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Novel approaches to the treatment of cachexia

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Cachexia is a complex syndrome. The main components of this pathological state are anorexia and metabolic abnormalities, such as glucose intolerance, fat depletion and muscle protein catabolism among others. The aim of the present article is to review the recent therapeutic approaches that have been designed to fight and counteract muscle wasting in different pathological states such as cancer, AIDS and chronic heart failure.

Introduction

Perhaps the most common manifestation of severe disease, such as acquired immunodeficiency syndrome (AIDS), chronic heart failure (CHF) and cancer, is the development of cachexia. Indeed, cachexia occurs in the majority of cancer patients before death and, according to Warren [1], it is responsible for the deaths of 22% of cancer patients. Interestingly, in studies performed before the era of highly active anti-retroviral therapy, estimates of prevalence of wasting as the first AIDS-defining diagnosis ranged up to 31% [2]. Fatigue, as a result of muscle wasting, is an extremely common symptom in cardiac cachexia patients. This condition is observed among a high percentage of chronic heart failure patients [3]. Cancer cachexia is a multiorgan syndrome associated with cancer, characterized by body weight loss (at least 5%), muscle and adipose tissue wasting and inflammation, often associated with anorexia. The abnormalities associated with cachexia include alterations in carbohydrate, lipid and protein metabolism (Figure 1) [4].

Although anorexia represents a very important factor in the development of cachexia, it has to be pointed out that, in many cases, the use of total parenteral nutrition does not stop the loss of body weight (Figure 2) [5]. It seems, therefore, quite evident that metabolic disturbances present in the host (increased energy inefficiency, insulin resistance and abnormal carbohydrate metabolism, adipose tissue dissolution and hypertriglyceridemia and muscle wasting) have a definitive role in the development of cachexia [4].

Bearing in mind the fact that both anorexia and metabolic disturbances are involved, the development of different therapeutic strategies has focused on these two factors.

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Recent studies on fighting anorexia

MEGACE

Megestrol acetate (MEGACE) and medroxyprogesterone (MPA) are synthetic, orally active derivatives of the naturally occurring hormone, progesterone. In humans, these compounds have been found to improve appetite, caloric intake and nutritional status in several clinical trials [6–8]. In the case of MEGACE, the reason for the associated weight gain is mostly unknown, although it has been postulated that the effect is partially mediated by neuropeptide Y, a potent central appetite stimulant [9]. On the contrary, MPA has been shown to reduce the *in vitro* production of serotonin and cytokines (interleukin-1-β (IL-1), interleukin-6 (IL-6) and TNF-alpha) by peripheral blood mononuclear cells of cancer patients [10]. All of these humoural factors have been implicated in the cachectic–anorexic response. Oral suspension of the progestational agent may be particularly useful in patients with far advanced disease, where taking larger amount of pills may lead to the decrease of patient compliance. Recent data by Tomíska *et al.* [11] showed that an oral MEGACE suspension given to patients with far advanced cancer suffering from anorexia and weight loss resulted in an improvement of appetite and quality of life.

Grhelin

The orexigenic mediator, ghrelin – a novel endogenous ligand for the growth hormone secretagogue receptor – has recently been reported as having a key role in increasing appetite and, therefore, food intake. In addition to increasing food intake, an experimental study has shown that repeated administration of ghrelin improves cardiac structure and function and attenuates the development of cardiac cachexia in CHF. These results suggest that ghrelin has

