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(57) Abstract: The use of interferon-alpha to treat overweight or obese individuals is disclosed. In one embodiment, individuals are administered lozenges comprising low dose interferon-alpha to achieve weight loss. Interferon-alpha treatment in the range of from about 50 to about 2000 International Units per day over 3-6 months produces desirable weight loss without the side effects commonly associated with high dose injectable interferon-alpha.



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TREATMENT OF OBESITY WITH AN INTERFERON

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority under 35 U.S.C. § 119(e) to U.S.

- 5 Provisional Application Serial No. 61/059,961, filed June 9, 2008, the disclosure of which is incorporated herein by reference in its entirety.

BACKGROUND

Obesity is a world wide pandemic. In Mexico, Egypt, and South Africa
10 more than half of adults are overweight or obese (Popkin, *Scientific American*, 2007, 297, 3, 88). In most of Latin America and much of the Middle East and North Africa, at least one quarter of adults is overweight. In Egypt, a study in 1998 found that 59.1% of adults were overweight or obese. In Mexico, a study in 2006 found the percentage of adults overweight or obese to be 69.3%.

15 More Americans are overweight than ever before. The incidence of obesity has rapidly increased and the associated health care costs have risen. Recent reports show that 66% of Americans are overweight or obese (Centers for Disease Control and Prevention, Obesity and Overweight: U.S. Obesity Trends 1985-2005, available at <http://www.cdc.gov/nccdphp/dnpa/obesity/trend/maps/>; Ogden & Carroll,
20 *JAMA*, 2006, 295, 13, 1549). A number of health problems are linked to obesity including heart disease, metabolic syndrome, diabetes, hypertension, stroke, cancer, dyslipidemia, gallbladder disease, sleep apnea, respiratory problems, reduced fertility, osteoarthritis, and increased overall mortality.

Approximately 280,000 deaths annually in the United States are
25 estimated to be attributed to obesity. The percentage of women and men trying to lose weight at any given time is 35-40% and 20-24%, respectively. Americans spend more than \$33 billion per year on weight control products and services, yet these efforts have had little or no effect on slowing the increase in prevalence of obesity (Greenwald, *Adv. Psychosom. Med.*, 2006, 27, 24).

30 A new approach for prevention and management of obesity is needed which may be facilitated by better understanding the etiology. One potential etiological factor is infection, for example, by a virus. In the last two decades, 10 adipogenic pathogens were reported, including human and nonhuman viruses, scrapie agents,

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bacteria, and gut microflora. Some of these pathogens may be associated with human obesity but a causative role has not been established.

SUMMARY

5 A method for treating overweight and obese patients is provided and comprises one or more of the following features or combinations thereof:

 In one embodiment, a method for inducing weight loss is provided by administering low dose interferon to an individual desirous of losing weight. In one exemplary embodiment, the interferon administered is interferon-alpha (IFN- α), and the
10 interferon is administered orally including for example in a saliva soluble dosage form. In one variation, interferon-alpha is administered at a dose range from about 50 to about 2000 IU per day. In another variation, interferon-alpha is administered from about 400 to about 1000 IU per day, to induce or maintain weight. In accordance with one
15 embodiment a method is provided for treating patients that are overweight or obese and help promote weight loss. Alternatively, in one embodiment a method is provided to prevent weight gain.

DETAILED DESCRIPTION

 While the invention is susceptible to various modifications and
20 alternative forms, specific embodiments will herein be described in detail. It should be understood, however, that there is no intent to limit the invention to the particular forms described, but on the contrary, the intention is to cover all modifications, equivalents, and alternatives falling within the spirit and scope of the invention.

25 DEFINITIONS

 In describing and claiming the invention, the following terminology will be used in accordance with the definitions set forth below.

 As used herein, the term "pharmaceutically acceptable carrier" includes any of the standard pharmaceutical carriers, such as a phosphate buffered saline solution,
30 water, emulsions such as an oil/water or water/oil emulsion, and various types of wetting agents. The term also encompasses any of the agents approved by a regulatory agency of the US Federal government or listed in the US Pharmacopeia for use in animals, including humans.

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As used herein, the term "treating" includes prophylaxis of the specific disorder or condition, or alleviation of the symptoms associated with a specific disorder or condition and/or preventing or eliminating said symptoms. For example, as used herein the term "treating obesity" will refer in general to inducing weight loss or
5 preventing weight gain or reducing complications associated with obesity including vascular disease (coronary artery disease, stroke, peripheral vascular disease, ischemia reperfusion, etc.), hypertension, onset of diabetes type II, hyperlipidemia and musculoskeletal diseases.

As used herein an "effective" amount or a "therapeutically effective
10 amount" of an anti-obesity composition comprising interferon refers to a composition comprising a nontoxic but sufficient amount of an interferon to provide the desired effect. For example one desired effect would be the reduction or maintenance of body weight. The amount that is "effective" will vary from subject to subject, depending on the age and general condition of the individual, mode of administration, and the like.
15 Thus, it is not always possible to specify an exact "effective amount." However, an appropriate "effective" amount in any individual case may be determined by one of ordinary skill in the art using routine experimentation.

The term, "parenteral" means not through the alimentary canal but by some other route such as subcutaneous, intramuscular, intraspinal, or intravenous.

20 As used herein, the term "purified" and like terms relate to the isolation of a molecule or compound in a form that is substantially free of contaminants normally associated with the molecule or compound in a native or natural environment. As used herein, the term "purified" does not require absolute purity; rather, it is intended as a relative definition.

25 The term "isolated" requires that the referenced material be removed from its original environment (e.g., the natural environment if it is naturally occurring). For example, a naturally-occurring polypeptide present in a living animal is not isolated, but the same polypeptide, separated from some or all of the coexisting materials in the natural system, is isolated.

30 "Obese" is defined as having a body mass index (BMI) ≥ 30 .
"Overweight" is defined as having a body mass index from about 25 to about 29.9.
"Body mass index" is calculated as an individual's weight (in kilograms) divided the individual's height (in meters squared).

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“Interferon” is a term generally describing a group of cytokines exhibiting pleiotropic activity categorized as antiviral, antiproliferative and immunomodulatory. An international committee was assembled to devise a system for orderly nomenclature of interferons and defined “interferon” as follows: “To qualify as
5 an interferon a factor must be a protein which exerts virus non-specific, antiviral activity at least in homologous cells through cellular metabolic process involving synthesis of both RNA and protein” (Journal of Interferon Research, 1980, 1, p. vi). “Interferon” as used herein in describing in the present invention shall be deemed to have that definition and shall contemplate proteins and glycoproteins, including for example, the subtypes:
10 interferon-alpha, interferon-beta, interferon-delta, interferon-epsilon, interferon-gamma, interferon-kappa, interferon-lambda, interferon-omega and interferon-tau, regardless of their source or method of preparation or isolation.

