

# Biotech weighs up the options in obesity

The perfect diet pill has eluded the drug industry for decades, but now molecular genetics has put the field on the map and offered new ways to fight the “battle of the bulge”.

Alan Dove

In the past few decades, technological innovations have created a society where most forms of work are lighter, travel less strenuous, and lifestyles more sedentary. Add to this the overconsumption of food, in particular high-fat convenience foods, and you have the perfect recipe for a ballooning public health problem—obesity. With little insight into how body weight is controlled, to date most treatments for the dangerously overweight has been at best ineffective, but harmless, and at worst dangerous or invasive (e.g., surgical reductions in stomach volume). In recent years, however, genetics and molecular biology have helped elucidate some of the intricacies of the body's weight control system, serving up some potentially safe and effective therapeutic strategies.

## A growing problem

Obesity is not just a cosmetic issue, but a serious medical problem, the prevalence of which is steadily increasing. The World Health Organization (Geneva) and its International Obesity Task Force recently declared that obesity is a global epidemic that “pose[s] one of the greatest threats to human health and well being”. Public health experts have estimated that more than half of all Americans over the age of 20 years are overweight, and that at least 20% of males and 25% of females are clinically obese. The last comprehensive study carried out in the United Kingdom suggested 17% of men and 20% of women in England and Wales were obese, and studies in the late 1980s suggested that at least half of Europe's adult population was overweight (see “Whom are we calling fat?”).

The United States may be the leader in the obesity stakes, but other nations are catching up. Diverse reports show that the prevalence of the condition is increasing throughout the developed world, and obesity has become common in Southeast Asia, Latin America, and the Middle East (see Table 1).

Obesity has been recognized as a significant risk to health since 1959, when the Metropolitan Life Insurance Company published a set of actuarial tables showing a

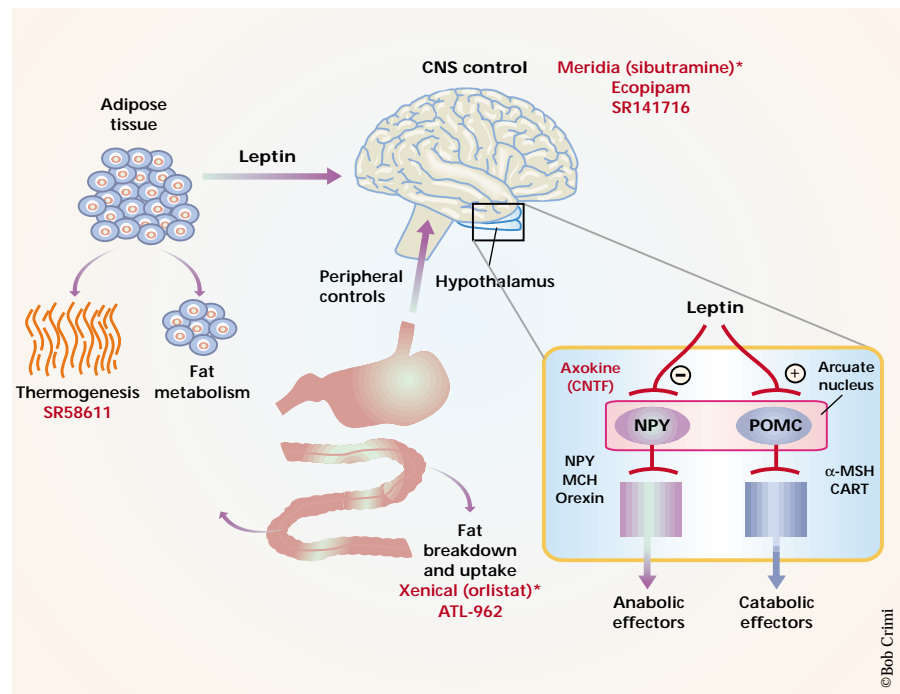


Figure 1. The key elements of the body's weight-control system, highlighting the potential routes for therapeutic intervention. Central to weight homeostasis is leptin, which balances anabolic (resulting in weight loss) and catabolic (resulting in weight gain) effectors through the hypothalamus. \* indicates compounds already approved by the Food and Drug Administration.

strong correlation between excess body weight (and thus Body Mass Index, BMI) and the risk of premature death. In what has become a classic study of the link between weight and mortality, 115,000 women enrolled in the Nurses' Health Study provided detailed information of the association of BMI with premature death and specific diseases. The risk of premature death increased with body weight over the healthy norm, and the risk doubled when the BMI exceeded 29. Data from other studies show similar results among men. Overweight or obesity also greatly increases the risk of hypertension, type 2 diabetes, cardiovascular disease, respiratory problems, and a number of cancers. The increased burden is also an economic drain on a nation. The Institute of Medicine estimates that the direct health care costs and

loss of productivity resulting from ill health costs the United States more than \$70 billion a year.

