

# Leading the charge in leptin research: an interview with Jeffrey Friedman

Jeffrey Friedman is a molecular geneticist whose group, in 1994, reported the long-sought identity and function of leptin (Zhang et al., 1994), a key fat-derived hormone that regulates feeding behaviour and body weight. This represented a massive step forward in our understanding of obesity, which is now one of the world's fastest-growing health problems. Here, he recalls his journey of discovery and offers his perspective on the future of obesity research.

Jeffrey Friedman was born in Florida and raised in the New York area. After completing high school, he entered a 6-year medical programme that required students to undertake research projects. His positive experience in the lab led him to abandon the final stage of his medical training to pursue questions related to the *ob/ob* mouse. He soon established his own lab at The Rockefeller University, where he focussed on identifying the *ob* gene, a search that took 8 years. This discovery proved the hypothesis that a key hormone secreted by fat cells – now known as leptin (after the Greek *leptos*, meaning thin) – instructs the brain how to regulate food intake. Mutations in leptin disrupt this homeostatic feedback loop and result in massive obesity, both in rodents and humans.

## What encouraged you to take up a career in research?

When I finished my medical residency, I had a year to fill before my fellowship in gastroenterology began. One of my clinical professors suggested I might enjoy research, and introduced me to a professor at Rockefeller, Mary Jeanne Kreek. I joined her lab for a year and fell in love with research, so I never ended up going back to complete my training in gastroenterology. Instead, I entered the PhD programme at Rockefeller, where I've stayed ever since.

## Did you begin by working on obesity?

I initially started working in another area, but this project introduced me to the *ob/ob* mouse. Mary Jeanne is interested in addiction; at that time, it was becoming evident that opiates mimic endogenous molecules now known as opioids. I became completely captivated by the notion that behaviour and affective state could be controlled by molecules. In the course of that year, I was introduced to Bruce Schneider at Rockefeller, whose work was focussed in part on the *ob/ob* mouse. On learning about this mouse, I became interested in the idea that a molecule encoded by the defective gene in *ob/ob* mice could control feeding behaviour. To me, this mouse provided the opportunity to find out what that molecule was.

## Can you fill us in on the history of the *ob/ob* mouse?

Every year at the Jackson Laboratories in Maine, they generate millions of mice – typically by inbreeding, which often uncovers recessive mutations. In 1949, one of the animal caretakers found a massively obese mouse. The lab of George Snell (who won the Nobel prize for his work on the histocompatibility complex) did some standard genetic crosses to determine that this mouse was obese because of a defect in a single gene, the effect of which is a mouse that weighs three times the amount of a normal mouse



(Ingalls et al., 1950). These mice also overeat voraciously and become diabetic. The fact that a defect in a single gene could cause such a change in eating behaviour was similar to the question that captivated me when I joined Mary Jeanne's lab: how do molecules control behaviour? As the next few years unfolded, methods for identifying defective genes were developed. When I started my own lab in 1986, we moved forward with the objective of identifying the defective gene in the *ob/ob* mouse.

## At the time, this was the Holy Grail in obesity research. How did you approach the issue?

Between 1953, when the *ob* gene was mapped, and 1994, when we published its identity, hundreds or even thousands of hypotheses were suggested to explain what the defect in the *ob/ob* mouse might be. None were successfully proven, but there were some experiments done by Doug Coleman in the 1970s that I thought were compelling. He used parabiosis experiments to propose that *ob/ob* mice lack a circulating

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factor that normally suppresses appetite, thus explaining their obesity. He further suggested that a second strain of mouse, the *db/db* mouse (which Coleman discovered and which has a phenotype identical to the *ob/ob* mouse), lacked the receptor for the factor encoded by the *ob* gene (Coleman, 1973). So, the next step was to identify the *ob* gene, and we set out to do this using the then-nascent technology of positional cloning,

Mouse genetics was still in its infancy in those days, so we had to do much of the groundwork ourselves. Now, or in the very near future, whole-genome sequencing could accomplish in a week what it took a group of people 8 years to accomplish. The main bottleneck for us, in the mid 1980s, was that there were no known genetic markers in proximity to the *ob* gene. We had to employ various techniques to find a marker near enough to the *ob* gene so that we could clone it. It was a bit of a needle-in-a-haystack situation, because the marker we were looking for would need to map to a segment approximately equal to 1/3000 of the genome. We took several approaches to enrich for markers in this very small region, but it was difficult and it took a long time. Once we found the markers and began cloning, things accelerated.

