United in Hope: PWS 2025 – Clinical and Scientific Conference Keynote Speaker

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Background: Dr. Jeffrey Friedman is a Professor at Rockefeller University and an Investigator at the Howard Hughes Medical Institute studying the physiologic and genetic mechanisms that regulate food intake and body weight. In 1994, his laboratory isolated the mouse ob gene and showed that it reduces food intake in mice. Current research is aimed at understanding the neural and physiological mechanisms by which leptin transmits its weight-reducing signal. He is a member of the National Academy of Science and has won numerous awards including the 2010 Albert Lasker Basic Medical Research Award, the 2019 Wolf Prize in Medicine, and the 2020 Breakthrough Prize in Life Sciences.

Title of Presentation: Obesity, Causes and Treatment: The End of the Beginning

Abstract: Food intake is controlled by short and long term systems that maintain optimal levels of both circulating nutrient and energy stores. The new anti-obesity therapeutics are ultra-stable versions of GLP1 and other intestinal hormones that target the short term system to induce satiety but mutations in these genes do not alter weight. In contrast, mutations in genes comprising the long term system cause obesity including Leptin, the leptin receptor and melanocortins.

Leptin is an adipose tissue hormone that maintains homeostatic control of adipose tissue mass. This endocrine system serves a critical evolutionary function by protecting individuals from the risks associated with being too thin (starvation) or too obese (predation). While most obese patients have high endogenous levels of leptin indicating that they are leptin resistant, massively obese patients with leptin mutations show reduced food intake and robust weight loss with leptin treatment. Studies of leptin gene regulation also suggest that leptin should be an effective treatment for the subset of obese patients with low endogenous levels of the hormone while recent studies have revealed the pathogenesis of leptin resistance. The identification of leptin has thus provided a framework for studying the regulation of feeding behavior and the pathogenesis of obesity. Leptin also links changes in nutrition to adaptive responses in other physiologic systems with effects on insulin sensitivity, fertility, immune function and neuroendocrine function (among others). Leptin is an approved treatment for generalized lipodystrophy, a condition associated with

severe diabetes, and has shown promise for the treatment of other types of diabetes and for hypothalamic amenorrhea, an infertility syndrome in females.

While the identification of components of the short term system has identified agents that have pharmacologic effects to induce weight loss, the elucidation of components of the long term system has illuminated the pathogenesis of obesity. Moreover, elements of the short term system interact with the long term system and preclinical and clinical studies have shown that these agents restore leptin signaling and synergize with it to induce even greater weight loss. These findings provide a basis for potential new therapies for obesity and metabolic disease.