Originally identified for their ability to induce cellular resistance to viral infection, interferons are currently known to be potent mediators in the host defense
15 mechanism and homeostasis, modulating both the innate and adaptive immune responses. The following is for illustrative purposes and is not meant to be limiting in any way. Interferons can be small, inducible, about 20 to about 25 KD, usually glycosylated proteins that are produced by vertebrate cells in response to various biological stimuli. Interferons mediate their biological activities by binding to receptors
20 present on the surface of target cells. Specific ligand-receptor interactions trigger intracellular signaling cascades downstream, resulting in the synthesis of proteins that mediate biological activity.

Interferons are classified into two groups: type I or type II, based on their structure, physicochemical properties and biological activities. Type I and type II
25 interferons exert their biological effects through different cellular receptors. In mammals, eight families of type I interferon have been described. These families include interferon-alpha, interferon-beta, interferon-delta, interferon-epsilon, interferon-kappa, interferon-lambda, interferon-omega and interferon-tau. Interferon-tau, also known as interferon trophoblast, is not inducible by viruses, and is found only in
30 ruminant ungulates where it is produced in the embryonic trophoectoderm at a specific time early during pregnancy. Its major function is to facilitate conditions for the completion of pregnancy. Interferon-delta, a polypeptide of about 149 amino acids, has been described only in pigs. This interferon is physiologically expressed by trophoblast

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during the period of implantation in uterus. Interferon-gamma is the sole representative of type II interferon in mammals. Interferons have generally been named in terms of the species of animal cells producing the substance, the type of cell involved (e.g., leukocyte/lymphoblastoid or fibroblast) and, occasionally, the type of inducing material responsible for the interferon production. The designations alpha (α), beta (β) and gamma (γ) have been used to correspond to the previous designations of leukocyte, fibroblast, and immune interferons, respectively. Alpha and beta interferons are usually acid-stable and correspond to what have been called Type I interferons; gamma interferons are usually acid-labile and correspond to what have been called Type II interferons. More recently, interferon tau has been described as an interferon-alpha related Type I interferon produced by bovine and ovine trophoblasts.

Interferon of human and murine origin is quantified in the art in terms of International Units (IU). Note that interferons of other than human or murine origin can also be used in accordance with the methods disclosed herein. In that certain practices may not extend the use of "International Units" to quantify non-human and non-murine interferons, it shall be understood that administration of amounts of non-human/non-murine interferons having the same efficacy as the quantities (IU) of human interferon specified in this description for treatment of overweight and obese patients is within the scope of the present disclosure.

EMBODIMENTS

In accordance with one embodiment a method of reducing weight gain or inducing weight loss is provided. The method comprises administering a composition comprising an interferon to a patient in need of weight reduction or weight maintenance. In one embodiment the patient is a human, however the methods disclosed herein are not limited to humans but also may include the treatment of animals including for example domesticated animals such as cats and dogs. In one embodiment a method for inducing weight loss in a human patient comprises orally administering low-dose interferon-alpha. In one embodiment the method comprises administering to a patient, such as a human, about 1 to about 1500 IU of interferon per day. In one embodiment the interferon is administered at a dosage of about 0.01 to about 5 IU/lb (from about 0.02 to about 11 IU/kg), or from about 0.25 to about 1.5 IU/lb (from about 0.55 to about 3.3 IU/kg) of patient body weight. The interferon may be administered buccally, sublingually, or by oral ingestion. In one embodiment the administered interferon is a

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type I interferon and in a further embodiment the type I interferon is selected from the group of interferon-alpha, interferon-beta, interferon-delta, interferon-epsilon, interferon-kappa, interferon-lambda, interferon-omega and interferon-tau. In one embodiment the administered composition comprises a type I interferon selected from
5 the group consisting of interferon-alpha, interferon-beta and interferon-tau, and in one embodiment the interferon is interferon-alpha.

The composition comprising interferon may be administered in unit dose forms once, twice or three times a day. In accordance with one embodiment the interferon is administered as a daily single unit dose form, comprising about 50 to about
10 2000 IU of interferon. In another embodiment the interferon is administered as a daily single unit dose form, comprising about 400 to about 1000 IU of interferon. The treatment can be continued indefinitely or until the desired weight loss is obtained. In one embodiment the interferon is administered for at least one to two weeks and in an alternative embodiment the treatment is continued for 1 to 6 months.

15 In accordance with one embodiment, a method for treating overweight and obese patients to produce a therapeutic response is provided. The method comprises the step of administering to a patient from about 1 to about 1500 IU of interferon per day. In one embodiment a pharmaceutical composition comprising interferon is administered orally. Such methods are expected to be useful in reducing body weight,
20 preventing weight gain, or treating obesity of various causes, including drug-induced obesity. A further benefit of such treatment is the expected reduction in complications associated with obesity, including vascular disease (coronary artery disease, stroke, peripheral vascular disease, ischemia reperfusion, etc.), hypertension, onset of diabetes type II, hyperlipidemia and musculoskeletal diseases.

25 The interferon compositions may be administered alone or in combination with other anti-obesity agents. When used in combination with known anti-obesity agents, the interferon can be administered either simultaneously or concurrently with the administration of the known anti-obesity agent. In accordance with one embodiment a single composition comprising an isolated interferon, a known
30 anti-obesity agent and a pharmaceutically acceptable carrier is provided. In another embodiment two separate pharmaceutical compositions are administered to a patient, the first comprising an isolated interferon and the second comprising a known anti-obesity agent. In one embodiment the separate interferon and anti-obesity compositions are

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administered within 0.5, 1, 2, 3, 4, 5, 6, 8, 12, or 24 hours of one another. In one embodiment the separate interferon and anti-obesity compositions are administered within 15 to 60 minutes of one another. In one embodiment the interferon composition comprises two or more interferon isotypes.

5 Anti-obesity agents known in the art or under investigation include appetite suppressants, including phenethylamine type stimulants, phentermine (optionally with fenfluramine or dexfenfluramine), diethylpropion (Tenuate®), phendimetrazine (Prelu-2®, Bontril®), benzphetamine (Didrex®), sibutramine (Meridia®, Reductil®); rimonabant (Acomplia®), other cannabinoid receptor
10 antagonists; fluoxetine hydrochloride (Prozac); Qnexa (topiramate and phentermine), Excalia (bupropion and zonisamide) or Contrave (bupropion and naltrexone); or lipase inhibitors, similar to xenical (Orlistat) or Cetilistat (also known as ATL-962), or GT 389-255. Another compound that induces weight loss is oxyntomodulin, a naturally occurring 37 amino acid peptide hormone found in the small intestine (see Diabetes
15 2005; 54:2390-2395).

