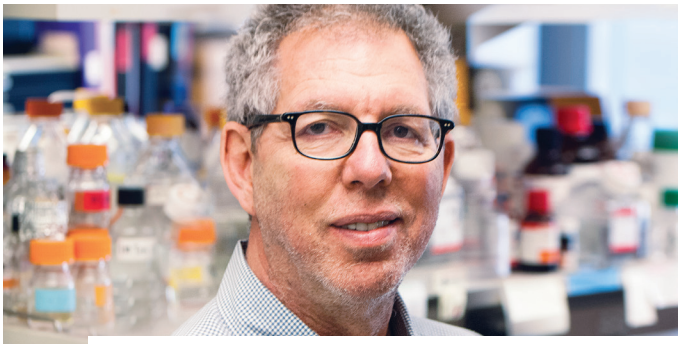

Jeffrey M. Friedman, M.D., Ph.D.

INVESTIGATOR, HOWARD HUGHES MEDICAL INSTITUTE • MARILYN M. SIMPSON PROFESSOR, LABORATORY OF MOLECULAR GENETICS

Friedman studies the molecular and neural mechanisms that regulate food intake and body weight. Genetic studies in mice led to the identification of leptin, a hormone made by fat tissue that plays a key role in controlling appetite and weight. His current work explores the mechanisms by which leptin regulates energy balance and seeks to identify other key regulators of body weight.

Leptin maintains body weight within a relatively narrow range. Increased fat mass increases leptin levels, which in turn reduces body weight; decreased fat mass decreases leptin levels and increases body weight. Defects in the leptin gene are associated with severe obesity, and leptin treatment normalizes weight in these patients. Leptin also improves the severe diabetes and abnormal lipids in patients with lipodystrophy, and is now an FDA-approved treatment for this condition.

Neural Circuits Regulating Food Intake

Leptin acts directly on multiple CNS sites to reduce food intake and body weight in animals and humans, providing an entry point to study the control of feeding. Feeding is a complex motivational behavior controlled by many inputs, including not just leptin but smell, taste, and other hormones. It is not known how or where these multiple inputs are processed to generate a "binary" decision: eat or don't eat. To begin to address the question of how this complex behavior is switched on (and off), the Friedman laboratory is using existing and newly developed methods for both identifying novel populations of nerve cells that are linked to feeding and testing their function. Recent studies have identified key neural populations in multiple brain regions, including the hypothalamus, brain stem, amygdala, and the insular cortex. The next challenge is to establish a hierarchy among these control nodes in order to identify the key node that activates this behavior to the exclusion of other complex behaviors, such as fight, flight, copulation, and grooming.

Regulation of Leptin Gene Expression

The Friedman lab has identified DNA regulatory sequences and a fat-specific long non-coding RNA that control leptin gene expression. They found that mice with a mutation in this RNA, called LncOb, show increased fat mass with reduced leptin levels. Mice that lack LncOb have lower leptin levels than controls and become more obese on a high fat diet, but show significant weight loss after leptin treatment. These studies suggest that obesity with low leptin levels might respond similarly.

Regulation of Fat Innervation

Leptin activates the sympathetic nervous system, which plays an important role in regulating how much energy fat cells store or burn. Recent studies have shown that fat in leptin-deficient animals almost completely lacks sympathetic nerves, and that leptin treatment restores these nerves within 7 to 10 days. Friedman's lab has established a role for neurons in the hypothalamus that express a protein called BDNF. Blocking BDNF signaling from the hypothalamus to the spinal cord blunts leptin's ability to induce nerve growth in fat. Current studies seek to understand how BDNF induces adipose tissue nerve growth.

Genetic Studies of Metabolic Disease in Humans

The Friedman lab is conducting genetic studies of consanguineous families with severe obesity or a hormonal condition called polycystic ovary syndrome (PCOS), in collaboration with Tayfun Özçelik at Bilkent University in Ankara, Turkey. The team is analyzing the DNA sequences from these populations, in collaboration with the Lifton laboratory, to identify DNA mutations that contribute to differences in weight or that lead to PCOS.

EDUCATION

B.S., 1973
Renssalaer Polytechnic Institute

M.D., 1977
Albany Medical College, Union University

Ph.D., 1986
The Rockefeller University

MEDICAL TRAINING

Internship in medicine, 1977–1978
Residency in medicine, 1978–1980
Albany Medical Center Hospital

POSITIONS

Assistant Professor, 1986–1991
Associate Professor, 1991–1995
Professor, 1995–
Co-director, Kavli Neural Systems Institute, 2015–2016
The Rockefeller University

Associate Physician, 1980–1983
The Rockefeller University Hospital

Assistant Investigator, 1986–1992
Associate Investigator, 1992–1996
Investigator, 1996–
Howard Hughes Medical Institute

AWARDS

Canada Gairdner International Award, 2005

Passano Award, 2005

Jessie Stevenson Kovalenko Medal, 2007

Danone International Prize, 2007

Shaw Prize, 2009

Keio Medical Science Prize, 2009

Albert Lasker Basic Medical Research Award, 2010

Pasarow Award, 2011

BBVA Frontiers of Knowledge Award, 2012

Fondation IPSEN Endocrine Regulation Prize, 2012

King Faisal International Prize, 2013

Harrington Prize for Innovation in Medicine, 2016

Wolf Prize in Medicine, 2019

Breakthrough Prize in Life Sciences, 2020

HONORARY SOCIETIES

National Academy of Sciences

National Academy of Medicine

Fellow, American Association for the Advancement of Science

Foreign Member, The Royal Society

Associate Member, European Molecular Biology Organization

SELECTED PUBLICATIONS

Ilanges, A. et al. Brainstem ADCYAP1+ neurons control multiple aspects of sickness behaviour. *Nature* 609, 761–771 (2022).

Stern, S.A. et al. Top-down control of conditioned overconsumption is mediated by insular cortex Nos1 neurons. *Cell Metab* 33, 1418–1432 (2021).

Wang, P. et al. A leptin–BDNF pathway regulating sympathetic innervation of adipose tissue. *Nature* 583, 839–844 (2020).

Dallner, O.S. et al. Dysregulation of a long noncoding RNA reduces leptin leading to a leptin-responsive form of obesity. *Nat Med* 25, 507–516 (2019).

Zhang, Y. et al. Positional cloning of the mouse obese gene and its human homologue. *Nature* 372, 425–432 (1994).