

Diabetes and Obesity Center (DOC)

University of Louisville, Louisville, KY

Diabetes in Kentucky

~ 8.5 % of the adult population in Kentucky

~ 29 % of diabetes cases are undiagnosed

-376,00 ~ 12% or 1 in 8 adult Kentuckians

-2000-2002 - 266,715 hospitalizations (16.2%) related to diabetes as primary or secondary Dx

-1/5 children under age 5 weigh too much

-2/3 of adults overweight

We are in the vortex of the current explosion in diabetes and obesity

A Diabetes Center (Joslin Clinic) was established 107 years ago in Boston. Massachusetts has the one of the lowest rates of diabetes and obesity in the country (4 % versus 8.5 % in KY)

Diabetes is a Cardiovascular Disease

Diabetes and heart disease share identical risk factors (the “common soil” theory).

Diabetes increases CVD risk by 2-15 fold

Heart disease accounts for 60-70 % of type 2 diabetic deaths (versus 30 % for non-diabetic).

Heart disease is also the leading cause of death for type 1 diabetes. By age 55, 35 % die of heart disease (versus 4 % of non-diabetic subjects)

All diabetics are now considered CAD risk equivalent (i.e., have the same risk as a person with established heart disease).

Current anti-diabetic therapies do not increase survival. Only statins do

All diabetics need aggressive CVD risk management

Center for Excellence in Diabetes and Obesity Research

CORE A: ADMINISTRATIVE CORE Bhatnagar and Bolli

Project 1: Redox Mechanisms of Hyperglycemic Injury
PI: Timothy O'Toole Mentor: Paul Epstein
Collaborator: David Samuelson

Project 2: Stem Cells and Diabetic Cardiomyopathy
PI Jia-Qiang He: Roberto Bolli
Collaborator: Qianhong Li

Project 3: Cardiac Stem Cells and Mitochondrial Bioenergetics
PI: Bradford Hill Mentor: Sumanth Prabhu
Collaborator: Mike Merchant

Project 4: Foam Cell Formation and Diabetic Atherogenesis
PI: Oleg Barski Mentor: Sanjay Srivastava
Collaborator: Chuang Hu

Project 5: Insulin resistance and inflammation of resolution
PI: Matthew Spite Mentor: Aruni Bhatnagar
Collaborator: Dave Powell

CORE B:
Imaging and
Flow Cytometry
Greg Rokosh

CORE C:
Cardiovascular
Pathology
Steve Jones
Yiru Guo

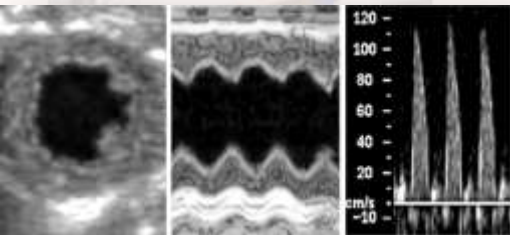
CORE D:
Animal Core Facility
Sanjay Srivastava

CORE E:
Cardiovascular
Imaging
and Function
Sumanth Prabhu



Cardiovascular Imaging and Function Core

Sumanth Prabhu, M.D.
Director



Two Dimensional, M-mode and continuous wave Doppler images of a mouse heart.

Core Functions

- Measurements of cardiovascular functional parameters such as regional myocardial wall motion, fractional shortening and ejection fraction, along with non-invasive blood flow hemodynamics by pulsed wave Doppler in aorta, carotids, and coronary arteries (Vevo 770). Beyond the ultrasonic parameters, the Core will also measure arterial systolic and diastolic blood pressure and heart rate non-invasively by volume-pressure tail cuff technique in conscious mice
- Core will also perform aortic and left ventricular (LV) catheterization using a Millar pressure volume conductance system (ARIA-1) for mice. This will provide direct measurements of hemodynamics and contractility including aortic and LV systolic and diastolic pressure, dP/dt , tau, LV pressure-volume loops, and derived indexes of LV contractility and chamber stiffness.
- Dr. Prabhu will supervise personnel in performing the echocardiographic and invasive hemodynamic studies in mice and assist COBRE PIs in data collection, analysis, and interpretation.
- Quantification of atherosclerotic plaque burden



