



NIH COBRE on Obesity and  
Cardiovascular Disease  
(P20RR021954, 9/1/08-5/30/13)

Program Director: L. Cassis  
University of Kentucky

# DIET-INDUCED OBESITY

## Central Hypothesis

Obesity induces changes in the production and release of adipokines and other inflammatory mediators to promote cardiovascular disease.



Adipocyte Hypertrophy/  
Macrophage infiltration into Tissues

Regulation of adipokines and  
inflammatory mediators

**CARDIOVASCULAR DISEASE**  
(Hypertension, Atherosclerosis, Thrombosis)

# Program Objectives

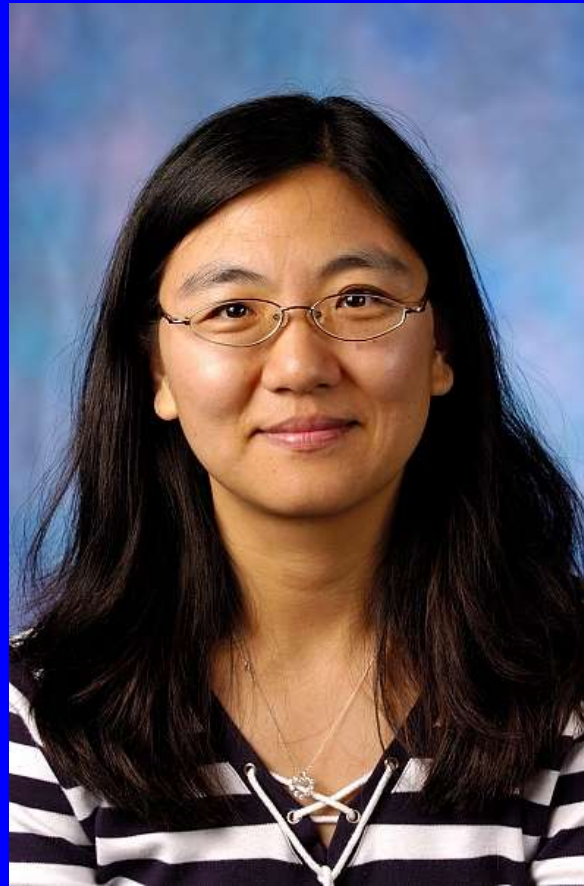
- Identify mechanisms linking obesity to cardiovascular disease
- Develop a multi-disciplinary research center around the unified theme that adipokines and inflammation link obesity to cardiovascular disease
- Use this focus as a platform to develop promising junior investigators and enhance their success at competing for NIH grant support

# Project 1: Thrombospondin 1 Mediates Macrophage Infiltration into Adipose Tissue and Promotes Atherosclerosis in Obese Mice