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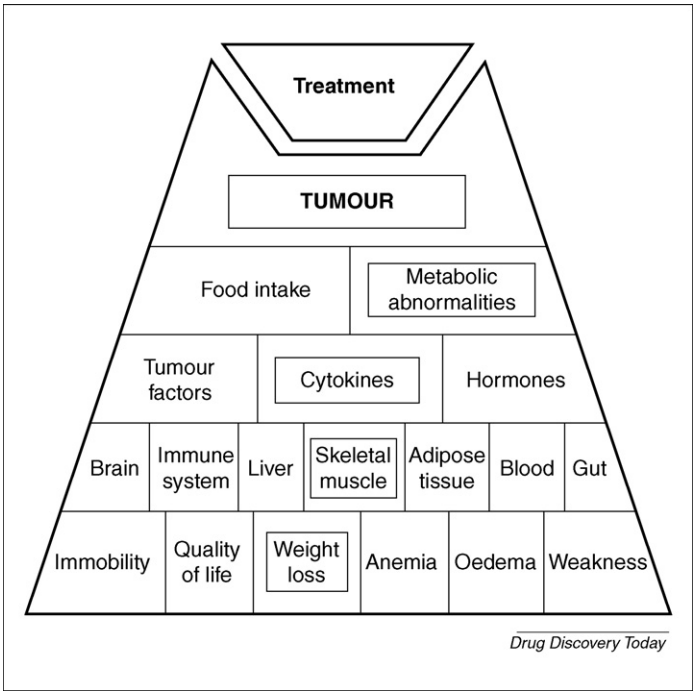

FIGURE 1

Cancer cachexia: the pyramid. Cancer cachexia is a complex pathological condition characterized by many metabolic changes involving numerous organs. These changes are triggered by alterations in the hormonal milieu, release of different tumour factors and a systemic inflammatory reaction characterized by cytokine production and release.

cardiovascular effects and regulates energy metabolism through GH-dependent and GH-independent mechanisms. Thus, administration of ghrelin may be a new therapeutic strategy for the treatment of severe CHF [12] (Table 1). A phase II randomized, placebo-controlled, double-blind study using an oral ghrelin mimetic demonstrated an improvement in lean body mass, total body mass and hand grip strength in cachectic cancer patients [13].

Cannabinoids

Cannabinoids, which are present in marijuana, have a definitive effect on weight gain and, bearing this in mind, have been used to increase food intake in cancer patients. The mechanism by which cannabinoids exert their effects has yet to be clarified. It was postulated that they may act via endorphin receptors, or by inhibiting prostaglandin synthesis [14]. Other reports suggest that the marijuana derivative may act by inhibiting cytokine production and/or secretion [15–17]. A recent clinical trial, however, has shown very little efficacy of either orally administered cannabinoid extract or delta-9-tetrahydrocannabinol in treating patients with cancer-related anorexia–cachexia syndrome [18] (Table 1).

Melanocortin antagonists

Melanocortin (MC4) receptor is involved in the anorexigenic cascade leading to a decrease in neuropeptide Y and, therefore, a decrease in food intake. The use of MC4 antagonists has been proven to be effective in preventing anorexia, loss of lean body mass and basal energy expenditure in experimental animals suffering from cachexia [19,20]. However, no data on human subjects are available and, therefore, future clinical trials may prove the efficacy of this type of antagonist in the treatment of human cachexia (Table 1).

Latest studies counteracting metabolic disturbances

Cytokines

Cytokines act on multiple target sites, such as bone marrow, myocytes, hepatocytes, adipocytes, endothelial cells and neurons,