 In accordance with one embodiment, a method for treating overweight and obese patients to produce a therapeutic response is provided. The method comprises the step of administering to a patient a composition comprising from about 1 to about 1500 IU of interferon per day. The interferon may be administered using standard
20 pharmaceutically acceptable carriers and routes of administration known to those skilled in the art, including parenterally, such as intravenously, intraperitoneally, subcutaneously or intramuscularly, intrathecally, transdermally, rectally, orally, nasally or by inhalation. In one embodiment the composition is administered buccally, sublingually, or by oral ingestion. "Therapeutic response" as used herein refers to a
25 patient response characterized by a reduction in weight or improvement of other clinical symptoms associated with obesity and being overweight. Buccal and sublingual administration comprises contacting the oral and pharyngeal mucosa of the patient with the dose of interferon. The interferon may be contained in either a pharmaceutically acceptable liquid dosage form or a saliva soluble dosage form, which is held in the
30 patient's mouth to form a saliva solution of the dose of interferon in contact with the oral and pharyngeal mucosa.

 Interferons useful in accordance with the presently disclosed composition and methods include both Type I and Type II interferons of either heterologous or

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homologous origin. In one embodiment the interferon is a Type I interferon selected from interferon-alpha, interferon-beta and interferon-tau. The interferons can be of human or non-human origin.

Methods for preparation and purification of such compositions are well known in the art. In one embodiment, the clinical agent useful for the treatment of overweight and obesity is human leucocyte interferon (human interferon-alpha) produced by art recognized procedures. Interferon-alpha can be mass produced by collection and purification of quantities of human buffy-coat leucocytes, induction of interferon production with a virus, and isolation from culture media; or interferon-alpha can be produced, for example, in accordance with the procedures described in U.S. Patent 4,276,282, the disclosure which is incorporated herein by reference. It should be appreciated that interferon-alpha is commercially available. Also acceptable for use in accordance with the methods disclosed herein are human interferon-alpha compositions produced by recombinant DNA technology.

In one embodiment, a method for treating overweight or obese patients comprises the step of orally administering to a patient about 50 to about 2000 IU of interferon-alpha per day. In one variation, interferon-alpha is administered from about 450 to about 1000 IU per day. The interferon-alpha can be of heterologous (non-human) or homologous (human) origin and can be formulated in a liquid or solid dosage form. In one embodiment the interferon composition is administered by oral ingestion or by buccal or sublingual administration.

In accordance with one embodiment, the interferon intended for buccal or sublingual administration is administered to the patient in a dosage form adapted to promote contact of the interferon with the oral and pharyngeal mucosa. Thus, the dosage form can be in the form of an interferon containing solution or syrup to be administered and used by the patient in a manner that promotes contact of the interferon component with oral mucosal tissues, for example, by holding the interferon solution in the mouth for up to about one minute. In one example, the interferon is formulated into a solid dosage form comprising a low dose of interferon, for example, interferon-alpha, and a saliva soluble carrier. Excipients, such as buffers or tableting aids, are optional. The solid dosage form is formulated to dissolve when held in an individual's mouth to form a saliva solution of the dose of interferon and promote contact of the interferon with the oral and pharyngeal mucosa. In one embodiment, the solid dosage form is in

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the form of a lozenge adapted to be dissolved upon contact with saliva in the mouth, with or without the assistance of chewing, to form a saliva solution of the interferon. In one example a lozenge is formulated to provide from about 0.01 to about 5 IU/lb (from about 0.02 to about 11 IU/kg), or from about 0.25 to about 1.5 IU/lb (from about 0.55 to about 3.3 IU/kg) of patient body weight of interferon-alpha in solution upon dissolution of the dosage form in saliva in the mouth. Lozenges for use in accordance with the methods disclosed herein can be prepared, for example, by art-recognized techniques for forming compressed tablets where the interferon is dispersed on a compressible solid carrier, optionally combined with any appropriate tableting aids such as a lubricant (e.g., sodium-stearate) and compressed into tablets. The solid carrier component for such tableting formulations can be a saliva soluble solid, such as cold-water-soluble starch or a monosaccharide or disaccharide, so that the lozenge will readily dissolve in the mouth to release the contained interferon in saliva solution for contact with and absorption by the oral/pharyngeal mucosa when the lozenge is held in the mouth.

In accordance with another embodiment, an interferon pharmaceutical composition is formulated to provide a therapeutic response in the treatment of overweight or obese patients. In one embodiment, the pharmaceutical composition comprises from about 1 to about 1500 IU of interferon-alpha in combination with a saliva soluble carrier. The pharmaceutical composition may comprise from about 5 to about 1000 IU of interferon-alpha in combination with a saliva soluble carrier. For example, in one embodiment the pharmaceutical composition comprises about 15 to about 150 IU of interferon-alpha in combination with a saliva soluble carrier.

Interferon can be administered in either a liquid (solution) or solid dosage form. For example, interferon can be administered dissolved in a buffered aqueous solution typically containing a stabilizing amount (about 1-5% by weight) of albumin or blood serum. Exemplary of a buffered solution suitable as a carrier of interferon is phosphate buffered saline prepared as follows:

A concentrated (20x) solution of phosphate buffered saline (PBS) may be prepared by dissolving the following reagents in sufficient water to make 1,000 ml of solution: sodium chloride, 160 grams; potassium chloride, 4 grams; sodium hydrogen phosphate, 23 grams; potassium dihydrogen phosphate, 4 grams; and optionally phenol red powder, 0.4 grams. The solution is sterilized by autoclaving at 15 pounds pressure

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for 15 minutes and then diluted with additional water to a single strength concentration prior to use.

Alternatively, the interferon for use in a composition administered by buccal, sublingual or oral ingestion routes can be formulated into flavored or unflavored solutions or syrups using a buffered aqueous solution of interferon as a base with added caloric or non-caloric sweeteners, flavor oils and pharmaceutically acceptable surfactant/dispersants. Solid dosage forms for oral ingestion administration can be prepared using standard tableting protocols and excipients to provide interferon-containing tablets, capsules, caplets, or gel seals.