CODA 6 device measures blood pressure non-invasively by tail-cuff using sensitive pressure volume recording sensors

Cardiovascular Pathology Core

Steven P. Jones, Ph.D.
Director

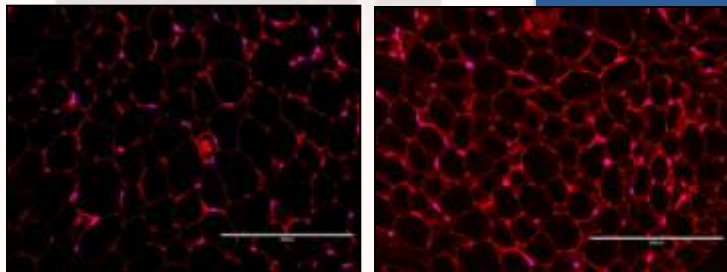


Core Functions

- Responsible for pathological analysis of cardiovascular tissues isolated from diabetic and non-diabetic mice.
- Directing the evolution of the thematic projects by cultivating investigative excellence in diabetic complications of cardiovascular disease and addressing the truly important, underlying questions.
- Mechanism for the development of new areas of research, refining ongoing areas of exploration, and ensuring that the current five project progress smoothly

Obese

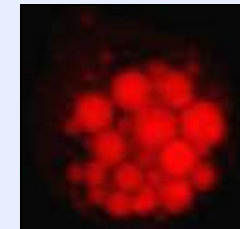
Lean



Phase
Contrast

Nile
Red

Overlay



Differentiated 3T3 adipocytes



Gregg Rokosh, Ph.D.
Director

The main functions of the core are to:

1. house, breed, genotype, and provide mouse models of diabetes and obesity;
2. Provide interactive training for PIs to learn about diabetic models, procedures and interventions; and
3. Facilitate acquisition and creation of novel transgenic and knockout mouse models to address key issues associated with the cardiovascular consequences of diabetes and obesity.

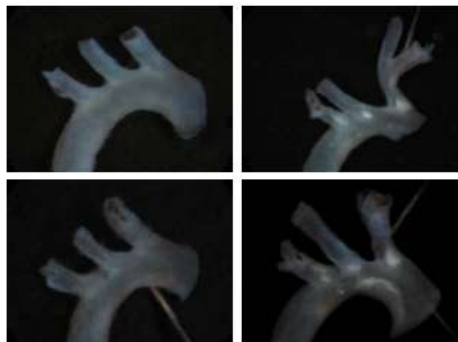


Sanjay Srivastva, Ph.D.
Co-Director

The Animal Core makes available a number of diabetic mouse models for studying the effects of diabetes on atherosclerosis, stem cell viability, cardiac glycolysis and myopathy and smooth muscle proliferation in neointimal formation.



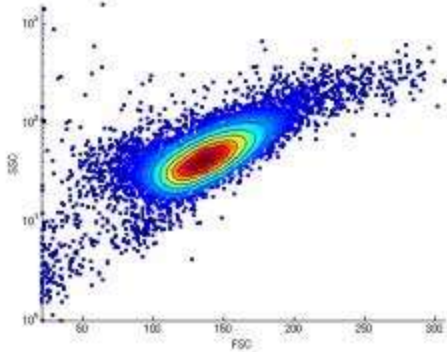
Atherosclerotic lesions in the aortic arch of diabetic mice



Control

STZ

The Animal Core maintains fidelity of mouse lines, and undertakes and manages breeding programs to generate new mouse lines. The Core also offers advice and perform design of constructs for generating transgenic and knockout mice to be used by Center investigators. Constructs can be cell-specific, as well as non-specific. In addition, cutting-edge systems that are being used include inducible cell-specific transgene expression or gene deletion, which allow for tetracycline transactivator 'on-off' expression in adult mice, eliminating developmental effects related to constitutive expression.