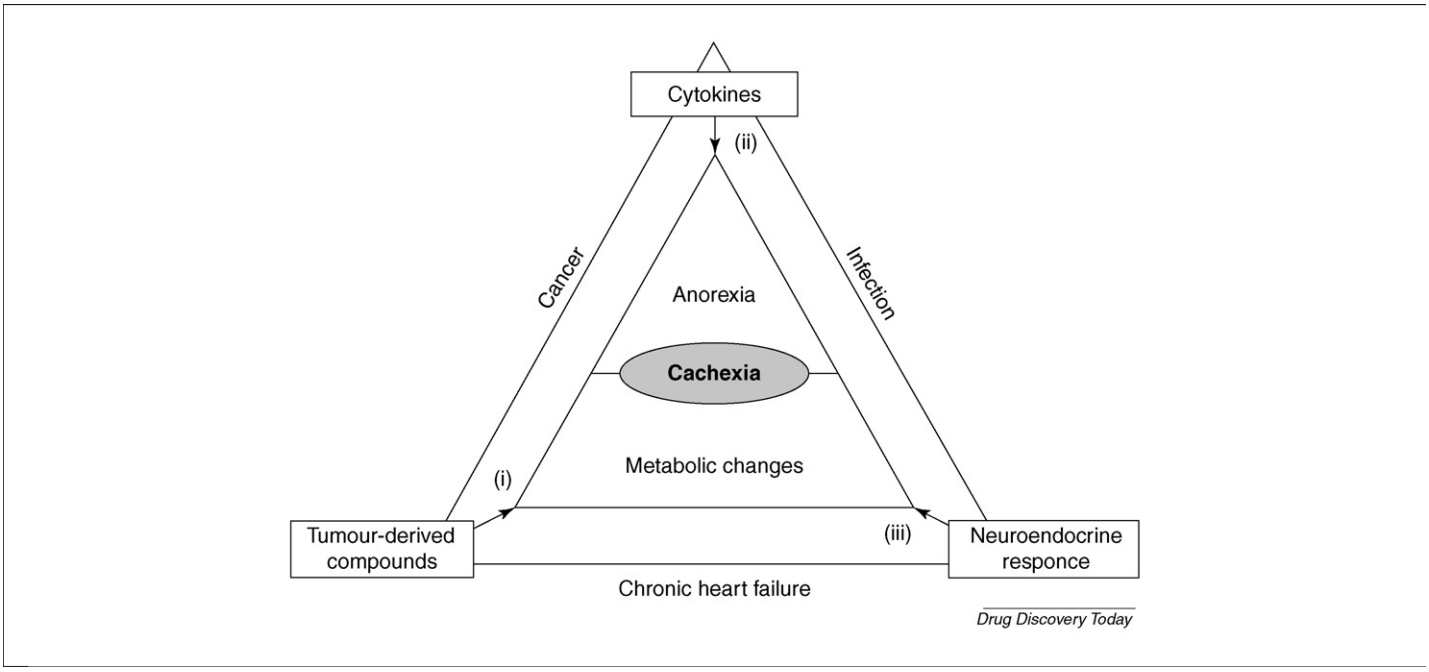

FIGURE 2

Mediators of the cachectic response. Among the compounds that trigger cachexia, we find cytokines, tumour-derived compounds and also endocrine changes. In a specific cachectic state, the balance of the three factors will determinate the degree of muscle wasting.

TABLE 1

Efficiency of the different treatments used in human wasting diseases

Drug	Cancer	Aids	Chf
Progesterone derivatives	+	+	?
Cannabinoids	++	++	?
Cyproheptadine	+	?	?
Insulin	++	++	?
Corticosteroids	+	?	?
Ghrelin	?	?	?
Pentoxifylline	−	+	?
Thalidomide	+	++	+
Anti-cytokine antibodies and soluble receptors	−/?	+	−
Anti-inflammatory cytokines	?	?	?
Growth hormone	−	+++	++
Insulin-like growth factor-I	−	+	?
Melatonin	+	?	?
Somatostatin	?	?	?
Anabolic steroids	+	+	?
β_2-Adrenergic agonists	?	?	−
***n*-3-Fatty acids**	++	?	?
Hydrazine sulfate	+	?	?
Prostaglandin inhibitors	+	?	?
ACE inhibitors	?	?	+
EPO	+	?	?
Beta-blockers	?	?	++
ATP	+	?	?
Creatine	?	?	+
Proteasome inhibitors	?	?	?

For more details, see text. Data referred to clinical trials only. +, slight beneficial effect; ++, relatively good results; +++, satisfactory treatment; −, unsuccessful trial; ?, not available. Table adapted from reference [56].

where they produce a complex cascade of biological responses, leading to the wasting associated with cachexia. The cytokines that have been implicated in this cachectic response are TNF-alpha, IL-1, IL-6 and interferon-γ (IFN-γ) (Figure 2). Interestingly, these cytokines share the same metabolic effects, and their activities are closely interrelated. In many cases, these cytokines exhibit synergic effects when administered together [21]. Therefore, therapeutic strategies have been based on either blocking their synthesis or their action [22].