Interferon in a solid dosage form can also be in the form of a lozenge adapted to be dissolved upon contact with saliva in the mouth with or without the assistance of chewing. Such a unitary dosage form is formulated to release from about 1 to about 1500 IU of interferon upon dissolution in the mouth for contact with the oral and pharyngeal mucosa. Thus, a unitary dosage form of interferon can be prepared by art recognized techniques for forming compressed tablets such as chewable vitamins. Similarly, interferon can be incorporated into starch-based gel formulations to form a lozenge which will dissolve and release interferon for contact with the oral mucosa when held in the mouth. Solid unitary dosage forms of interferon can be prepared utilizing art recognized dosage formulation techniques. The pH of such formulations can range from about 4 to about 8.5. In processing such unitary dosage forms, one should avoid heating a formulation after addition of interferon above about 50 °C.

The daily doses of interferon-alpha can be administered as single doses, or they can be divided and administered as a multiple-dose daily regimen. Further, a staggered regimen, for example, one to three days of buccal/sublingual interferon treatments per week, can be used as an alternative to daily treatment. For the purpose of defining this invention such intermittent or staggered regimens are considered to be equivalents of every day treatment and are within the scope of this invention.

Antiviral activity of low dose IFN- α

Low-dose oral interferon-alpha is effective against human diseases caused by DNA virus classes such as herpes virus, papilloma virus, or poxvirus (molluscum contagiosum). Another DNA virus, adenovirus, has been implicated as a contributing factor to obesity in a subset of obese human and animals. In humans,

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adenovirus infections are common causes of acute respiratory tract infections, enteritis, or conjunctivitis. The presence of antibodies to adenoviruses is common in the general population. Adenoviral DNA is detected in asymptomatic adult human lymphocytes and the number of positive cells increases with age. There are 6 subgroups (A-F) among 50 human adenoviruses. Each subgroup has a number of specific serotypes. Ad-36 belongs to subgroup D, serotype 36. Ad-36 was first isolated from a fecal sample obtained from a diabetic girl with enteritis. Ad-36 is serologically distinct from 48 types of human adenovirus but has a weak cross-reaction with Ad-29 (Pasarica et al., 2006, *Obesity*, 14, 11, pp. 1905-13).

Effects of human adenoviruses on adiposity and serum lipids

Human adenovirus-36 (Ad-36) increases adiposity in chickens, mice, and nonhuman primates and is associated with human obesity. Ad-36 increases adipocyte differentiation and triglyceride accumulation in 3T3-L1 preadipocyte cells *in vitro*, but, paradoxically, Ad-36 reduces serum cholesterol and triglycerides in animal models.

In one *in vivo* study, chickens were inoculated with human Ad-2, Ad-31, Ad-37, or media at age 3 weeks. Food intake and bodyweight were recorded for 3.5 weeks, then chickens were killed and visceral fat, body composition, serum lipids, and viral antibody status were determined. Visceral fat and total body fat were significantly elevated ($p < 0.001$) in the Ad-37 group compared with all other groups. Final body weights were higher in chickens inoculated with Ad-37 compared with Ad-2, but not significantly higher than in control or Ad-31 groups. Food intake did not differ among groups. Serum cholesterol was elevated in Ad-37 chickens compared with control ($p < 0.01$) but was not affected by other viruses. Triglycerides were reduced in Ad-37 chickens ($p < 0.0001$) but were not affected by other viruses.

In 3T3-L1 cells *in vitro*, Ad-31, Ad-36, and Ad-37, but not Ad-2, increased adipocyte differentiation and triglycerides accumulation. Ad-37 increased adiposity and reduced serum triglycerides in an animal model. However, the response of serum cholesterol to Ad-37 is opposite that of Ad-36 (Whigham et al., 2006, *Am J Regul Integr Comp Physiol*, 290, 1, pp. R190-94).

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Further effects of human adenovirus Ad-36 infection

Experimental infection of rats with Ad-36 improves insulin sensitivity and promotes adipogenesis. Even in the absence of adipogenic inducers, infection of 3T3-L1 preadipocytes and human adipose-derived stem cells (hASC) by Ad-36, but not Ad-2 (another human adenovirus), modulated regulatory points that panned the adipogenic cascade. These ranged from the upregulation of cAMP, phosphatidylinositol 3-kinase and p38 signaling pathways, downregulation of Wnt10b expression, and increased expression of CCAAT/enhancer binding protein-beta and peroxisome proliferator-activated receptor gamma 2 (PPAR- γ 2) and consequential lipid accumulation. The E4 open reading frame (orf)-1 gene of the virus was found to be necessary and sufficient for Ad-36-induced adipogenesis. Selective knockdown of E4 orf-1 by RNAi abrogated Ad-36-induced adipogenic signaling cascade in 3T3-L1 cells and hASC. Compared to the null vector, selective expression of Ad-36 E4 orf-1 in 3T3-L1 induced adipogenesis, which was abrogated when the PDZ-binding domain of the protein was deleted. Thus, it appears that Ad-36 E4 orf-1 is an inducer of rodent and human adipocyte differentiation processes (Rogers et al., 2008, *Int J Obes*, 32, 3, pp. 397-406).

Ad-36 causes adiposity in animal models and enhances differentiation and lipid accumulation in human and 3T3-L1 preadipocytes, which may, in part, explain the adipogenic effect of Ad-36. Preadipocytes (3T3-L1) were used to determine the effect of infection by human adenoviruses Ad-36, Ad-2, Ad-9 and Ad-37 on leptin secretion and lipid accumulation. Rat primary adipocytes were used to determine the effect of Ad-36 infection on leptin secretion and glucose uptake *in vitro*. In addition, the effect of Ad-36 on the expression of leptin and selected genes of *de novo* lipogenesis pathway of visceral adipose tissue were compared *ex vivo* between Ad-36 infected and uninfected control rats.

Ad-36 suppressed the expression of leptin mRNA in 3T3-L1 cells by approximately 58% and 52% on days 3 and 5 post-infection, respectively. Leptin release, normalized to cellular lipid content, was 51% lower ($p < 0.002$) in the Ad-36 infected 3T3-L1 cells. Lipid accumulation was significantly greater and leptin secretion was lower for the 3T3-L1 cells infected with other human adenoviruses, Ad-9, Ad-36, or Ad-37. Human adenovirus Ad-2 did not influence cellular lipid accumulation or the leptin release.

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In rat primary adipocytes, Ad-36 reduced leptin release by about 40% in the presence of 0.48 nM ($p < 0.01$) or 1.6 nM insulin ($p < 0.05$). Ad-36 infection increased glucose uptake by 93% ($p < 0.001$) or 18% ($p < 0.05$) in the presence of 0 nM or 0.48 nM insulin, respectively. The adipose tissue of Ad-36 infected rats showed 2- to 5-fold lower leptin mRNA expression. The expression of Acetyl Co-A carboxylase-1 and fatty acid synthase, key genes of *de novo* lipogenesis, were also measured. The adipose tissue of Ad-36 infected rats showed 1.6- to 21-fold greater expression of acetyl Co-A carboxylase-1 mRNA, and 1.2- to 6.3- fold greater expression of fatty acid synthase mRNA compared to uninfected controls matched for weight and adiposity.

