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 Özlüelik 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.