Thalidomide (α-*N*-phthalimidoglutaramide) is a drug that in the past has been, unfortunately, associated with tragedy. Indeed, its use as a sedative in pregnant women caused over 10 000 cases of severe malformations in newborn children. However, a certain revival has improved the drug's profile, since it has been demonstrated to suppress TNF-alpha production in monocytes *in vitro* [23] and to normalize elevated TNF-alpha levels *in vivo* [24]. A recent randomized placebo-controlled trial in patients with cancer cachexia showed that the drug was well-tolerated and effective at attenuating loss of weight and lean body mass in patients with advanced pancreatic cancer [25].

A similar approach is the use of anti-cytokine strategies such as etanercept (fusion protein directed against p75 TNF-alpha receptor). Although the use of this strategy in CHF or cancer has led to a poor clinical outcome [26], Monk *et al*. [27] showed, in a clinical pilot study with several advanced malignancies, that patients treated with etanercept combined with an anti-tumour agent (docetaxel) had less fatigue and an improved tolerability to the anti-tumour treatment. Another phase II trial using an anti-TNF-alpha monoclonal antibody, infliximab, to improve symptoms of cachexia (lean body mass) in pancreatic cancer patients was unsuccessful.

The degree of the cachectic syndrome is dependent not only on the production of the above-mentioned cytokines, known as catabolic pro-inflammatory cytokines, but also on the so-called anti-inflammatory cytokines, such as interleukin-4, interleukin-10 and interleukin-12 (IL-4, IL-10, IL-12). Interleukin-15 (IL-15) has been reported to be an anabolic factor for skeletal muscle [28]. From this point of view, this cytokine is able to decrease protein degradation, decrease the rate of DNA fragmentation and increase UCP3 expression in skeletal muscle, these being the most important trends associated with muscle wasting during cancer cachexia [29,30]. *In vitro* experiments carried out using both isolated incubated muscle, and muscle cells in culture, corroborate the *in vivo* observations and indicate a direct action of the cytokine upon skeletal muscle [31]. Although no clinical data are available, treatment of cachectic experimental animals with IL-15 leads to an improvement of muscle mass and performance [29] (Table 1).

n-3-Polyunsaturated fatty acids

n-3-Polyunsaturated fatty acids (PUFA), present in large amounts in fish oil, have been proposed as very active in reducing either tumour growth [32,33] or the associated tissue wasting, particularly that of the adipose mass [34]. In fact, the interest in *n*-3-PUFA was originated from the observation that populations consuming a diet rich in such constituents showed the lowest incidence of certain types of cancer. An improvement in the lean body mass and quality of life was observed in a randomized double-blind trial using a protein and energy dense *N*-3-fatty acid-enriched oral supplement [35], provided that its consumption was equal to or in excess of 2.2 g EPA/day. However, recent data, arising from a large multicentre double-blind placebo-controlled trial, indicate that eicosapentaenoic acid (EPA) administration alone is not successful in the treatment of weight losing patients with advanced gastrointestinal or lung cancer [36]. Moreover, a recent meta-analysis based on five trials concluded that there were insufficient data to establish whether oral EPA was better than placebo. Comparisons of EPA combined with a protein energy supplementation versus a protein energy supplementation (without EPA) in the presence of an appetite stimulant (MEGACE) provided no evidence that EPA improves symptoms associated with the cachexia syndrome often seen in patients with advanced cancer [37]. In CHF, fish oils produce anti-inflammatory effects by decreasing TNF-alpha production and improve body weight [38] (Table 1).

