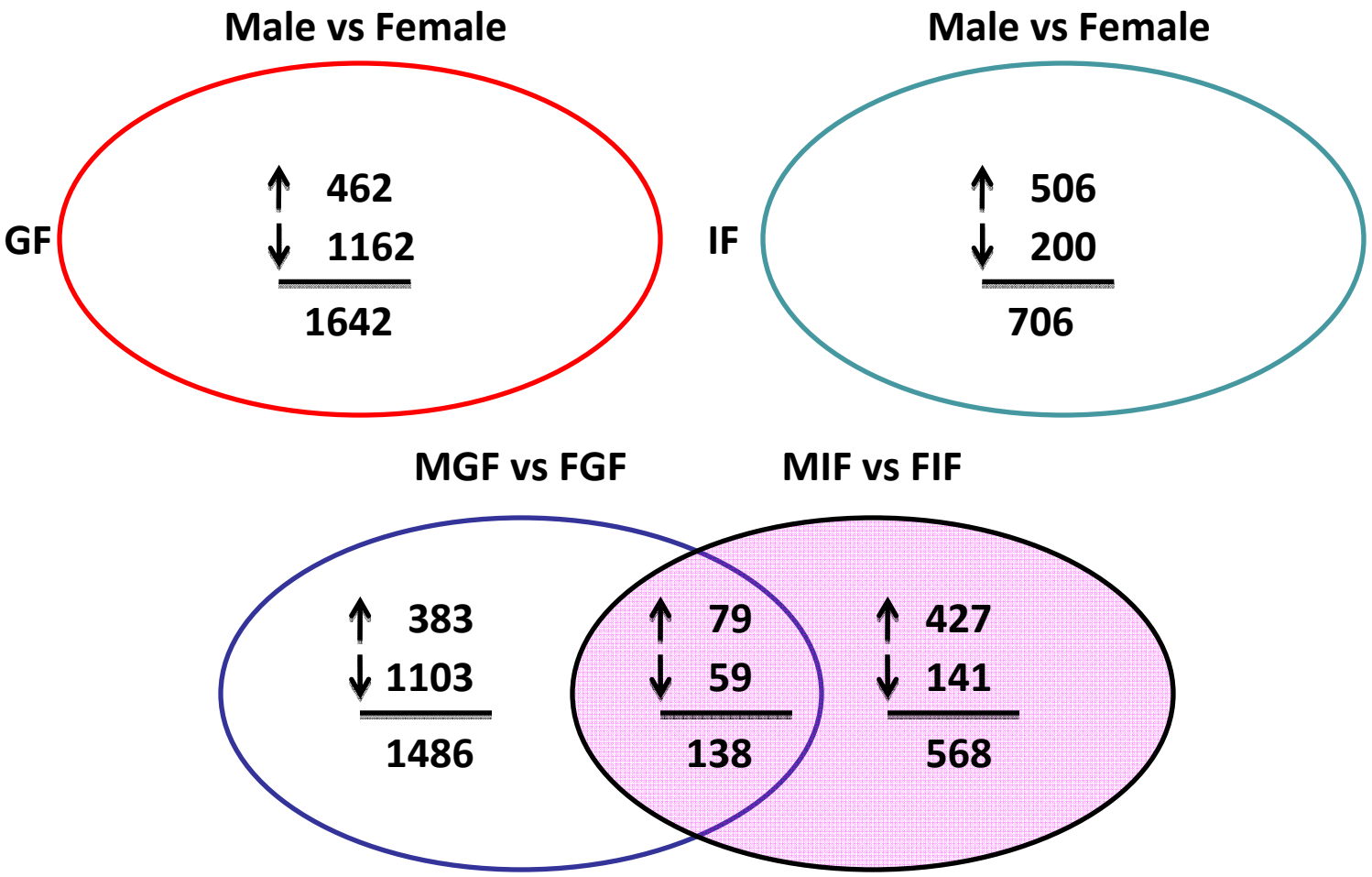
- Transplant model: probe for sex differences in adipose function
  - Influence at systemic level
    - Glucose tolerance, adipokines, inflammatory markers, etc
      - » *(circulating metabolome/proteome) – can we find a depot-specific, sex-specific 'adipose hormone'?*
    - – Influence at tissue/cell level (transplant vs. endogenous)
      - » Adipose, liver, muscle (transcriptisome, epigenome, proteome)

Group project will provide us with novel preliminary data that we can use as a launching pad for collaborations