The main functions of the core are to:

1. Perform detection and analysis of antigen expression in fixed myocardial sections and cells, including cardiomyocytes.
2. Acquire high-resolution images, render 3D reconstruction of serial images to specifically identify the subcellular location of antigens.
3. Detect intracellular generation of radicals
4. Examine mitochondrial membrane integrity and function; analyze expression of surface antigens in stem cells and the change in antigen expression during differentiation.
5. Isolate stem cells utilizing multiple surface markers; monitor antigenic shift during macrophage transformation
6. Quantify cell cycle events as necessary

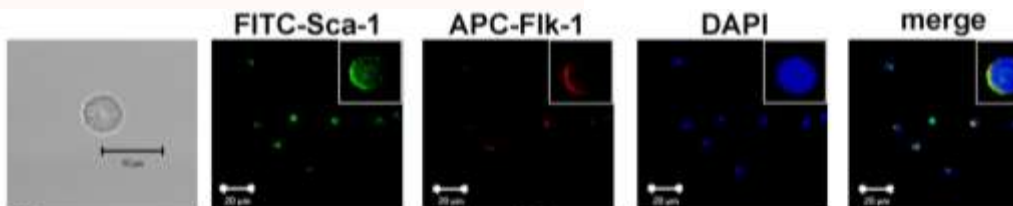


James McCracken, Ph.D.
Core Director

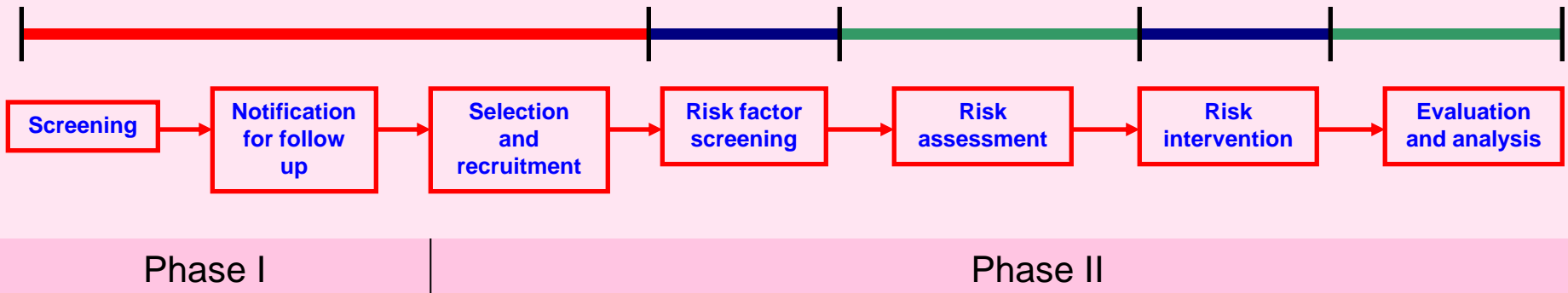
The Confocal Microscopy Unit is responsible for all confocal image acquisition, processing, and analysis; the Flow Cytometry Unit is responsible for analysis and sorting of fluorescent labeled cells.

The Core Units provide the expertise and equipment needed for high resolution confocal microscopic image acquisition and analysis and flow cytometric analysis of antigen expression on cell surface and cell sorting support for cardiovascular research in diabetes and obesity at the University of Louisville.

The functions of these two Units will be inextricably intertwined, as the Microscopy Unit will guide the selection of antigens to be analyzed by the Flow Cytometry Unit, and the Flow Cytometry Unit will produce the cells to be imaged by the Confocal Microscopy Unit.