β_2-Adrenergic agonists

These molecules are potentially very interesting since they have important effects on protein metabolism in skeletal muscle, favouring protein deposition. Apart from the older β2-adrenergic agonists, such as clenbuterol, the interest has been recently focused on newer drugs such as formoterol. In particular, the use of this β2-adrenergic agonist in experimental animals has proved to be very useful in reversing muscle wasting associated with cancer [39]. In addition to its relatively low toxicity, formoterol is able to reverse the muscle-wasting process. The anti-wasting effects of the drug were based on both an activation of the rate of protein synthesis and an inhibition of the rate of muscle

proteolysis. Northern blot analysis revealed that formoterol treatment resulted in a decrease in the mRNA content of ubiquitin and proteasome subunits in gastrocnemius muscles; this, together with the decreased proteasome activity observed, suggested that the main anti-proteolytic action of the drug may be based on inhibition of the ATP-ubiquitin-dependent proteolytic system [39]. Interestingly, the β2-agonist was also able to diminish the increased rate of muscle apoptosis present in tumour-bearing animals, and also formoterol was able to facilitate muscle regeneration by stimulating satellite cells proliferation. The results indicate that formoterol exerted a selective, powerful protective action on heart and skeletal muscle by antagonizing the enhanced protein degradation that characterizes cancer cachexia, and it could be revealed as a potential therapeutic tool in pathological states wherein muscle protein hypercatabolism is a crucial feature, such as cancer cachexia or other wasting diseases [39] (Table 1).

Erythropoietin

The administration of erythropoietin (EPO) to cancer patients results in a clinical benefit both in patients with subnormal or even normal haemoglobin levels [40]. Interestingly, Kanzaki *et al.* [41] have shown that the positive therapeutic effects of EPO in cancer cachexia in tumour-bearing mice are not only due to improving metabolic and exercise capacity via an increased erythrocyte count but also attenuation of cachectic manifestations by decreasing production of the cachexia-inducing cytokine, IL-6 (Table 1).

Ace inhibitors

In CHF, inhibition of the angiotensin-converting enzyme (ACE) by administration of enalapril reduces the risk of weight loss and it is linked to improved survival [42]. Preliminary results demonstrate increased subcutaneous fat (increased skin fold thickness) and greater muscle bulk (increased mid-upper arm and tight circumferences), together with a significant elevation in plasma albumin and the hematocrit [43]. In fact, ACE inhibitors, like captopril, seem to act by decreasing the production of TNF-alpha by mononuclear cells, suggesting a mechanism to account for the beneficial effects (related to body weight) observed in heart failure patients [44]. The highly lipophilic ACE inhibitor imidapril attenuated the development of weight loss in mice bearing the MAC16 tumour, suggesting that angiotensin II may play a role in the development of cachexia in this model [45] (Table 1).

β-*Blockers*

These drugs can reduce body energy expenditure and improve efficiency of substrate utilization. Interestingly, patients with CHF treated with β-blockers can increase total body fat mass and partially reverse cachexia [46] (Table 1).

Anabolic steroids

Although treatment with derivatives of gonadal steroids can have significant side effects, such as masculinization, fluid retention and hepatic toxicity, they promote protein accumulation and, from this point of view, they could be used to counteract the progressive nitrogen loss associated with cachexia. Recent data, involving a double-blind placebo-controlled trial, suggest that nandrolone decanoate is effective in the treatment of cachectic AIDS patients, increasing lean body mass, quality of life and decreasing anti-AIDS treatment toxicity [47]. A recent clinical trial using a non-steroidal selective androgen receptor modulator (SARM) carried out to increase lean body mass and improve physical performance in healthy elderly subjects was successful and, therefore, the potential activity of this class of drugs should be taken into consideration for cancer cachexia [48].

Other new promising therapeutic strategies

Myostatin, a transforming growth factor-beta (TGF-beta) superfamily member, has been well-characterized as a negative regulator of muscle growth and development. Myostatin has been implicated in several forms of muscle wasting, including the severe cachexia observed as a result of conditions such as AIDS and liver cirrhosis. McFarlane *et al.* [49] have demonstrated that myostatin induces cachexia through an NF-kappaB-independent mechanism by antagonizing hypertrophy signalling through regulation of the AKT-FoxO1 pathway. Anti-myostatin strategies are, therefore, promising and should be considered in future clinical trials involving cachectic patients.

The corticotropin realeasing factor 2 receptor (CRF2R) has many biological activities, including modulation of the stress response and has been involved in the prevention of skeletal muscle wasting resulting from a variety of physiological stimuli. From this point of view, the use of CRF2R agonists has proved successfully in partially blocking muscle wasting in several models of experimental cachexia [50,51]. However, a paucity of clinical data exists.