The *in vitro* and *ex vivo* studies show that Ad-36 modulates adipocyte differentiation, leptin production, and glucose metabolism (Vangipuram et al., 2007, *Int J Obes*, 31, 1, pp. 87-96).

Adenovirus association with human obesity

The prevalence of Ad-36 antibodies in obese and non-obese humans was determined to evaluate the association of Ad-36 antibodies with body mass index (BMI) and serum lipids. Volunteers from obesity treatment programs, communities, and a research study were evaluated. Obese and non-obese volunteers at the University of Wisconsin (Madison, WI), and the Bowen Center (Naples, FL); obese and thin volunteer research subjects; and 89 twin pairs at Columbia University (New York, NY) were evaluated.

In one study of 502 subjects, serum neutralization assays for antibodies to Ad-2, Ad-31, Ad-36, and Ad-37 were performed and serum cholesterol and triglycerides were also measured. In a second study, BMI and percent body fat in 28 twin pairs discordant for Ad-36 antibodies were evaluated. A significant ($p < 0.001$) association of obesity and positive Ad-36 antibody status was noted, which was independent of age, sex, and collection site. Ad-36 antibodies were noted in 30% of obese and 11% of non-obese subjects. Lower serum cholesterol and triglycerides ($p < 0.003$) were found in Ad-36 antibody-positive compared to Ad-36 antibody-negative subjects. Antibody-positive twins had higher BMIs (24.5 ± 5.2 vs. 23.1 ± 4.5 kg/m², $p < 0.03$) and higher percent body fat ($29.6 \pm 9.5\%$ vs. $27.5 \pm 9.9\%$, $p < 0.04$) than antibody-negative twins. In this study, Ad-36 was associated with increased body weight and lower serum lipids in humans (Atkinson et al., 2005, *Int J Obes*, 29, 3, pp. 281-86).

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The adiposity promoting effect of a human adenovirus (Ad-36) was investigated in two different animal models. The findings were replicated in experiments using a chicken model (three times) and a mammalian model (once). In four separate experiments, chickens and mice were inoculated with human adenovirus Ad-36. Weight-matched groups inoculated with tissue culture media were used as non-infected controls in each experiment. Ad-36 inoculated and non-infected control groups were housed in separate rooms under at least Biosafety Level 2 containment. The first experiment included an additional weight-matched group of chickens that was inoculated with CELO (chick embryo lethal orphan virus), an avian adenovirus. Food intake and body weight were measured weekly. At the time of sacrifice, blood was drawn and visceral fat was separated and weighed. Total body fat was determined by chemical extraction of carcass fat. Animals inoculated with Ad-36 developed a syndrome of increased adipose tissue, but low levels of serum cholesterol and triglycerides. This syndrome was not seen in chickens inoculated with CELO virus. Sections of the brain and hypothalamus of Ad-36 inoculated animals did not show any overt histopathological changes. Ad-36 DNA could be detected in adipose tissue, but not skeletal muscles, of randomly selected animals for as long as 16 weeks after Ad-36 inoculation. Data from these animal models further supports the role of viral disease in the etiology of human obesity (Dhurandhar et al., 2000, *Int J Obes Relat Metab Disord*, 24, 8, pp. 989-96).

Recent evidence on animal and human adenoviruses shows that these adenoviruses may infect adipocytes to alter enzymes and transcription factors, resulting in accumulation of triglycerides and differentiation of preadipocytes into mature adipocytes. The E4 orf1 gene of Ad-36 has been shown to be responsible for its adipogenic effect. It appears that a portion of the worldwide epidemic of obesity since 1980 could be due to infections with human adenoviruses (Atkinson, 2008, *Int J Pediatr Obes*, 3, Suppl 1, pp. 37-43).

Two viruses have been identified, SMAM-1, an avian adenovirus, and Ad-36, a human adenovirus, that produce a syndrome of visceral obesity in chickens and mice but decreased serum cholesterol and triglycerides. Nonhuman primates were used to investigate the potential of Ad-36 to promote adiposity. In one study, spontaneously occurring Ad-36 antibodies in 15 male rhesus monkeys were found. The monkeys were observed for 18 months after appearance of the antibodies was detected, and a

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significant longitudinal association of positive antibody status with weight gain and plasma cholesterol lowering was found. In a second study, which was a randomized controlled experiment, three male marmosets that were inoculated with Ad-36 had a threefold body weight gain ($41.4 \pm 11.2\text{g}$ vs. $10.8 \pm 13.4\text{g}$), a greater total fat gain ($36.3 \pm 6.1\text{g}$ vs. $23.0 \pm 3.09\text{g}$) and lower serum cholesterol at 28 weeks post inoculation relative to baseline ($p < 0.05$) than three uninfected controls. These studies illustrate that the adiposity-promoting effect of Ad-36 occurs in two nonhuman primate species and demonstrate the usefulness of nonhuman primates for further evaluation of Ad-36-induced adiposity (Dhurandhar et al., 2002, *J Nutr*, 132, 10, pp. 3155-60).

10 The metabolic and molecular mechanisms responsible for Ad-36-induced adipogenesis are unknown. However, as a potential adipogenic mechanism, Ad-36 was examined to determine if it enhanced differentiation of preadipocytes. Immunofluorescence studies showed adenoviral attachment to 3T3-L1 cells, and reverse transcriptase-polymerase chain reaction (RT-PCR) showed expression of the Ad-36 E1A gene in the infected cells. Ad-36, but not Ad-2, increased the number of differentiated adipocytes, glycerol 3-phosphate dehydrogenase (GPDH) enzyme levels, and total cellular lipid content. Also, Ad-36, but not Ad-2, increased GPDH levels in human preadipocytes. Taken together, these experiments show that Ad-36 enhanced differentiation of preadipocytes, which may be a contributory mechanism to its adipogenic effect *in vivo*. The lack of effect of Ad-2 on differentiation demonstrated that the observed findings were not a common characteristic of all adenoviruses. Future understanding of the molecular interactions of cellular and viral genes responsible for enhanced differentiation may reveal signaling pathways and controls of preadipocyte differentiation (Vangipuram et al., 2004, *Int J Obes*, 31, 1, pp. 87-96).