There is little doubt that the cause of obesity is both social and behavioral. “Twin and family studies indicate that genetic factors play a role in most individuals who are obese,” says Gregory Barsh, an obesity researcher at Stanford University (Stanford, CA), but genetics is not the major factor driving the current epidemic. “A combination of extrinsic conditions are able to cause obesity in individuals who are ... genetically predisposed,” says Barsh.

## The dieter's dilemma

The cause of obesity is ultimately a question of simple thermodynamics: if calorific intake exceeds the output then the surplus accumulates as fat. In theory, drugs could work



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through any of four mechanisms (see Figure 1): reducing the amount of fat absorbed, increasing fat metabolism, curbing appetite, or resetting the central controls of body weight.

In the first category is Xenical (orlistat), Roche's (Basel, Switzerland) drug that blocks the breakdown and absorption of about 30% of dietary fats. However, the side effects, which include fatty stools and fecal urgency, have deterred many patients. An alternative strategy is to permit fat digestion to take place in the gut, but then block the uptake of fatty acids. The discovery of a fatty acid transporter (FATP4) may provide a target for the development of small-molecule therapeutics that work in this manner.

Enhancing energy expenditure, primarily by stimulating thermogenesis (heat production), is a second strategy. Thyroid hormones, for example, "burn off" fats, although they cause detrimental side effects like loss of bone calcium.

Alternative targets include uncoupling proteins (UCPs), which were first discovered in brown fat and also metabolize fats, creating heat. Increasing the expression of UCPs could be one approach to treating obesity. Agonists of the  $\beta_3$ -adrenergic receptor are also under investigation as targets for increasing energy expenditure and Sanofi-Synthelabo (Le Plessis, France) has one such product in development (see Table 2).

An alternative means of controlling consumption is by harnessing peripheral control of feeding. Peptides produced by the gastrointestinal system and pancreas naturally regulate feelings of satiety ("fullness") and the amount of food consumed. One of the best understood is cholecystokinin (CCK), and others include neuromedin B, gastrin-releasing peptide, and enterostatin. Such peptides could be used as targets for drugs that could modulate the amount of food consumed during a meal, but would likely not be effective at longer term control of body weight.

To date, centrally acting appetite sup-

**Table 1. The expanding world: the prevalence of obesity (BMI>30) globally**

Country	Prevalence in men	Prevalence in women	Trend
United States	20%	25%	Increasing
United Kingdom	15%	16.5%	Increasing
Brazil	5.9%	13.3%	Increasing
Canada	12%	14%	Increasing
Australia	11.5%	13.2%	Increasing
Western Samoa	58.4%	76.8%	Increasing
Thailand	3.0%	3.8%	Increasing
Mauritius	5.3%	15.2%	Increasing
Former German Democratic Republic	20.5%	26.8%	Increasing

Source: International Obesity Task Force

pressants have proved the most commercially viable (see Table 2). However, the fate of two highly publicized weight-reducing drugs has cast a long shadow over the field. The highly publicized withdrawal of Redux (dexfenfluramine) and fenfluramine, which were used in combination with phentermine in the fen-phen diet drug (see "Heartache for AHP"), has left the public with lingering doubts about new obesity therapies. Indeed, Xenical has struggled to become the blockbuster drug it was touted to become. However, a new sense of optimism has been created within the industry following genetic studies first focused on a grossly overweight mouse.

#### Million-dollar mice

In 1994, great excitement was generated when researchers at the Howard Hughes Medical Institute at the Rockefeller University (New York, NY) discovered what appeared to be a fat-regulating hormone, leptin.

Jeffrey Friedman and his team had identified and sequenced the *ob* gene, which underlies the gross obesity in the *ob/ob* strain of mice<sup>1</sup>. When leptin was injected back into the *ob/ob* mice their appetites shrank and they quickly shed the excess weight. Researchers were most excited to see that fat was lost and lean mass spared—the ideal diet drug.