As previously stated, enhanced protein degradation in skeletal muscle during cachexia involves activation of the ubiquitin/proteasome system in muscle. Therefore, inhibitors of this proteolytic system such as peptide aldehyde, lactacystin and β-lactone – which effectively can block up to 90% of degradation of normal proteins and short-lived proteins in the cells – are potential drugs for the treatment of muscle wasting [52]. However, the toxicity of such compounds is fairly high, since they are not specific inhibitors of the proteolytic system in muscle tissue [53]. Bearing this in mind, a substance that can specifically block myofibrillar protein degradation in skeletal muscle is still waiting to be discovered. From this point of view, the discovery of specific muscle ubiquitin-ligases (Atrogin-1 and MuRF1) [54] is particularly interesting, since a tissue-specific inhibition of ubiquitin/proteasome proteolysis could be achieved if inhibitors of these ligases were discovered.

Combined approaches

From all the data presented, one can speculate that one single therapy may not be completely successful in the treatment of cachexia. From this point of view, treatments involving different combinations are more likely to be successful. A very interesting phase II study, involving the administration of anti-oxidants, pharmaconutritional support, progestagen and anti-cyclooxygenase-2 drugs, showed efficacy and safety in the treatment of patients with advanced cancer of different sites suffering cachexia [55] based on the results of the phase II study, a randomized phase III study started in 2005 (and is still in progress) with the aim of including more than 300 cachectic cancer patients. These data clearly reinforce the use of these multitargeted therapies in the treatment of the cachexia-anorexia syndrome in different clinical conditions such as cancer, AIDS and CHF.

Conclusions

In the opinion of the authors, nutritional strategies are not sufficient to reverse the cachectic syndrome. Indeed, patients on total parenteral nutrition are still subject to a significant waste, therefore emphasizing the role of the metabolic abnormalities in cachexia. It is perhaps for this reason that any therapeutic approach based on increasing food intake has to be combined with a pharmacological strategy to counteract metabolic changes. Moreover, timing is very important and has to be considered seriously when designing the therapeutic approach. A very important aspect to be taken into consideration when treating cancer patients is that any nutritional/metabolic/pharmacological support should be started early in the course of the disease, before severe weight loss occurs. The loss of muscle mass is a hallmark of cancer cachexia, and it is essentially caused by an increase of myofibrillar protein (especially myosin heavy-chain degradation, sometimes accompanied by a decrease in protein synthesis. The enhanced protein degradation is caused by an activation of the ubiquitin-dependent proteolytic system. Therefore, therapeutic approaches based on the neutralization of the enhanced myofibrilar protein degradation should be encouraged. Another important problem associated with the design of the ideal therapeutic approach is that no definite mediators of cachexia have been identified as yet. Since the therapy against wasting during cachexia has concentrated on either increasing food intake or normalizing the persistent metabolic alterations that take place in the patient, it is difficult to apply a therapeutic approach based on the neutralization of the potential mediators involved in muscle wasting (i.e. TNF-alpha IL-6, IFN-gamma, proteolysis-inducing factor (PIF)) because many of them are involved at the same time in promoting the metabolic alterations and the anorexia present in the cancer patients. Bearing this in mind, it is obvious that a good understanding of the molecular mechanisms involved in the signalling of these mediators may be very positive in the design of the therapeutic strategy. This is especially relevant because different mediators may be sharing the same signalling pathways. At the moment there are few studies describing the role of cytokines and tumour factors in the signalling associated with muscle wasting. In conclusion, although both tumoural and humoural (mainly cytokines) factors – that trigger cachexia – may share common signalling pathways and, therefore, it is not very likely a single drug will block the complex processes involved in cachexia. In addition, some of the mediators proposed for the wasting syndrome also play a role in the regulation of body weight in absolutely opposite states such as obesity. In conclusion, the future treatment of the cachectic syndrome will no doubt combine different pharmacological approaches to efficiently reverse the metabolic changes described above and, at the same time, ameliorate the anorexia of the patients. Defining this therapeutic combination of drugs is an exciting project that will stimulate many scientific efforts.