25 The serum of 52 humans with obesity in Bombay, India was screened for antibodies against SMAM-1 virus using the agar gel precipitation test (AGPT) method. Bodyweights and serum cholesterol and triglyceride levels were compared in SMAM-1-positive (P-AGPT) and SMAM-1-negative (N-AGPT) groups. Ten subjects were positive for antibodies to SMAM-1, and 42 subjects tested negative for SMAM-1 antibodies. The P-AGPT group had a significantly higher bodyweight ($p < 0.02$) and body mass index ($p < 0.001$) ($95.1 \pm 2.1\text{ kg}$ and $35.3 \pm 1.5\text{ kg/m}^2$, respectively) compared with the N-AGPT group ($80.1 \pm 0.6\text{ kg}$ and $30.7 \pm 0.6\text{ kg/m}^2$, respectively). Also, the P-AGPT group had significantly lower serum cholesterol ($p < 0.02$) and

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triglyceride ($p < 0.001$) values (4.65 mmol/L and 1.45 mmol/L, respectively) compared with the N-AGPT group (5.51 mmol/L and 2.44 mmol/L, respectively). Two subjects positive for SMAM-1 antibodies had antibodies against each others' serum, suggesting the presence of antigens in one or both. When these two serum samples were inoculated into chicken embryos, macroscopic lesions consistent with SMAM-1 infection developed. The inoculation of serum from N-AGPT subjects did not produce such lesions. The presence of increased obesity, antibodies to SMAM-1, reduced levels of blood lipids, and viremia that produced a typical infection in chicken embryos suggested that SMAM-1, or a serologically similar human virus, may be involved in the cause of obesity in some humans (Dhurandhar et al., 1997, *Obes Res*, 5, 5, pp. 464-69).

Ad-36 increases adiposity and reduces serum lipids in chicken, mouse, and non-human primate models, and it is linked to obesity in sero-epidemiological studies in humans. Involvement of the central nervous system (CNS) or adipose tissue in the mechanism of Ad-36-induced adiposity is unknown. The effects of Ad-36 on adiposity and on the neuroendocrine system were investigated in a rat model. Five-week-old male Wistar rats were inoculated intraperitoneally with Ad-36 ($n=25$) or medium ($n=25$). Despite similar food intakes, infected rats attained significantly greater body weight and fat pad weight by 30 weeks post-inoculation. Epididymal-inguinal, retroperitoneal, and visceral fat pad weights of the infected group were greater by 60%, 46%, and 86%, respectively ($p < 0.00001$). The fasting serum insulin level and homeostasis model assessment index indicated greater insulin sensitivity in the infected group. Visceral adipose tissue expression of GPDH, peroxisome proliferator-activated receptor gamma (PPAR- γ), and CCAAT/enhancer-binding protein alpha and beta was markedly increased in the infected animals compared with controls. Ad-36 also decreased norepinephrine levels significantly in the paraventricular nucleus in infected vs. control rats (mean $\pm$ standard error, 8.9 ± 1.1 vs. 12.8 ± 1.2 pg/ μ g protein; $p < 0.05$). Ad-36 decreased serum corticosterone in infected vs. control rats (mean $\pm$ standard error, 97 ± 41.0 vs. 221 ± 111 ng/mL; $p < 0.005$). The results suggest that the pro-adipogenic effect of Ad-36 may involve peripheral as well as central effects. The male Wistar rat may be a good model for the elucidation of metabolic and molecular mechanisms of Ad-36-induced adiposity (Pasarica et al., 2006, *Obesity*, 14, 11, pp. 1905-13).

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SMAM-1, an avian adenovirus from India, acts directly on adipocytes and is an animal virus that is associated with human obesity. The three human adenoviruses that are associated with obesity, Ad-36, Ad-37, and Ad-5, also affect adipocytes directly. These viruses stimulate enzymes and transcription factors that
5 cause accumulation of triglycerides and differentiation of preadipocytes into mature adipocytes. Ad-5 and Ad-37 have been shown to cause obesity in animals. Ad-36 has been studied further and has been linked with human obesity. Ad-36, which causes obesity in chickens, mice, rats, and monkeys, was present in 30% of obese humans and 11% of non-obese humans. In a study of twins discordant for infection with Ad-36, the
10 infected twins were heavier and fatter than their control twins. The evidence demonstrating that viruses can produce human obesity supports the concept that at least some of the worldwide epidemic of obesity in the past 25 years is due to viral infections (Atkinson, 2007, *Mayo Clin Proc*, 82, 10, pp. 1192-98).

15 Observations of weight gain in animals given low-dose oral interferon

In cattle and swine, oral interferon administration was found to cause weight gain. Feeder calves (137) in Nebraska were given oral interferon or placebo once daily for 3 consecutive days upon arrival at a feedlot. Calves given natural human interferon-alpha (1 IU/lb of body weight) gained an average of 18.3 lbs per calf at 14
20 days versus only 0.1 lb per calf given placebo (Bohlender, 1984, Study Number: 84-151-A).

Fifty six feeder calves were given different doses of recombinant or natural human interferon-alpha or placebo once daily for 4 consecutive days. The oral treatments began 2 days before virulent infectious bovine rhinotracheitis virus (IBR) was
25 inoculated intranasally. Some doses of interferon resulted in significantly ($p < 0.05$) greater weight gain, shorter duration of fever and fewer days of antibiotic therapy (Cummins et al., 1993, *Arch Immunol Ther Exp*, 41, 3-4, pp. 193-97).

Recombinant human interferon-alpha or placebo was given orally to 264 veal calves in Indiana. Interferon or placebo was placed in the milk replacer once daily
30 for 5 consecutive days. Calves were observed for respiratory tract infections, nasal discharge, ear infections, diarrhea and fever through their 11th week in the veal barn. Calves given interferon had a significantly ($p < 0.05$) shorter duration of diarrhea, fewer ear infections (otitis media), and lower incidence of nasal secretions. The incidence of

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mild or severe diarrhea was reduced significantly ($p < 0.0001$ and $p < 0.004$, respectively). Calves given interferon gained an average of 13.1 pounds more per calf than calves given placebo (Cummins et al., 1993, *Arch Immunol Ther Exp*, 41, 3-4, pp. 199-203).

5 In Texas, 112 feeder calves were given a single oral dose of human interferon-alpha or placebo upon arrival at the feed yard. Calves given 48 IU/calf had significantly ($p < 0.05$) improved average daily weight gain and had better feed efficiency 14 and 28 days after treatment (Chirase and Greene, 2000, *Proc West Sect Am Soc Animal Sci*, 51, pp. 411-14).

10 The effect of natural human interferon-alpha on rotavirus diarrhea was studied in 99 calves in Japan. The oral treatment was given once daily at 0.5 IU/kg body weight for 5 consecutive days. Calves given interferon had significantly ($p < 0.05$) greater weight gain, less virus excretion, and fewer days of diarrhea.