THE LOUISVILLE HEALTHY HEART PROJECT: STUDY DESIGN

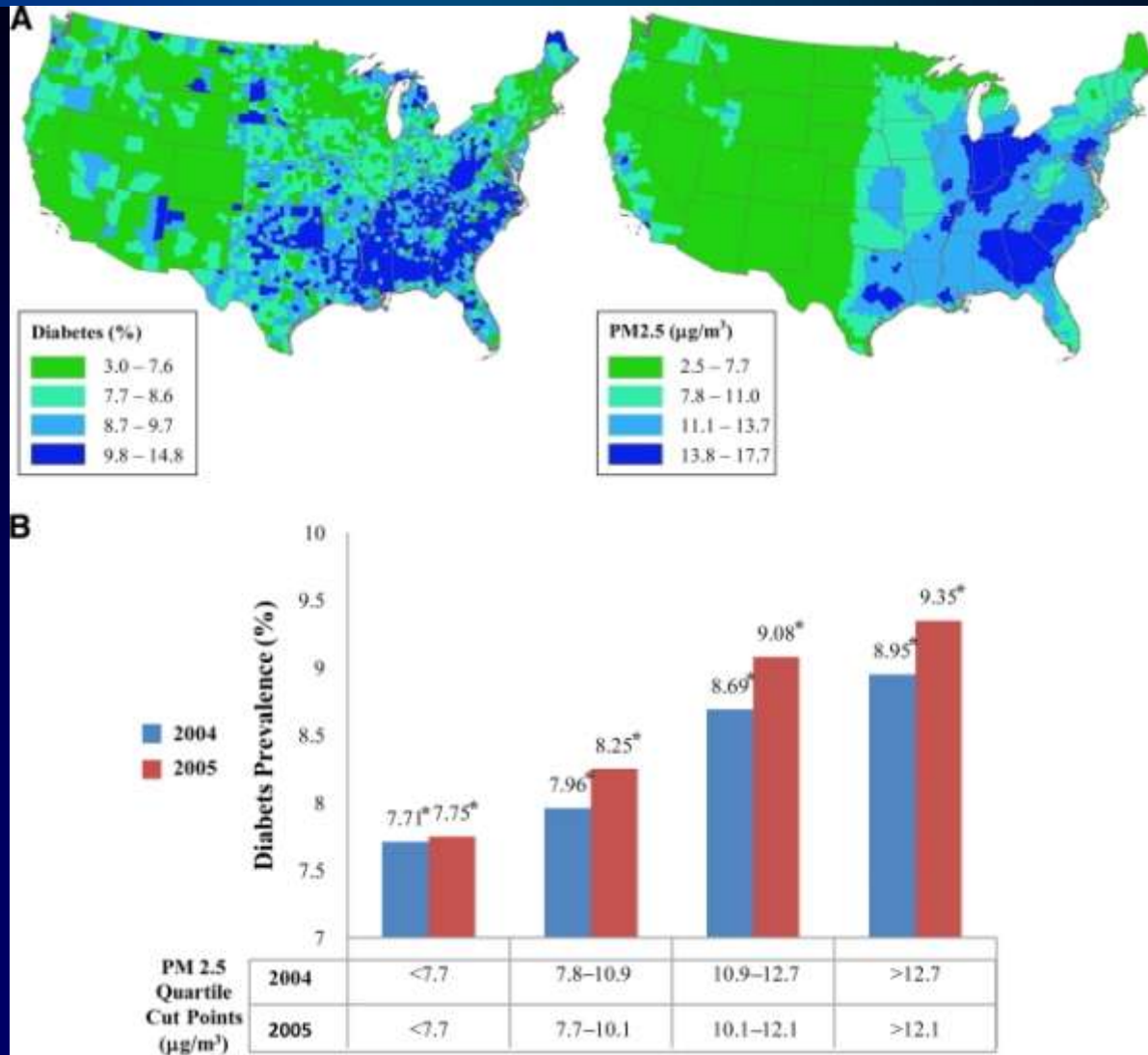


A comprehensive cardiovascular risk assessment of individuals in Louisville over a two-year period.

