Mechanisms controlling formation of brown versus white fat cells -Potential importance of therapeutics that can convert white to brown adipocytes.

Stephen R. Farmer[1], Cecile Vernochet[1], Sidney B. Peres[1], Li Qiang[1], Hong Wang[1], Meghan MacDonald[1], Kathryn E. Davis[2], and Philipp E. Scherer[2] *

[1]Department of Biochemistry, Boston University School of Medicine,
Boston, MA 02118 and [2] Touchstone Diabetes Center, Departments of Internal Medicine and Cell Biology, University of Texas Southwestern Medical Center, Dallas, TX

White adipose tissue (WAT) stores energy in the form of triglycerides, whereas brown tissue expends energy primarily by oxidizing lipids. WAT also secretes many cytokines and acute phase proteins that contribute to insulin resistance in obese subjects. We are investigating the mechanisms by which activation of PPARγ with synthetic agonists induces the brown phenotype in white adipocytes. Our studies show that this phenotypic conversion *in vitro* and *in vivo* is characterized by repression of a set of white fat genes including resistin, angiotensinogen and chemerin in addition to induction of brown-specific genes such as UCP-1. Inhibition of white adipose gene expression by PPARγ agonists involves critical amino acids within helix 7 of the ligand-binding domain of PPARγ and depends on the expression of C/EBPα. The data further show that repression of resistin and angiotensinogen genes involves recruitment of the corepressor, carboxy terminal binding protein (CtBP), along with PPARγ and C/EBPα to the minimal promoter of the corresponding genes in response to the PPARγ . Additionally, we demonstrate that knockdown of either CtBP1 or CtBP2 prevents the repression of resistin and angiotensinogen by PPARγ in 3T3-L1 adipocytes. These and other data will be presented along with a discussion of novel targets for development of therapeutics for obesity-associated disorders including type 2-diabetes.