 The effect of orally administered natural human interferon-alpha was
15 studied on feeder calves in Tennessee before shipment to Texas. Three daily oral doses of interferon-alpha resulted in a significant ($p < 0.05$) weight gain in calves that did not have a fever at the time of interferon treatment (Cummins et al., 1999, *J Interferon Cytokine Res*, 19, 8, pp. 907-10).

 The oral use of human interferon-alpha upregulated hundreds of
20 interferon stimulated genes (ISG) in the peripheral blood of calves in Japan. An oral dose of 1.0 IU/kg body weight was given once daily for 5 days. Blood was drawn for testing before interferon treatment and 4 hours after the final oral dose of interferon. Hundreds of ISG had at least a 4-fold increase in expression as measured by cDNA microarrays (Namangala et al., 2006, *J Interferon Cytokine Res*, 26, pp. 675-81).

25

Interferon facilitated weight gain in pigs

 Weanling piglets (15 per treatment group) with an average starting weight of about 6.5 kg were given placebo or human interferon (at approximately 0.014, 0.022, 0.135, or 0.319 IU/kg body weight per day) in their feed for 21 days. The
30 average daily weight gain in controls was 211 grams. The average daily weight gain was greater in all interferon treatment groups, ranging from 222 to 376.5 grams per day (Table 1).

Table 1: Mean Weight Gain in Weanling Piglets

	Group 1	Group 2	Group 3	Group 4	Control
Dosage (mg/kg feed)	0.4	0.8	4	8	0
First bodyweight (kg)	6.72	6.57	6.46	6.49	6.62
Last bodyweight (kg)	11.43	11.01	12.05	13.42	10.85
Daily feed intake (g)	419.50	318.75	415.50	530.75	346.50
Daily weight gain (g)	235.5	222	279.5	376.5	211.5
Feed conversion ratio	1.78	1.44	1.49	1.53	1.64
Diarrhea percentage %	1.2	1.8	2	0.5	1.9

Table 1 shows weight gain in piglets administered placebo or human interferon in their feed for 21 days at 0.014, 0.022, 0.135, or 0.319 IU of interferon/kg body weight. The average daily weight gain was higher in all interferon treatment groups, ranging from 222 grams to 376.5 grams, compared to an average weight gain of 211 grams in controls.

Interferon induced weight loss in human clinical studies

Low-dose orally administered interferon-alpha therapy 1-3 times per day (total daily dose of 50, 150, 450, 1000 or 2000 IU) for 3-6 months resulted in greater weight loss in female subjects than did placebo (Tables 2-5). A statistically significant percentage of participants were found to have greater than 5% weight loss at interferon-alpha doses of 450 and 1000 IU per day (Table 2). Of the heaviest 50% of females examined, a statistically significant percentage of participants were found to have greater than 5% weight loss at interferon-alpha doses of 450 and 1000 IU per day (Table 3). Of the heaviest 33% of females examined, a statistically significant percentage of participants were found to have greater than 5% weight loss at an interferon-alpha dose of 1000 IU per day (Table 4). Of the heaviest 25% of females examined, a statistically significant percentage of participants were found to have greater than 5% weight loss at an interferon-alpha dose of 1000 IU per day (Table 5). This effect of weight loss in humans is unlike the effects observed in cattle and swine, in which interferon was found to enhance weight gain. The females in this clinical study were not tested for antibodies to Ad-36, but it has been reported that 30% of obese people have antibodies to Ad-36

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compared to 11% of people with a normal weight (Atkinson, 2008, Int J Pediatr Obes 3 Suppl 1, pp 37-43).

Table 2: Interferon Induced Weight Loss in Females from 3 Controlled Studies

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Dose	Total n	>5% loss	5% loss%	<5% loss	P-value
0	224	10	4.5%	214	--
50	39	0	0%	39	ns
150	39	2	5.1%	37	ns
450	248	24	9.7%	224	0.029
1000	16	6	37.5%	10	0.0002
2000	16	1	6.3%	15	n

Table 2 demonstrates the percentage of female clinical trial participants losing at least 5% of total bodyweight after administration of interferon-alpha (0-2000 IU per day) over 3-6 months. As compared to controls, a statistically significant percentage of participants were found to have greater than 5% weight loss at interferon-alpha doses of 450 and 1000 IU per day

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Table 3: Interferon Induced Weight Loss in Heaviest 50% of Females from 3 Controlled Studies

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Dose	Total n	>5% Loss	5% Loss%	<5% Loss	P-Value
0	110	7	6.4%	103	--
50	20	0	0%	20	ns
150	19	1	5.3%	18	ns
450	115	13	11.3%	102	ns
1000	8	4	50.0%	4	0.0025
2000	8	0	0%	8	ns

Table 3 shows the percentage of the heaviest 50% of female clinical trial participants losing at least 5% of total bodyweight after administration of interferon-alpha (0-2000 IU per day) over 3-6 months. As compared to controls, a statistically significant percentage of participants were found to have greater than 5% weight loss at interferon-alpha doses of 450 and 1000 IU per day.

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Table 4: Interferon Induced Weight Loss in Heaviest 33% of Females from Controlled Studies

Dose	Total n	>5% Loss	5% Loss%	<5% Loss	P-Value
0	79	5	6.3%	74	--
50	17	0	0%	17	ns
150	11	0	0%	11	ns
450	72	7	9.7%	65	ns
1000	6	4	66.7%	2	0.0008
2000	6	0	0%	6	ns

5 Table 4 shows the percentage of the heaviest 33% of female clinical trial participants in three controlled studies losing at least 5% of total bodyweight after administration of interferon-alpha (0-2000 IU per day) over 3-6 months. As compared to controls, a statistically significant percentage of participants were found to have greater than 5% weight loss at an interferon-alpha dose of 1000 IU per day.

10

Table 5: Interferon Induced Weight Loss in Heaviest 25% of Females from Controlled Studies

Dose	Total n	>5% Loss	5% Loss%	<5% Loss	P-Value
0	64	5	7.8%	59	--
50	11	0	0%	11	ns
150	9	0	0%	9	ns
450	51	6	11.8%	45	ns
1000	3	2	66.7%	1	0.027
2000	5	0	0%	5	ns

15

Table 5 shows the percentage of the heaviest 25% of female clinical trial participants in three controlled studies losing at least 5% of total bodyweight after administration of interferon-alpha (0-2000 IU per day) over 3-6 months. As compared to controls, a statistically significant percentage of participants were found to have greater than 5% weight loss at an interferon-alpha dose of 1000 IU per day.