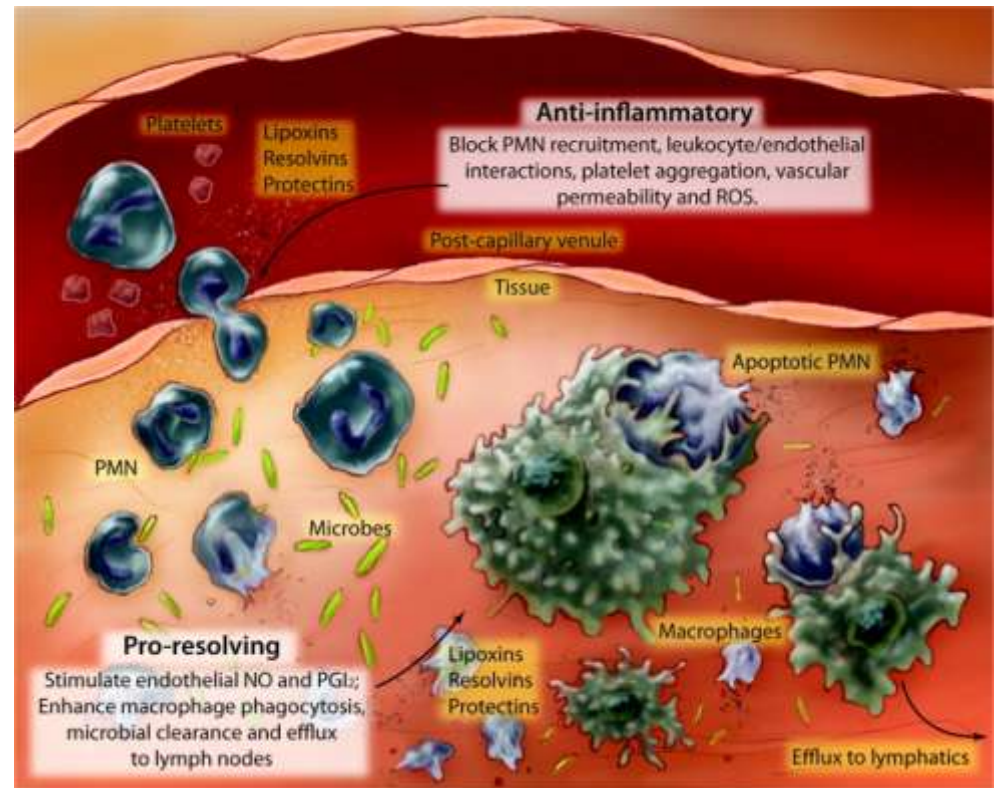
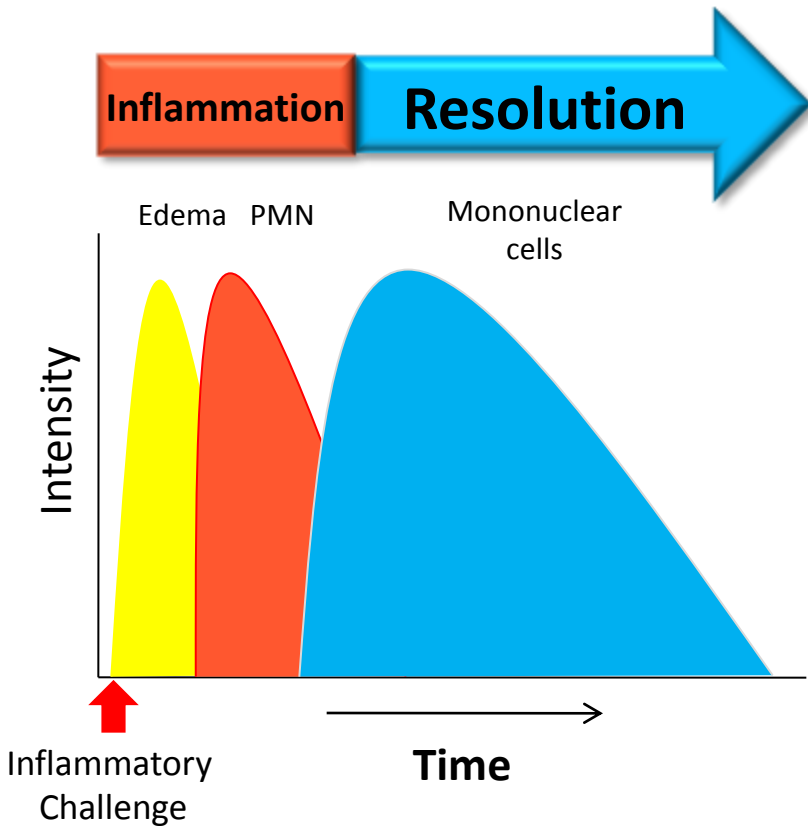
Develop interventions aimed to prevent acute cardiovascular disease and diabetes

