**Dr. Sharon Wardlaw**

## Project Summary/Abstract

This proposal centers on diet and drug induced weight loss in human subjects. The success of dieting can be enhanced by pharmacotherapy but there is considerable individual variability and there is no way to predict who will respond well to a particular drug. The overall objectives of this proposal are to validate biomarkers that can be used to predict responses to a given weight loss medication and to characterize counterregulatory responses to drug therapy that may limit efficacy. Studies will focus on the weight loss drug, lorcaserin, and the hypothalamic melanocortin (MC) system, including the proopiomelanocortin (POMC)-derived MSH peptides, the MSH antagonist, agouti related protein (AgRP) and brain MC-Rs, which are key mediators of the central response to weight loss. Lorcaserin is a serotonin (5HT2cR) agonist that works primarily by activation of POMC neurons and melanocortin signaling. During the previous funding period we have found that measurements of the POMC prohormone in cerebrospinal fluid (CSF) can serve as a marker of central POMC activity in humans; plasma AgRP measurements have also emerged as a potential biomarker of brain AgRP activity. The current proposal will study the acute (1 wk) effects of lorcaserin vs placebo on these biomarkers and on feeding behavior, in response to a laboratory test meal, as predictors of the longer-term (24-wk) response to lorcaserin. Counterregulatory mechanisms that may limit the effectiveness of lorcaserin treatment will also be characterized with a focus on the hypothalamic-pituitary-adrenal (HPA) axis and changes in AgRP levels. The 5HT2cR is expressed on CRH neurons and can mediate stimulatory effects of lorcaserin on the HPA axis; increases in cortisol could attenuate lorcaserin-induced weight loss. HPA activity will be assessed using plasma, salivary, urine and CSF measurements. The final Aim will characterize interactions between the HPA axis and AgRP neurons (which express glucocorticoid receptors) and will test the hypothesis that AgRP mediates some of the effects of glucocorticoids on body weight and metabolism. Studies will be performed during short-term (1 wk) administration of hydrocortisone. Changes in food intake during a test meal will be assessed in relation to changes in cortisol and AgRP. The relationship between cortisol and AgRP in CSF and plasma and their diurnal rhythms will also be studied. The validation of biochemical markers (CSF and plasma neuropeptides) and behavioral markers (feeding response) that are predictive of drug efficacy would facilitate the choice of drug when initiating therapy. Furthermore understanding the counterregulatory responses that develop in response to weight loss and drug therapy could lead to interventions that improve drug efficacy.