Amgen (Thousand Oaks, CA) moved quickly to pay \$25 million for the rights to

develop leptin as a treatment for obesity. Clinical results, however, have been disappointing. "There were some reasons to wonder how well it would work, given the presence of high levels of endogenous leptin in [obese] people," explains Jeff Flier, an obesity researcher at Harvard's Beth Israel Deaconess Hospital (Boston, MA). It seemed unlikely that further elevations would restore the patients' sensitivity to leptin. Indeed, Amgen ended clinical trials of leptin in 1999 after a series of unimpressive results. The company is now testing a new formulation of the protein, which may be more stable, and last longer, in the bloodstream.

"I don't like to say it's over for leptin," says Louis Tartaglia, vice president for metabolic diseases at Millennium Pharmaceuticals. The hormone, he says, could still be used to treat a subset of obese patients. For example, leptin has been used successfully to treat a handful of severely obese children who have an inherited deficiency in the hormone.

#### Lessons from leptin

However, the discovery of leptin marked the beginning of molecular medicine for the treatment of obesity, giving the field a credibility hitherto lacking. Leptin's discovery touched off some fundamental research into the mechanisms controlling body weight, producing a trove of new molecular targets for obesity therapies.

Shortly after the discovery of leptin, Tartaglia and his colleagues identified a receptor for leptin, OBR. A truncated form of the receptor, so-called OBR-A, shuttles leptin across the blood-brain barrier. Researchers now suspect that obese people appear to be resistant to leptin because the hormone is not transported into the brain. Indeed, studies suggest that the level of leptin in the cerebrospinal fluid of obese individuals is much lower than anticipated considering their high blood concentrations. OBR-A is therefore an as yet unexplored target for treatment.

### Whom are we calling fat?

BMI (kg/m <sup>2</sup> )	WHO classification	Popular description
<18.5	Underweight	Thin
18.5–24.9	–	"Healthy", "normal"
25.0–29.9	Grade 1 overweight	Overweight
30.0–39.9	Grade 2 overweight	Obese
≥40	Grade 3 overweight	Morbid obese

Although there is controversy over how obesity should be measured, a commonly used measure is the body mass index (BMI), which is defined as the individual's weight (kg) divided by the square of their height (m).



Leptin is produced by fat cells, circulating in the blood to the hypothalamus where it works through a number of nuclei and pathways to reset the body's weight controller. As fat levels increase, leptin levels rise, triggering a reduction of food intake and increasing metabolism. As shown in Figure 1, leptin mediates its effects through at least two subtypes of neurons of the arcuate nucleus of the hypothalamus, those expressing neuropeptide Y and those expressing pro-opiomelanocortin (POMC).

#### Sites for intervention

Leptin inhibits the release of neuropeptide Y (NPY), a small protein that increases appetite. Research efforts have now focused on developing NPY antagonists, and companies such as Neurogen (Bradford, CT) and Synaptic Pharmaceuticals (Paramus, NJ) are targeting specific subtypes of receptor, NPY1 and NPY5, which have been implicated in feeding.

Another element in the leptin signaling pathway is  $\alpha$ -melanocyte-stimulating hormone ( $\alpha$ -MSH), which is actually a fragment of the precursor protein POMC. Mutations in the *POMC* gene cause a rare hereditary form of obesity.  $\alpha$ -MSH acts through the MCR-4 receptor to reduce appetite. According to Barsh's data, mutations in MCR-4 account for 2–3% of cases of severe obesity, and agonists of the MCR-4 receptor make obvious choices for the development of a treatment for obesity and one that Millennium is currently pursuing.

In addition to its effects on  $\alpha$ -MSH, leptin increases the production of the SOCS-3 (suppressor of cytokine signaling-3) protein, which terminates its activity at the leptin receptor. The SOCS-3 protein is probably a regulator of the leptin signaling pathways in healthy individuals. If this pathway is overactive in obese patients, drugs that target SOCS-3 might have considerable potential.

Finally, a new target appeared in June 2000, when researchers at Johns Hopkins University (Baltimore, MD) discovered that the molecule malonyl coenzyme A inhibits NPY independently of leptin, decreasing appetite in mice<sup>2</sup>. The team also developed an inhibitor that prevents malonyl CoA from being broken down in the body, resulting in its accumulation and leading to weight loss.