Gain a better understanding of the impact of environmental pollutants have on cardiovascular risk, diabetes and obesity

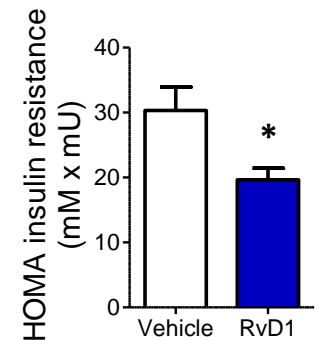
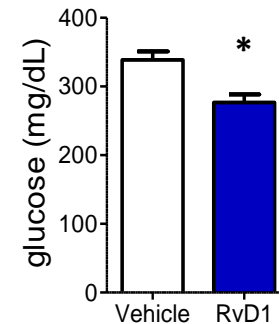
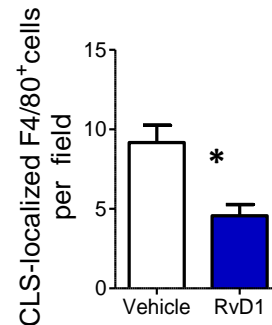
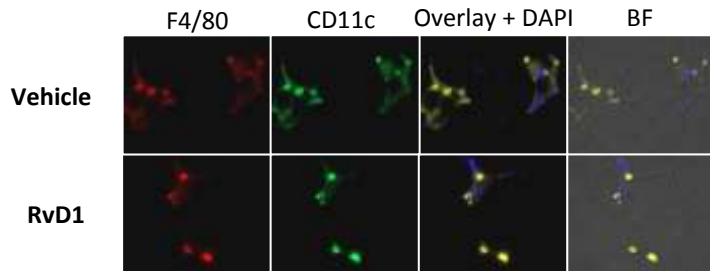
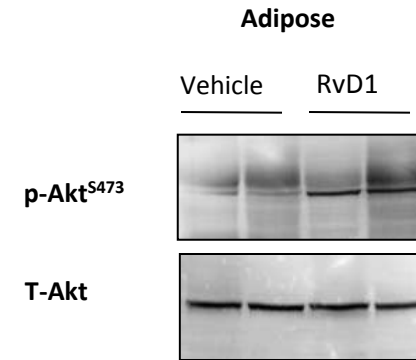
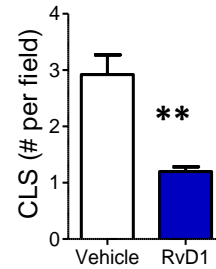
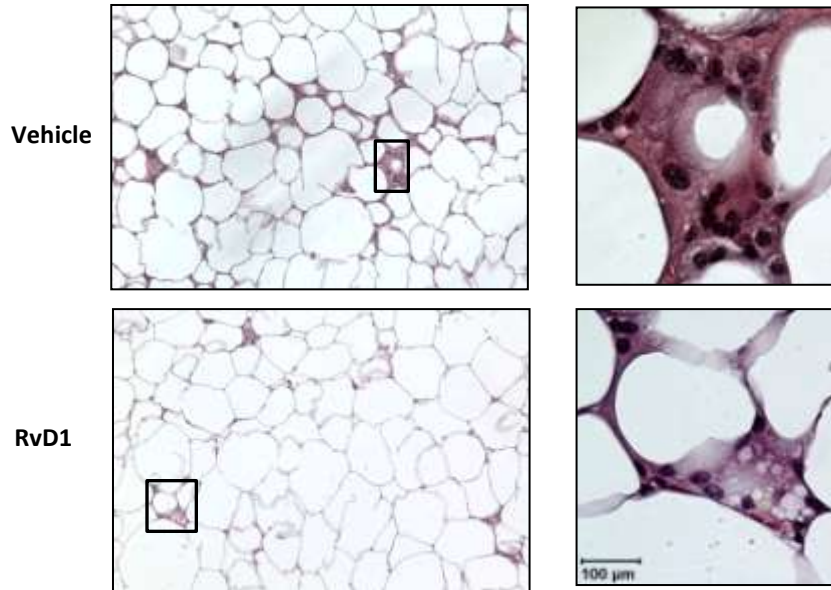
PM_{2.5} and Diabetes



Resolution of inflammation is an active process regulated in part by lipid mediators termed resolvins



Resolvin D1 decreases inflammatory adipose tissue macrophage accumulation and improves insulin sensitivity in obese-diabetic mice



Exposure to pollutants is associated with obesity

West Louisville cohort

Mostly male (54.2%), white (51.7%) or black (46.1%) with a mean age of 50.4 (SD=10.5).

