Rudolph L. Leibel, M.D.

Bio Sketch

Dr. Leibel has worked in obesity research for over 25 years. His initial research efforts were focused on adrenergic receptor-mediated effects on lipolysis, and on the control of fatty acid re-esterification in human adipose tissue. He was among the first investigators to describe anatomic site-related differences in alpha 2 and beta 1 adrenoreceptor activity in human adipose tissue, and to assess their roles in determining the sexual dimorphism in human adipose tissue distribution. His studies of the re-esterification pathway in human adipose tissue led to the development of a microassay system for quantifying this process and to insights into the control of circulating free fatty acids in humans.

For the past 25 years, Dr. Leibel and his associates have conducted studies on the metabolic consequences of experimental weight perturbation in obese and never-obese human subjects. These studies have been performed in Clinical Research Center venues, permitting rigorous control of diet and physical activity. These were the first studies to document and quantify the persistent lowering of energy expenditure-beyond that explicable by altered body mass and composition-that accompanies the maintenance of a reduced body weight. Subsequent studies have shown that altered skeletal muscle metabolism in low work states is an important contributor to the reduction in energy expenditure. Using *in-vitro* NMR and biochemical/molecular analysis of skeletal muscle biopsy samples, the molecular mechanisms for these changes are being sought.

Recently, Leibel and his associate, Michael Rosenbaum, have shown that many of the most important physiological aspects of the formerly-obese state are rectified by the administration of very low (“replacement”) doses of exogenous leptin. These studies suggest that the reduced- obese state is, in some regards, a state of relative leptin deficiency due to reduced body fat. These observations point

to potential therapeutic approaches to correcting this phenotype, and improving success at long term maintenance of reduced body weight.

In 1985 Dr. Leibel and his associates (then at Rockefeller University) began a series of experiments to produce molecular maps of mouse single gene obesity mutations: *ob*, *db*, *fat* and *tub*. These efforts, in collaboration with the Friedman laboratory at Rockefeller, led to the cloning of the *ob* (leptin) gene in 1994. This discovery, by identifying a major signal of adipose tissue mass to the brain, has had an important impact on obesity research in animals and humans. Among other effects of this discovery has been the elaboration of detailed molecular pathways within the hypothalamus for the control of energy homeostasis in mammals. As part of a comparative mapping project, Dr. Leibel's group showed that the fatty mutation in the Zucker (*fa*) study rat was in the same gene as the mouse *db* mutation. In 1995, working with collaborators at Millennium, Leibel and his associate Dr. Streamson Chua (co-director of the Molecular Biology/Molecular Genetics Core, NYORC) showed that an apparent leptin receptor cloned from a choroid plexus library using leptin as ligand, mapped to a physical map that included *db* and *fa*. This experiment confirmed cloning of the leptin receptor.

Leibel's group went on to find the *Lepr* mutations that account for the obesity of the Zucker and Koletsky (corpulent) rats, and to describe the mechanism by which the *fa* mutation (a single amino acid transversion) interferes with function of LEPR.

Dr. Leibel's group has subsequently worked out the fine structure of many of the genes in the leptin response pathway, and in collaboration with investigators around the world, have studied the contribution of allelic variation in these genes to aspects of body composition, obesity and type 2 diabetes in humans. In addition, his group has performed studies relating to sexual dimorphism in circulating leptin concentrations to energy expenditure in humans. Many of these studies have been conducted in collaboration with other scientists at the New York Obesity Research Center (NYORC) of which Dr. Leibel is co-Director.

Leibel's group has also been instrumental in describing the molecular bases for other mutations of the leptin receptor in mice and rats, and has established small colonies of mice and rats segregating for these

mutations on various inbred backgrounds. In 2002 his group reported the cloning of the mouse mahogonoid mutation (named mahogunin = *Mgrn1*). This gene is an E3 ubiquitin ligase that when inactivated by null mutation is epistatic to the coat color and obesity of the yellow (*Ay*) mouse. His group is now actively investigating the molecular physiology of this protein, and has screened human subjects for sequence variants in the ortholog.

Among other areas of active research in Leibel's Division of Molecular Genetics at Columbia are: characterization of the molecular physiology of genes related to energy homeostasis in humans; transgenic analysis of the effects of organ-specific expression of leptin receptor isoforms in the mouse; autocrine and other control mechanisms for anatomic depot-specific regulation of leptin expression; molecular genetic analysis of derangements in the growth hormone axis in humans.

Most recently, Leibel and his collaborators have been endeavoring to clone genes that mediate susceptibility to type 2 diabetes in the context of obesity. This project has resulted in the creation of a large number of mouse congenic lines in which short segments of DNA conveying susceptibility are segregated on non-susceptible genetic backgrounds. Using a variety of strategies, efforts are underway to clone the responsible genes. This project has led to the development of new computational tools for comparing and displaying DNA sequence analysis among mouse strains, and to novel uses of microarrays for gene and pathway identification.

For the past 4 years Leibel has worked with his associate, Anthony Ferrante, and MD/PhD graduate student, Stuart Weisberg, to identify the molecular bases for the inflammatory state associated with obesity. They discovered that adipose tissue macrophages and monocyte/macrophages elsewhere in the body are among the major sources of the cytokines implicated in the inflammatory process. They are now using genetic approaches in mice to identify the molecules that mediate the accession of monocytes (hence macrophages) to specific organs such as adipose tissue, liver, muscle and islets.

Dr. Leibel is internationally recognized for this work and has received a number of prizes and honorary lectureships. He is a member of the

Institute of Medicine of the National Academy of Sciences, and a member of the Federal Advisory Council for NIDDK. His laboratory has trained many students at all levels in research related to obesity and diabetes. Within the past 7 months, three of Dr. Leibel's students have received PhD's from Columbia University. All these projects were related to the molecular physiology of obesity and/or diabetes in mice. Dr. Leibel is Co-Director of the Naomi Berrie Diabetes Center, and Executive Director of the Berrie Program in Cellular Therapies of Diabetes. He is also Co-Director of the New York Obesity Research Center and the Columbia University Diabetes and Endocrinology Research Center. Both are NIH-funced Centers.

Dr. Leibel serves on the editorial boards of the Journal of Clinical Investigation, International Journal of Obesity and Obesity Research.