Mitch Lazar, M.D., Ph.D.
University of Pennsylvania

“Transcriptional Control of Circadian and Metabolic Physiology”
Transcriptional Control of Circadian and Metabolic Physiology. Mitchell A. Lazar, The Institute for Diabetes, Obesity, and Metabolism and Division of Endocrinology, Diabetes, and Metabolism, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA 19104 USA.

The epidemics of diabetes and obesity represent major challenges for modern societies. Obesity is a major risk factor for insulin resistance, which is a key component of the pathophysiology of type 2 diabetes. These diseases have a strong genetic basis, yet their inexorable rise has been largely due to environmental factors including fattening diets, insufficient physical activity, and exposure to light around the clock. Nuclear receptors (NRs) respond to signals derived from the environment and, in this context, we are particularly interested in PPARγ and Rev-erbα. PPARγ is highly expressed in adipocytes and is the target of antidiabetic drugs, while Rev-erbα links circadian rhythms to metabolism. Both of these NRs differentially regulate gene expression in a cell type- and individual-specific manner. When bound to the genome, NRs reshape the epigenome by recruiting NR corepressor complexes containing Histone Deacetylase 3 (HDAC3). Conditional depletion of HDAC3 leads to tissue-specific derangements in organismal metabolism, highlighting its role as a tissue- and gene-specific controller of physiological metabolism that contributes to homeostatic protection from challenges to the circadian, nutritional, and thermal environment.