Although a number of other neuropeptides are known to be involved in the central control of appetite, many of these are not suitable targets for drug development because they play roles in a wider range of physiological processes. Further research into neuropeptides such as corticotropin-releasing hormone (CRH), orexin, galanin, and cocaine- and amphetamine-regulated

transcript (CART) may, however, help clarify the workings of the weight control system.

Drugs targeting any of these pathways would act primarily as appetite suppressants, and strike at the heart of the dieter's problem. Drugs that reduce fat absorption or increase fat metabolism may help shift body fat, but in turn they will modulate leptin levels triggering the compensatory changes in feeding and metabolism.

### The old 'diet and exercise' approach has clearly not worked very well, so there's plenty of room for improvement.

Ultimately, appetite suppressants, which work by resetting the body's weight control system, is what drug developers are placing their bets on.

However, even then Tartaglia argues that therapies may have to be tailored to specific subpopulations of patients. "Right now it's very difficult to predict which of these different mechanisms is going to really result in the most effective obesity drugs, and in fact I think it's very likely that different drugs acting on different mechanisms will be more or less effective in different people."

#### Fat chance

A deeper understanding of the molecular mechanisms underlying weight control has

helped to inform many drug development efforts, but serendipity has also played a role. Regeneron (Tarrytown, NY) initially tested Axokine (ciliary neurotrophic factor, CNTF) as a treatment for amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease). Although Axokine did not alleviate ALS, it caused the patients to lose weight. Subsequent studies revealed that Axokine "used the same signaling pathway [as leptin], and it was doing it in an overlapping part of the brain...", says George Yancopoulos, chief scientific officer at Regeneron.

So far, CNTF has fared better than leptin in clinical trials. In a phase 2 trial involving 170 obese people, patients given the drug lost 3 to 9 lb over a 12-week period. One group of patients was followed for a few weeks after they stopped taking the drug, and Yancopoulos says that they didn't regain their body weight. "They actually stayed at that plateau of the body weight that they had lost." This finding raises the possibility that the drug could reset the body weight for the longer term.

Others are less optimistic that weight loss can be maintained without chronic and long-term treatment. "It's very ... unreasonable to expect that you are ever going to be able to take a [weight loss] drug for a short period of time and then be able to stop taking it and stay thin. Short of something radical like gene therapy, I think that would be an unrealistic expectation at this point," says Tartaglia.

#### A difficult delivery

The prospect of long-term administration raises another problem with many of the

### Heartache for AHP

The appetite suppressants dexfenfluramine and fenfluramine looked to American Home Products (Madison, NJ) like potential blockbusters when they first licensed them from Interneuron (Lexington, MA). Finally approved by the Food and Drug Administration in 1996, dexfenfluramine (Redux) was one of the first new appetite-reducing drugs in over 20 years. Dexfenfluramine boosts serotonin levels by stimulating its release and inhibiting its reuptake. Sold alone under the brand name Redux, dexfenfluramine, and the so-called fen-phen diet drug (a combination of fenfluramine and phentermine (a noradrenaline reuptake inhibitor)), were taken by millions of Americans. However, a spate of cases of heart valve damage, thought to be linked to fen-phen cocktail, rang the regulator's alarm bells. Concerned, both dexfenfluramine and fenfluramine were withdrawn from the market in 1996.

Although the cause of the damage is poorly understood, AHP has been the target of a number of court cases by affected patients. About 200,000 people have now joined in the settlement that could cost AHP \$3.75 billion in compensation. Interneuron is also suing AHP for "deliberately withholding and concealing information about the potential health risks associated with the drug", and the impact that it had on the company's share price. Although drug companies continue to be interested in serotonergic control systems that modulate feeding, they have focused their attention of a specific subtype of the 5-HT receptor, 5-HT2c. Studies from knockout mice have indicated that much of the weight-reducing effects of fenfluramine were mediated through the 5-HT2c subtype of receptor.