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References

1 Warren, S. (1932) The immediate cause of death in cancer. *Am. J. Med. Sci.* 184, 610–613
2 Mulligan, K. and Schambelan, M. (2002) Anabolic treatment with GH, IGF-I, or anabolic steroids in patients with HIV-associated wasting. *Int. J. Cardiol.* 85, 151–159
3 Anker, S.D. and Sharma, R. (2002) The syndrome of cardiac cachexia. *Int. J. Cardiol.* 85, 51–66
4 Argilés, J.M. *et al.* (1997) The metabolic basis of cancer cachexia. *Med. Res. Rev.* 17, 477–498
5 Ng, E.H. and Lowry, S.F. (1991) Nutritional suport and cancer cachexia. Evolving concepts of mechanisms and adjunctive therapies. *Hematol. Oncol. Clin. North Am.* 5, 161–184
6 Loprinzi, C.L. *et al.* (1993) Phase III evaluation of megestrol acetate as therapy for patients with cancer anorexia and/or cachexia. *J. Clin. Oncol.* 11, 762–767
7 Bruera, E. *et al.* (1990) A controlled trial of megestrol acetate on appetite, caloric intake, nutritional status and other symptoms in patients with advanced cancer. *Cancer* 66, 1279–1282
8 Neri, B. *et al.* (1997) Effect of medroxyprogesterone acetate on the quality of life of the oncologic patient: a multicentric cooperative study. *Anticancer Drugs* 8, 459–465
9 McCarthy, H. *et al.* (1994) Megestrol acetate stimulates food and water intake in the rat: effects on regional hypothalamic neuropeptide Y concentrations. *Eur. J. Pharmacol.* 265, 99–102
10 Mantovani, G. *et al.* (1997) Medroxyprogesterone acetate reduces the *in vitro* production of cytokines and serotonin involved in anorexia/cachexia and emesis by peripheral blood mononuclear cells and cancer patients. *Eur. J. Cancer* 33, 602–607
11 Tomíska, M. *et al.* (2003) Palliative treatment of cancer anorexia with oral suspension of megestrol acetate. *Neoplasma* 50, 227–233
12 Nagaya, N. *et al.* (2006) Ghrelin, a novel growth hormone-releasing peptide, in the treatment of cardiopulmonary-associated cachexia. *Intern. Med.* 45, 127–134
13 Garcia, J. *et al.* (2007) A phase II randomized, placebo-controlled, double-blind study of the efficacy and safety of RC-1291 (RC) for the treatment of cancer cachexia. *ASCO Annual Meeting Proceedings Part I. Vol 25 J. Clin. Oncol.* (June 20 Supplement), 9133
14 Mitchelson, F. (1992) Pharmacological agents affecting emesis: a review. *Drugs* 43, 295–315
15 Watzl, B. *et al.* (1991) Marijuana components stimulate peripheral blood mononuclear cell secretion of interferon-gamma and suppress interleukin-1-alpha *in vitro*. *Int. J. Immunopharmacol.* 13, 1091–1097
16 Srivastava, M.D. *et al.* (1998) Delta9 tetrahydrocannabinol and cannabidiol alter cytokine production by human immune cells. *Immunopharmacology* 40, 179–185
17 Facchinetti, F. *et al.* (2003) Cannabinoids ablate release of TNFalpha in rat microglial cells stimulated with lypopolysaccharide. *Glia* 41, 161–168
18 Strasser, F. *et al.* (2006) Comparison of orally administered cannabis extract and delta-9-tetrahydrocannabinol in treating patients with cancer-related anorexia–cachexia syndrome: a multicenter, phase III, randomized, double-blind, placebo-controlled clinical trial from the Cannabis-In-Cachexia-Study-Group. *J. Clin. Oncol.* 24, 3394–3400
19 Scarlett, J.M. and Marks, D.L. (2005) The use of melanocortin antagonists in cachexia of chronic disease. *Expert Opin. Investig. Drugs* 14, 1233–1239
20 DeBoer, M.D. and Marks, D.L. (2006) Therapy insight: use of melanocortin antagonists in the treatment of cachexia in chronic disease. *Nat. Clin. Pract. Endocrinol. Metab.* 2, 459–466
21 Evans, R.D. *et al.* (1989) Metabolic effects of tumour necrosis factor-α (cachectin) and interleukin-1. *Clin. Sci.* 77, 357–364
22 Yamamoto, N. *et al.* (1998) Effect of FR143430, a novel cytokine suppressive agent, on adenocarcinoma colon-26-induced cachexia in mice. *Anticancer Res.* 18, 139–144
23 Sampaio, E.P. *et al.* (1991) Thalidomide selectively inhibits tumor necrosis factor-α production in stimulated human monocytes. *J. Exp. Med.* 173, 699–703
24 Sampaio, E.P. *et al.* (1993) The influence of thalidomide on the clinical and immunological manifestation of erithema nodosum leprosum. *J. Infect. Dis.* 168, 408–414
25 Gordon, J.N. *et al.* (2005) Thalidomide in the treatment of cancer cachexia: a randomised placebo controlled trial. *Gut* 54, 447–448
26 Anker, S.D. and Coats, A.J. (2002) How to RECOVER from RENAISSANCE? The significance of the results of RECOVER, RENAISSANCE, RENEWAL and ATTACH. *Int. J. Cardiol.* 86, 123–130