Mentor



Lisa Cassis, Ph.D.  
Professor and Chair,  
GCNS



Shuxia Wang, Ph.D.  
Associate Professor, GCNS

Mentor



David Randall, Ph.D.  
Professor, Dept Physiology

EAC: R. Eckel

# Project 2: MPGES-1 Deficiency Attenuates Diet-Induced Obesity

Mentor



Phil Kern, MD/PhD  
Director, BBD OC, CCTS



Victoria King, Ph.D.  
Assistant Professor, Div  
Cardiology  
Dept Internal Med

Mentor



Nancy Webb, Ph.D.  
Professor, Div Endocrinol  
Dept Int Med

EAC: P. Tso

# Project 3: Development Origins of Health and Disease

Mentor



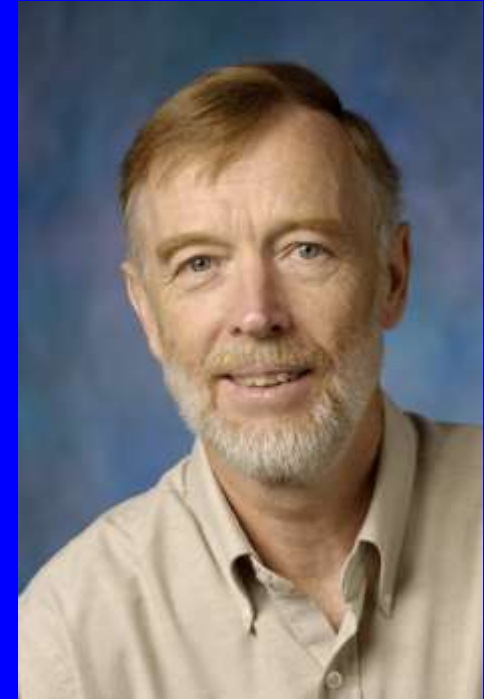
Andrew Morris, Ph.D.  
Professor, Div Cardiology  
Dept Int Med

EAC: R. Eckel



Kevin Pearson, Ph.D.  
Assistant Professor, GCNS

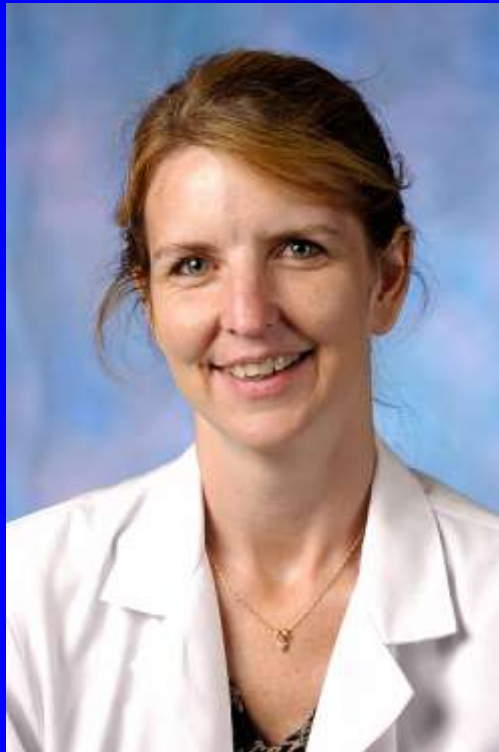
Mentor



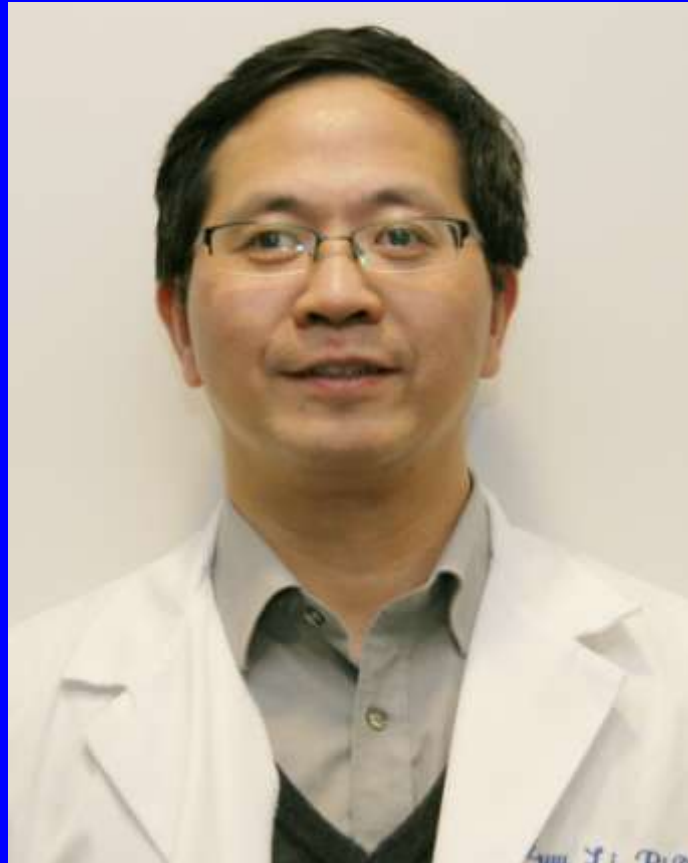
Deneys van der Westhuyzen,  
Ph.D.  
Professor, Div Endocrinol  
Dept Int Med