High rate of smoking 43.6%

Current smokers smoked an average of 2.74 packs per week

Average FRS was 7.63 (SD=7.1)

Levels of the metabolite of the environmental pollutant acrolein were correlated with:

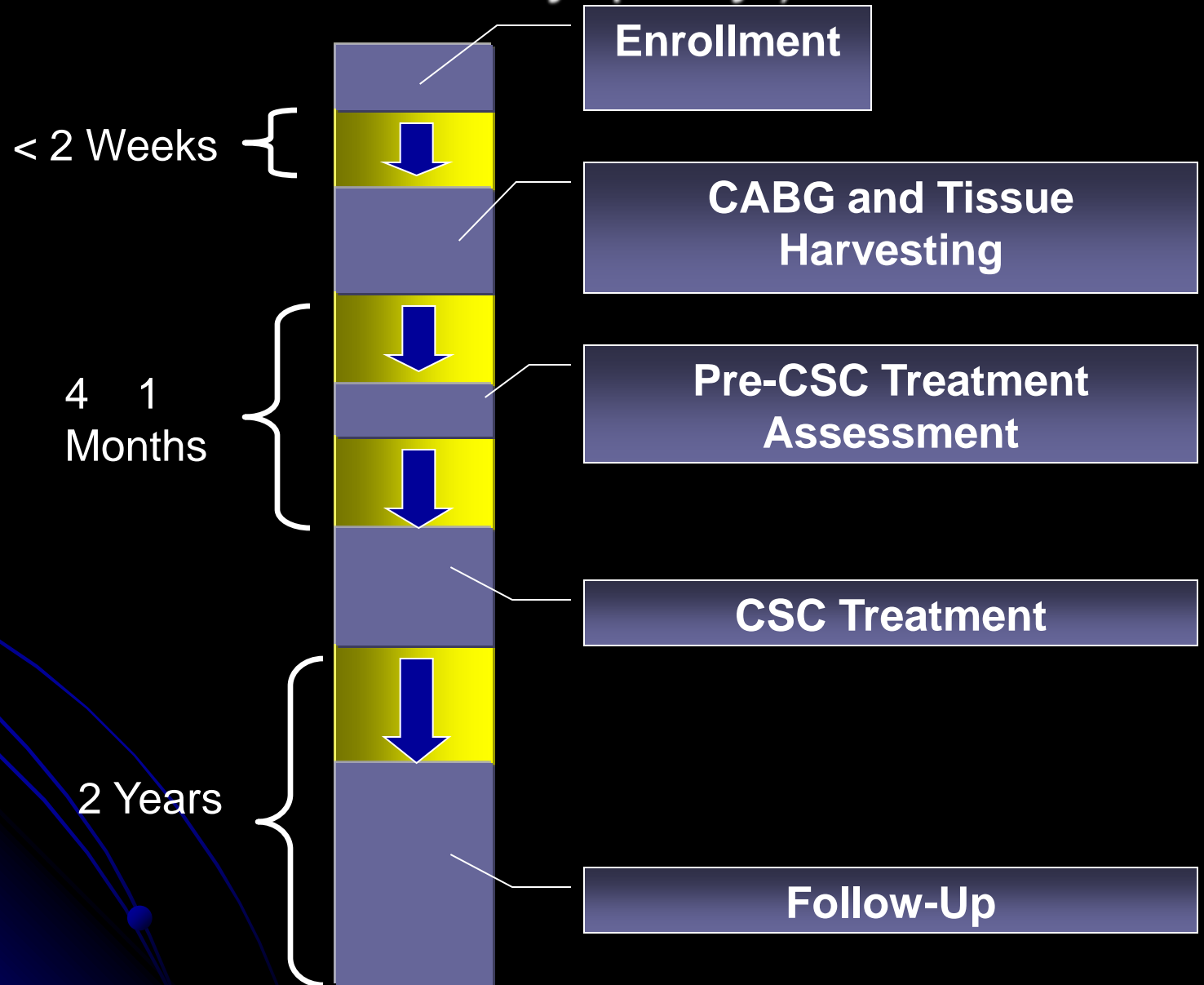
Race ($p=0.0289$)