Unique Resources

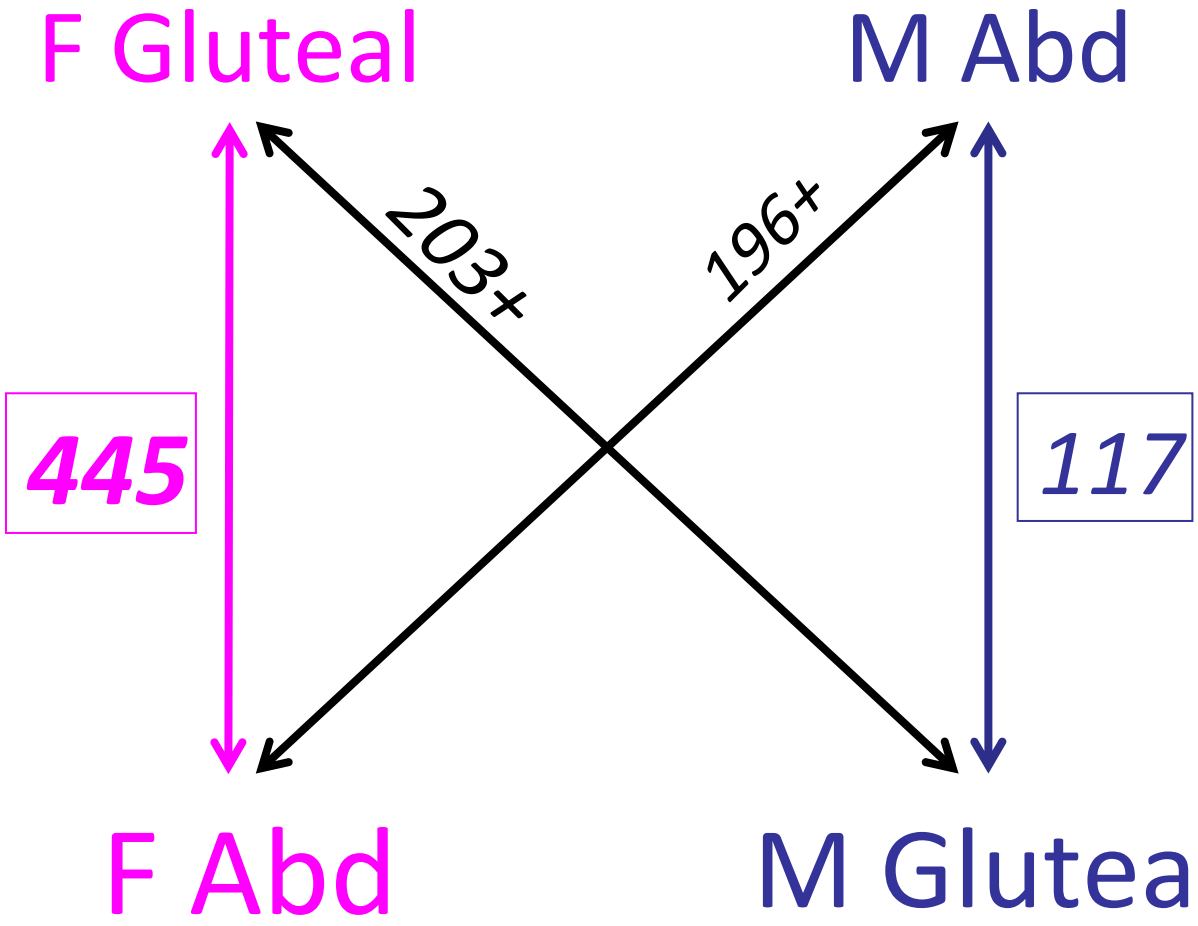
- **Microarrays of *adipose tissues***
  - **Mice fed a high fat diet**
    (2 fat depots (Gonadal, sc from M, F, OVX)
  - **Humans:**
    - **M, pre and post-menopausal F**
    - **Gluteal & abdominal**
    - **Omental and Abd Sc (Females)**
      (males in literature)
    - **Kirkland/BONRC**
      -- preadipocytes from Om, Sc, Mes
  - Mouse model neonatal androgen (Bhasin)
    - Sex diff in response
  - Samples from Greenberg lab –
  - Tissues and cells from estrogen-treated OVX