# Project 4: Platelet Activation with Obesity Promotes Atherothrombotic Vascular Events

Mentor



Susan Smyth, M.D./Ph.D.  
Professor, Div Cardiology  
Dept Int Med



Zhenyu Li, Ph.D.  
Assistant Professor, Div Cardiology  
Dept Int Med

Mentor



Wally Whiteheart, Ph.D.  
Professor, Dept Biochem

EAC: R. Hegele

# Project 5: Dietary Fat Promotes Chylomicron-dependent Intestinal Absorption of Gut Antigens in Adipose Tissue

Mentor



Alan Daugherty, Ph.D.  
Professor and Director, CVRC  
Div Cardiology  
Dept Int Med  
EAC: P. Tso



Erik Eckhardt, Ph.D.  
Assistant Professor  
Div Gastroenterology  
Dept Int Med

Mentor



Andrew Morris, Ph.D.  
Professor, Div Cardiology  
Dept Int Med

# Core A: Administrative

- Program Director: L. Cassis
- Administrative Staff: Mary Lowell
- Executive Committee
- EAC: Drs. Eckel, Tso, Hegele
- COBRE Website
- Pilot Projects
- Statistical Consultant: R. Charnigo, Dept Statistics

# Core B: Obesity-Related Physiologic Cores

- Analytical: Director = Andrew Morris; Staff, Manjula Sunkara; MS Lipidomics, Bioplex multiple analytes
- Diabetes: Director = Susan Smyth, hyperglycemic euglycemic clamps
- Cardiovascular: Director = Alan Daugherty, quantification of atherosclerosis, radiotelemetry measurements of blood pressure
- Obesity: Director = Lisa Cassis; Staff, Wendy Katz, EchoMRI, DEXA-IR, Metabolic chambers
- Pathology: Wendy Katz, tissue processing and sectioning (paraffin, frozen), stains, immunohistochemistry



## **COCVD Pathology Research Core Equipment and services**

**A. Paraffin embedding**

**B. Paraffin sections**

**C. Staining**

**H&E**

**Masson Trichrome**

**PAS added this year**

**D. Nikon 55i upright microscope with 12 MP camera; NIS Elements**

**BR software**

**E. Instruction in image capture and analysis**

# **COCVD Metabolic Research Core**

## **Equipment and services**

**24 Calorimetry Chambers (TSE)**  
for measurement of food and  
water intake, physical activity,  
indirect calorimetry.

**24 acclimation cages.**

**Eight metabolism (urine-feces  
collection) cages for collection  
of urine/feces when food/water  
intake is quantified.**



# Other equipment within Obesity/Diabetes Core

- EchoMRI for quantification of lean/fat mass.
- DEXA-IR for lean/fat mass and bone density.
- Equipment for hyperinsulinemic, euglycemic clamps in mice.

# Cardiovascular Core

- 20 platforms for radiotelemetry in mice.
- Multiple dissecting microscopes for quantification of atherosclerosis (en face).
- 2 Visitech tail cuff systems for measurement of systolic blood pressure.
- 2 Kent systems for measurement of blood pressure.