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Low dose orally administered interferon-alpha produced weight loss in females without the adverse side effects observed in patients treated with high dose injectable interferon. Common gastrointestinal disorders attributed to high dose injectable interferon (typically from about 3 to about 10 million IU) include diarrhea, anorexia, nausea, and taste alteration, which occur in up to 24-69% of subjects (Physician's Desk Reference, 2008). As shown in Table 6, the adverse effects of diarrhea, nausea, taste alteration and abdominal pain occurred no more often in oral

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interferon-treated subjects than in placebo-treated subjects. These results demonstrate that low-dose interferon-alpha, administered orally, can produce desirable weight loss that is distinguishable from secondary weight loss that may result from gastrointestinal disorders caused by high-dose injected interferons.

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Table 6: Incidence of adverse events in female patients

Gastrointestinal System Adverse Events	IFN-alpha		Placebo		P-value
	Number	Incidence	Number	Incidence	
appetite loss	2	6.1%	0	0.0%	0.58
bullous eruption in throat	1	3.0%	0	0.0%	0.77
celiac disease	1	3.0%	0	0.0%	0.77
colitis	0	0.0%	1	10.0%	0.23
diarrhea	3	9.1%	1	10.0%	0.67
duodenum ulcer	1	3.0%	0	0.0%	0.77
flatulence	1	3.0%	1	10.0%	0.42
gastrointestinal distress	1	3.0%	0	0.0%	0.77
indigestion	0	0.0%	1	10.0%	0.23
nausea	5	15.2%	0	0.0%	0.25
reflux	2	6.1%	0	0.0%	0.58
stool looseness	1	3.0%	0	0.0%	0.77
swollen gums	1	3.0%	0	0.0%	0.77
taste decreased	1	3.0%	0	0.0%	0.77
tongue discomfort	2	6.1%	0	0.0%	0.58

10 Table 6 shows the incidence of gastrointestinal adverse events of female patients administered IFN-alpha compared to placebo. No statistically significant differences were found.

15 It should be noted that all aforementioned patent and scientific journal article references are expressly incorporated by reference herein.

While the invention has been illustrated and described in detail in the foregoing description, such an illustration and description is to be considered as exemplary and not restrictive in character, it being understood that only the illustrative embodiments have been described and that all changes and modifications that come within the spirit of the invention are desired to be protected. Those of ordinary skill in the art may readily devise their own implementations that incorporate one or more of the features described herein, and thus fall within the spirit and scope of the present invention.

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WHAT IS CLAIMED IS:

1. A method of reducing weight gain or inducing weight loss in a patient, said method comprising administering to said patient an effective amount of a composition comprising an interferon.
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2. The method of claim 1 wherein said composition comprises a type I interferon.
3. The method of claim 2 wherein said composition comprises an
10 interferon-alpha.
4. The method of claim 3 wherein said composition comprises about 50 to about 2000 IU of interferon and said composition is administered daily.
- 15 5. The method of claim 3 wherein the patient is a human and the amount of interferon is from about 400 to about 1000 IU per day, administered orally.
6. The method of claim 5 wherein the interferon is administered in a saliva soluble solid dosage form.
20
7. The method of claim 5 wherein the interferon is administered buccally.
8. The method of claim 5 wherein the interferon is administered
25 sublingually.
9. The method of claim 5 wherein said composition further comprises an anti-obesity agent selected from the group consisting of phentermine, diethylpropion, phendimetrazine, benzphetamine, sibutramine, rimonabant,
30 oxyntomodulin, fluoxetine hydrochloride, Qnexa (topiramate and phentermine), Excalia (bupropion and zonisamide), Contrave (bupropion and naltrexone), xenical (Orlistat), Cetilistat, and GT 389-255.

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10. The method of claim 5 wherein the human patient is an overweight female.

11. The method of claim 5 wherein the human patient is an obese female.

12. A method of reducing weight gain or inducing weight loss in a patient, said method comprising co-administering to said patient an effective amount of a first composition comprising an interferon and a second composition comprising an anti-obesity agent selected from the group consisting of phentermine, diethylpropion, phendimetrazine, benzphetamine, sibutramine, rimonabant, oxyntomodulin, fluoxetine hydrochloride, Qnexa (topiramate and phentermine), Excalia (bupropion and zonisamide), Contrave (bupropion and naltrexone), xenical (Orlistat), Cetilistat, and GT 389-255.

13. The method of claim 12 wherein the first and second composition are administered within 12 hours of one another.

14. The method of claim 12 wherein the interferon is interferon-alpha.

15. A pharmaceutical composition comprising a purified interferon and an anti-obesity agent selected from the group consisting of phentermine, diethylpropion, phendimetrazine, benzphetamine, sibutramine, rimonabant, oxyntomodulin, fluoxetine hydrochloride, Qnexa (topiramate and phentermine), Excalia (bupropion and zonisamide), Contrave (bupropion and naltrexone), xenical (Orlistat), Cetilistat, and GT 389-255.

16. The composition of claim 15 wherein the interferon is selected from the group consisting of interferon-alpha, interferon-beta and interferon-tau.

17. The composition of claim 15 wherein the interferon is interferon-alpha.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 09/46748

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 38/21 (2009.01)

USPC - 424/85.7

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC(8) - A61K 38/21 (2009.01)

USPC - 424/85.7

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

IPC(8) - A61K 45/00 (2009.01)

USPC - 424/85.4, 85.1

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

USPTO PubWest (PGPB, USPT, USOC, EPAB, JPAB); Google

Search Terms Used:

obesity, type 1 interferon, weight loss, buccally, interferon dissolvable tablets, coadministration phentermine, female obesity

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X — Y	US 6,270,756 B1 (ERICSSON) 07 August 2001 (07.08.2001), col 1-3	1-5 — 6-14, 17
Y	US 2005/0147588 A1 (LIU, et al.) 07 July 2005 (07.07.2005), para [0069]	6-8
Y	US 2007/0129400 A1 (DUAN, et al.) 07 June 2007 (07.06.2007), para [0122]	9, 12-17
Y	US 2006/0009514 A1 (GADDE, et al.) 12 January 2006 (12.01.2006), para [0056]	10, 11
Y	WO 2005/049068 A1 (LIU, et al.) 02 June 2005 (02.06.2005), para [0001], [0039]	15-17
Y	US 2007/0190041 A1 (SASAHARA, et al.) 16 August 2007 (16.08.2007), para [0179]	13

☐ Further documents are listed in the continuation of Box C.

* Special categories of cited documents:

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

17 July 2009 (17.07.2009)

Date of mailing of the international search report

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