Smoking status ($p=0.0103$),

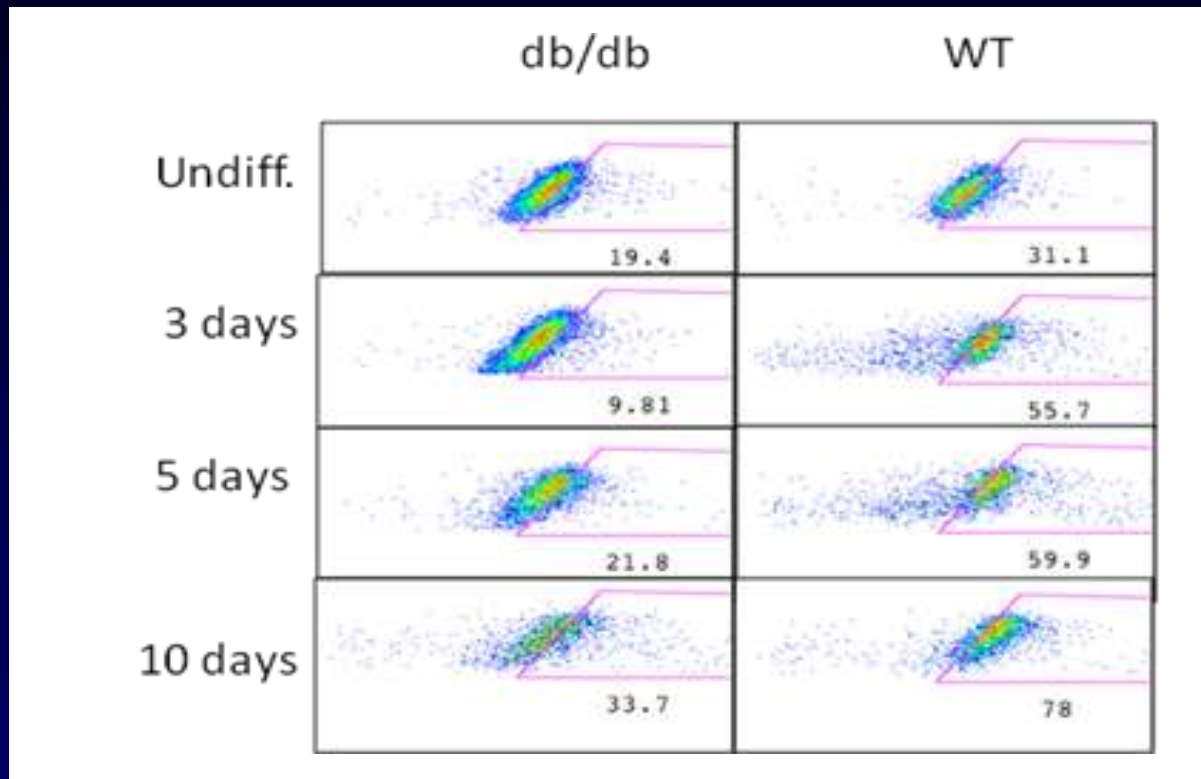
Body mass Index ($p=0.0308$)



The SCIPIO (Stem Cell Infusion in Patients with Ischemic Cardiomyopathy) Trial



Diabetes Decreases the Differentiation of Cardiac Stem Cells



Stem cells were differentiated with dexamethasone, withdrawn on indicated days and stained with anti-NKx2.5 antibody. The cells were gated by FSC/SSC for % NKx2.5⁺ cells