## Existing Capabilities

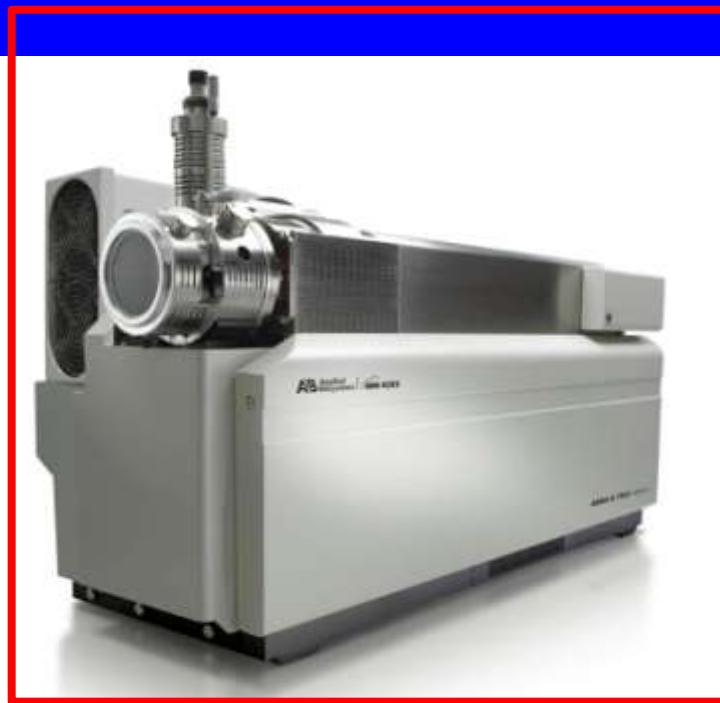


**Biorad Bioplex Suspension Array Reader**

**Agilent GC FID**

*Nikon A1R Resonance Scanning Confocal Microscope (Smyth/Morris/Biochem. Dept)*

**Quantitation/Analysis and Structural Characterization of Small Molecule Therapeutics and Metabolites by Tandem Mass Spectrometry**



# Awarded Pilot Projects



Mark Bonnell, MD  
Assistant Professor, Surgery

- Obesity and Heart Failure:
- Hypothesis 1: Cardiac myocytes from obese patients have higher passive stiffness values than myocytes from non-obese patients.
- Hypothesis 2: Elevated myocardial stiffness in obese patients contributes to the pathophysiology of heart failure.

# Awarded Pilot Projects



Anisa Jahangiri, Ph.D.  
Assistant Professor, Internal Med

- The Influence of SAA and CETP activity on HDL remodeling during active weight loss
- Aim 1: To determine the CETP content of plasma in obese subjects and to determine if the CETP:HDL ratio and thus HDL remodeling is increased during active weight loss.
- Aim 2: To determine if altered SAA expression in obesity and during weight loss affects the expression of CETP, thus influencing HDL remodeling.

# Awarded Pilot Projects



Lei Cai, Ph.D.  
Assistant Professor, Internal Med

- The role of SRB1 in adipose tissue function and inflammation
- Aim 1: Obtain the fundamental physiological or pathological parameters on metabolism in SR-BI deficient mice fed a western diet.
- Aim 2: Identify possible function of SR-BI in primary adipocytes
- Aim 3: Determine whether macrophage SR-BI affects adipocyte differentiation and lipid accumulation

# Awarded Pilot Projects



Preetha Shridas, Ph.D.  
Assistant Prof, Internal Med

- Role of Group X Secretory Phospholipase A2 in Glucose-Stimulated Insulin Release
- Aim 1: Determine whether GX sPLA2 modulates LXR target gene expression, cholesterol content, and GSIS in  $\beta$ -islet cells.
- Aim 2: Investigate age-related changes in GSIS by pancreatic islet cells in wild type mice and determine whether GX sPLA2 deficiency ameliorates  $\beta$ -islet dysfunction.

# Program Statistics: Current year

Core Title	Publications
Analytical Core	7
Pathology Core	3
Obesity Core	7
Investigator publications	12
Totals	29