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**This was quite a journey – what kept you going?**

In the first half of the project, it was the excitement about possibly finding out what this defective gene encoded, and testing whether it might be a hormone that regulated weight – that was just exhilarating. In the second half of the project, it was too late to turn back! There was still excitement, but the pressure was starting to build, internally and from funding sources. We needed to get this done. I was absolutely certain that the approach we were taking was correct, but the real concern was that other groups might be working on the same problem. When we started our efforts to positionally clone the *ob* gene, three other groups were

using similar approaches to clone different genes. Two of those groups would have been successful but were unlucky because it was found that genes that were cloned for other reasons happened to be allelic with the mutations they were trying to clone. We were more fortunate.

**How did it feel to finally make that discovery?**

I think it was the singular most exciting moment of my professional life – it was completely overwhelming. The initial data showed not only that we had identified the *ob* gene, but also suggested that the gene product was under feedback control and probably encoded a hormone. This amplified the sense of excitement, because it was the first indication that Coleman's and our overall hypothesis was correct.

**In retrospect, how do you view that period of your career?**

The period when we were trying to clone the *ob* gene was both the most difficult and the most exciting time in my career. At that point I felt that there was a singular purpose to our work, and that it was worthy. Theodore Roosevelt has a great quote in this regard: “Far and away the best prize that life has to offer is the chance to work hard at work worth doing”. This is the best advice I can offer to young scientists: come up with a question that you believe is really worth answering, and then work as hard as you can to answer it.

**More recently, you have been studying how leptin affects neuronal plasticity. Can you tell us about this?**

Leptin changes the types and patterns of connections among neurons. This has been reported by our group and also others. But this isn't unique to leptin: it's becoming increasingly appreciated that this is how many factors that modulate neural activity work – that the connections between neurons are very dynamic and can be modified by many different signals. In terms of leptin, this happens in ways that provide explanatory power for how the hormone reduces food intake – but how it happens at the cellular or molecular level isn't really known, and this is a very interesting question for the future. We'd like to understand more about how leptin modulates the activity of different types of neurons, and ultimately develop a deeper understanding of the larger

circuit that these neurons are part of. These investigations will require a better understanding of how leptin remodels neural circuits, but there are likely to be other mechanisms by which leptin alters neural activity.

**Your lab is working on several projects. What are you most excited about at the moment?**

One of the main projects in the lab is the one we've been discussing – delineating the neural circuitry that regulates food intake and body weight. This has been challenging because you have to study the system in vivo. Recently, however, there have been some developments that have advanced our ability to meaningfully probe the system. In particular, we're very excited about a new technology developed by Karl Deisseroth that uses channelrhodopsin to modulate neural activity in response to light. He pioneered the use of a light-sensitive cation channel that, when expressed in individual cells, causes firing of action potentials in response to light. This technique is now being used to study the specific role of individual populations of nerve cells in numerous biological processes. We just published a paper using this method to study the relationship between leptin and reward (Domingos et al., 2011).

Following on from this, we wanted to develop a means to identify the nerve cells that respond to a stimulus such as leptin. This has been difficult, but we have now developed a method that enables the generation of transcriptional profiles from the specific cells that have been activated or inactivated in response to an acute stimulus (still unpublished). We're hoping to use this method to identify the nerve cells that respond to a certain stimulus in the parts of the brain that we believe are important in regulating feeding, and then to study the function of these nerve cells using the channelrhodopsin method. I'm really excited about the potential of this combined approach to develop a deeper understanding of how weight and food intake are regulated.

There is a very important issue underlying this, and that is that feeding is what's known as a complex motivational behaviour. This means that many factors influence the likelihood that you'll eat but none guarantee it. This is in contrast to a reflex, where a defined stimulus gives an

invariant response. Feeding is influenced by many things, such as leptin and other nutritional signals, sensory stimuli such as taste and smell, emotional state, and even the higher cognitive wish to eat more or less. We don't know how complex information of this sort is represented and processed in the brain, or where in the brain it is processed. We'd really like to understand more about how complex information is translated into behavioural responses. The hope is that these new methods that allow us to identify and test the function of specific neural populations will help lead us further down this road.