Sex Dependent genes in adipose tissue: *High Fat fed C57/BL6 mice*



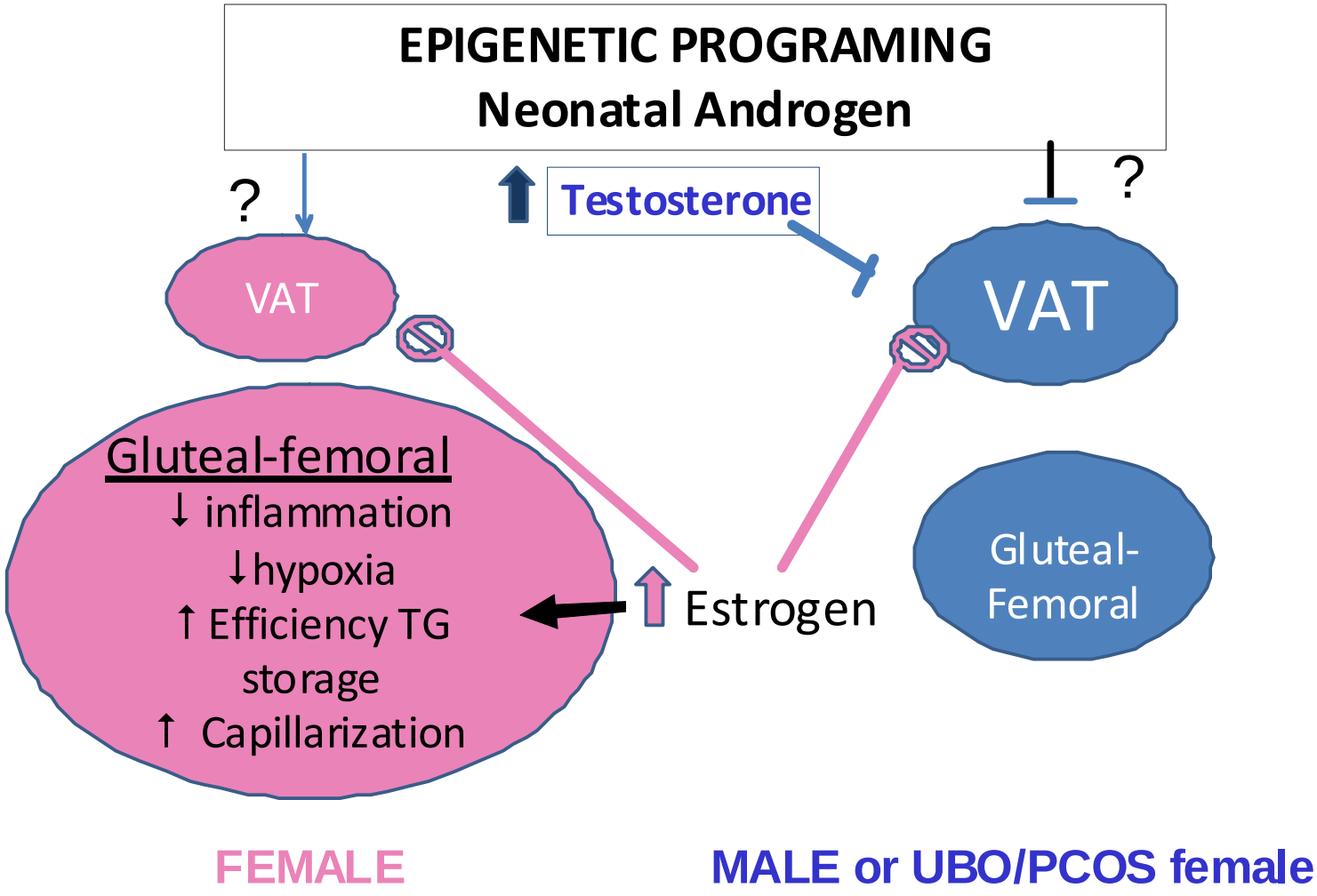
INITIAL microarray analysis results: Abd vs Gluteal Sc adipose tissue of healthy **men** compared to **women**

(Collaboration with Steven Smith and the ISIS network)



Other available resources

- CORES
  - proteomics
  - genomics
  - imaging
  - small animal phenotyping (mice/rats)
    - BF
    - BF distribution
    - In vivo imaging of reporters
- Clinical
  - fat aspirations
  - bariatric surgery program
  - BONRC adipocyte core


EPIGENETIC PROGRAMING
Neonatal Androgen
?
Testosterone
?
VAT
VAT
Gluteal-femoral
↓ inflammation
↓hypoxia
↑ Efficiency TG storage
↑ Capillarization
Estrogen
Gluteal-Femoral
FEMALE
MALE or UBO/PCOS female