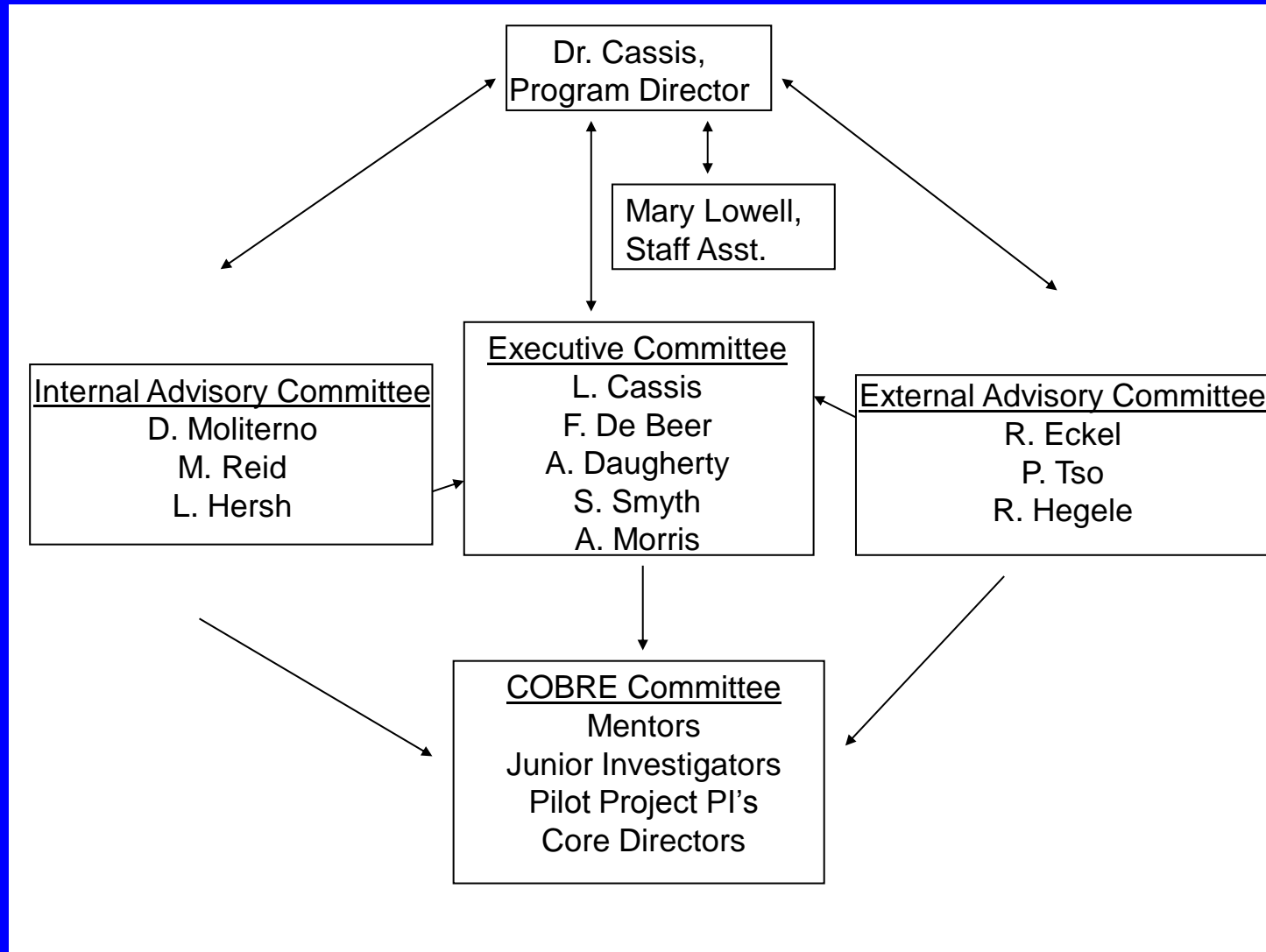
- 8 Graduates to date (year 3)

# Obesity/Diabetes Research Day

- Annual symposia was a stated goal of the program
- Administrative Core organized symposia in conjunction with NIH T32 on Nutrition and Oxidative Stress, and in collaboration with BBDOC
- Inaugural symposia to be held on May 17, 2011
- 80 abstracts/posters
- 221 registrants

# Administrative Structure

## P20 RR021954-01



# Stated ways to meet these objectives

- Examine crucial experimental questions
- Establish mechanisms to promote multi-disciplinary research
- Mentor junior faculty
- Develop and support shared-use core facilities
- Facilitate pilot projects
- Strategic hiring of faculty

# Core A, cont.

- Functions of administrative staff:
  - Schedules all meetings
  - Staff administration for COBRE retreat
  - Maintains data base for all junior investigators/pilot projects, assists in preparation of progress report and updates
  - Coordinates pilot project program (solicitation of grants and reviews)
  - Developed and maintains website
  - Financial reconciling of purchases from Cores
  - Works with Dept Administrator for parent grant accounting
  - Maintains schedules (electronic read-only) for use of:
    - EchoMRI
    - LabMaster TSE
    - Telemetry