There are also other projects we're working on that I'm excited about at the moment. In one, we would like to understand how the leptin gene is regulated. We know that leptin gene expression is markedly increased when animals or people are obese, and that its expression goes down when animals lose weight or are fasted – but we don't understand how the leptin gene is regulated in response to these nutritional changes. Evidence suggests that leptin expression is highly correlated with the amount of lipid in a fat cell, and we hypothesize that there must be some sort of lipid-sensing mechanism that is read out with changes in leptin gene expression. We're now beginning experiments that aim to determine how the leptin gene is regulated, hopefully to uncover this lipid-sensing system. In another, we'd like to understand how leptin elicits its anti-diabetic effects. It turns out that leptin improves diabetes independent of its ability to reduce food intake or body weight. Consistent with this, leptin has anti-diabetic effects in several clinical settings. This is best documented in the setting of lipodystrophy, in which patients do not make fat. Consequently, lipid is deposited throughout the body, and the patients develop increased plasma triglycerides and diabetes. Leptin treatment reduces tissue lipid accumulation and also has a very beneficial effect on their diabetes. There's been an application submitted to the FDA to approve leptin for the treatment of this condition. However, the benefits of leptin on diabetes are not limited to lipodystrophy. It also markedly improves leptin in animal models of type 1 diabetes, and clinical studies to test this in humans have already begun. We'd like to understand how leptin benefits diabetes beyond its effects on body weight.

### **Is obesity research in rodents directly translatable to humans?**

My view is very positive in that regard. Several mutations that cause obesity in rodents have been found to cause obesity in humans, so I think there's reason to believe that the circuitry is similar enough that we can learn useful information from studying rodents. However, it's important to acknowledge the differences between rodents and humans. With respect to feeding, humans have a large cerebral cortex that enables us to think about things that mice don't think about. For example, humans might consciously decide that they want to eat more or less, even in cases where the basic biological system that regulates energy balance is pushing them in the opposite direction. This isn't the case with rodents or other mammals – they just eat when they're hungry. So, another interesting challenge moving forward will be to understand how the higher regions of the human brain interact with the centres that control the basic drive to eat. These are big questions that can't be studied in other animals. They are also questions that aren't restricted to the obesity field – they cross over to many other fields of behaviour and brain function too – so I think that understanding the molecular and cellular basis of making behavioural decisions is going to be a very important and exciting area for future research.

### **“I think that understanding the molecular and cellular basis of making behavioural decisions is going to be a very important and exciting area for future research”**

### **What types of anti-obesity drugs do you believe will be most promising?**

I think it's still premature to say specifically which classes of drugs will emerge, although a new drug that modulates serotonin signalling has recently been approved for the treatment of obesity. There have been molecules developed that reduce weight, but many are not especially effective, and some have safety concerns. In general, the molecules that have been developed so far have had a target that is more broadly expressed than you would optimally want. Typically, if you have a broad spectrum of cellular effects or a broad range of cell types that are affected, then the

likelihood of side effects goes up. The hope is that the delineation of the neural circuit that regulates food intake will give us a more refined set of targets that will limit side effects. Understanding these circuits will provide the foundation for a new generation of anti-obesity therapies – although this will take time.

### **“To develop drugs that normalize weight will be a more difficult task moving forward, but I am optimistic that safe molecules that reduce weight enough to improve diabetes, hypertension and other complications associated with obesity will be developed”**

It's also important to consider what we should be looking for in an anti-obesity drug. The objective should be to improve people's health, and not to address what some would call a cosmetic problem. In this regard it's important to note that reducing weight a modest amount has a disproportionate health benefit. That is, if a person is obese or extremely obese, it's not necessary to normalize weight to reap an enormous improvement in health. A problem that clinicians face is that patients don't just want to reduce weight a modest amount – enough to improve health – but to really normalize their weight. To develop drugs that normalize weight will be a more difficult task moving forward, but I am optimistic that safe molecules that reduce weight enough to improve diabetes, hypertension and other complications associated with obesity will be developed.

### **If you could go back to the bench or clinic now, what project or what disease would you tackle?**

I think many of the deepest questions in science pertain to how the brain works, so I think that would be a very exciting area to focus on. I would also want to identify human patients with rare but definable alterations in central nervous system function, and to use whole-genome sequencing to figure out the genetic basis of those alterations – and then to study those genes and see where they lead. The potential of whole-genome sequencing to advance this and other areas is enormous,

and it could transform our understanding of human disease and biology.

*DMM greatly appreciates Jeffrey Friedman's willingness to share his unique thoughts and experiences. He was interviewed by Sarah Allan, Scientific Editor for DMM. This piece has been edited and condensed with approval from the interviewee.*

#### COMPETING INTERESTS

Jeffrey Friedman currently acts as a consultant for Envoy Therapeutics and Bay City Capital, and formerly consulted for Amylin Pharmaceuticals, which is seeking to develop leptin as a human therapeutic.

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