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Table 2. Selected obesity treatments in development

Company	Drug/Mechanism of action	Stage of development
<i>Inhibitors of fat absorption</i>		
Roche (Basel, Switzerland)	Xenical (orlistat); blocks pancreatic lipases and inhibits fat absorption	Approved
Alizyme (Cambridge, UK)	ATL-962; lipase inhibitor	Phase I completed
<i>Stimulators of fat metabolism</i>		
Pfizer (Parke Davis; New York, NY) Metabolic Pharmaceuticals (Melbourne, Australia)	Synthetic 15d-prostaglandin J; stimulant of fat breakdown AOD9604; a peptide fraction of human growth hormone that triggers fat metabolism	Undisclosed Preclinical
<i>Stimulators of thermogenesis</i>		
Sanofi-Synthelabo (Le Plessis, France)	SR58611; $\beta_3$ - adrenoceptor agonist	Entering Phase 1
<i>Centrally acting appetite suppressants</i>		
Knoll Pharmaceuticals (Mount Olive, NJ) Amgen (Thousand Oaks, CA)	Meridia (sibutramine); selective serotonin reuptake inhibitor Leptin; appetite suppressant	FDA approved Trials discontinued, analogs being developed Phase 2
Regeneron (Tarrytown, NY)	Axokine (ciliary neurotrophic factor); targets a pathway in the hypothalamus similar to the leptin pathway	
Schering-Plough (Kenilworth, NJ) Sanofi-Synthelabo (Le Plessis, France) Phytopharm (Godmanchester, UK) /Pfizer Neurogen (Branford, CT)/Pfizer	Ecopipam; dopamine D1/D5 receptor antagonist SR141716; small-molecule cannabinoid antagonist P-57; mode of action undisclosed NPY 1 and 5 antagonists; targets the leptin pathway Melanin-concentrating hormone (MCH) antagonists Melanocortin-4 (MC-4) agonists; targets the leptin pathway NPY subtype 1 and 5 antagonist; targets leptin pathway Zolofit (sertraline); selective serotonin reuptake inhibitor	Phase 2 Phase 2 Phase 1 Preclinical Preclinical Preclinical Preclinical Approved as an antidepressant, being tested as appetite suppressant

potential biotechnology-based obesity treatments: as proteins, they will need to be injected, and many have short half-lives. Regeneron is currently working with Emisphere (Tarrytown, NY) to develop oral formulations of CNTF, but Yancopoulos says that those are hurdles that will have to be crossed in the future.

However, he is optimistic about the prospects for injected treatments: "I think that the barrier for an injection is much lower ... than people would have you think. These are very small amounts of drug that we need to inject, so I think for severe obesity an injectable is not going to be much of a problem."

Tartaglia takes a similar tack: "It's certainly a challenge to get proteins that have very long durations of action, but that's also a challenge for orally administered small molecules. I don't really see it as a special issue unique to proteins [as obesity treatments]." The advantages and disadvantages of the two approaches should become clear as the large number of small-molecule and protein-based therapeutics move through clinical development (see Table 2),

Indeed, most researchers are optimistic about the prospects for new obesity therapies. "I expect new pharmacological treatments will be implemented over the next 5–15 years. It would not be surprising to see new drugs available in the next 2–3 years, but it will take another 2–3 years to measure their effectiveness," says Barsh.

A healthy diet and regular exercise are still the best ways to prevent obesity, but something more will be needed to combat the current obesity epidemic. According to Flier, "The old 'diet and exercise' approach has clearly not worked very well, so there's plenty of room for improvement."

## Crossing the thin line

Parallel to the rise in prevalence of obesity in developed countries, there has been a boom in the market for weight loss products, despite considerable evidence that most of them are ineffective. The obsession with being thin, along with the fen-phen debacle, has highlighted the potential danger of providing drugs to an overly keen market. "Our goal ... is to develop drugs that will improve metabolic health, but I certainly, of course, recognize the potential for overprescription and I think it is a concern," says Louis Tartaglia, vice president for metabolic diseases at Millennium Pharmaceuticals. Although the potential for abuse is widely appreciated, past experience suggests that there may be little that a pharmaceutical or

biotechnology company could, or would, do to prevent doctors from overprescribing a blockbuster drug. However, anti-obesity medications based on hormone signaling pathways (see main text) may have some built-in safeguards. Jeff Flier, an obesity researcher at Harvard's Beth Israel Deaconess Hospital, says that many of the therapies currently in development restore balance to the body's natural weight control systems, so that they may have "some limitations as to how lean they would make you, such that the desire to abuse these [drugs] would be limited". In addition, many of the new protein-based treatments will have to be injected on a regular basis, which would make abuse less likely.

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1. Zhang, Y. *et al. Nature* **372**, 425–432 (1994).
2. Loftus, T.M., *et al. Science* **288**, 2379–2381 (2000).