27 Monk, J.P. *et al.* (2006) Assessment of tumor necrosis factor alpha blockade as an intervention to improve tolerability of dose-intensive chemotherapy in cancer patients. *J. Clin. Oncol.* 24, 1852–1859

28 Quinn, L.S. *et al.* (1995) Interleukin-15: a novel anabolic cytokine for skeletal muscle. *Endocrinology* 136, 3669–3672

29 Carbó, N. *et al.* (2001) Interleukin-15 mediates reciprocal regulation of adipose and muscle mass: a potential role in body weight control. *Biochim. Biophys. Acta* 1526, 17–24

30 Figueras, M. *et al.* (2004) Interleukin-15 is able to suppress the increased DNA fragmentation associated with muscle wasting in tumour-bearing rats. *FEBS Lett.* 569, 201–206

31 Busquets, S. *et al.* (2005) Interleukin-15 decreases proteolysis in skeletal muscle: a direct effect. *Int. J. Mol. Med.* 16, 471–476

32 Anti, M. *et al.* (1992) Effect of omega-3 fatty acids on rectal mucosal cell proliferation in subjects at risk for colon cancer. *Gastroenterology* 103, 883–891

33 Rose, D.P. and Connolly, J.M. (1993) Effects of dietary omega-3 fatty acids on human breast cancer growth and metastases in nude mice. *J. Natl. Cancer Inst.* 85, 1743–1747

34 Tisdale, M.J. (1993) Mechanism of lipid mobilization associated with cancer cachexia: interaction between the polyunsaturated fatty acid, eicosapentaenoic acid, and inhibitory guanine nucleotide-regulatory protein. *Prostaglandins Leukot. Essent. Fatty Acids* 48, 105–109

35 Fearon, K.C. *et al.* (2003) Effect of a protein and energy dense *N*-3 fatty acid enriched oral supplement on loss of weight and lean tissue in cancer cachexia: a randomised double blind trial. *Gut* 52, 1479–1486

36 Fearon, K.C. *et al.* (2006) Double-blind, placebo-controlled, randomized study of eicosapentaenoic acid diester in patients with cancer cachexia. *J. Clin. Oncol.* 24, 3401–3407

37 Dewey, A. *et al.* (2007) Eicosapentaenoic acid (EPA, an omega-3 fatty acid from fish oils) for the treatment of cancer cachexia. *Cochrane Database Syst. Rev.* 24, CD004597

38 Mehra, M.R. *et al.* (2006) Fish oils produce anti-inflammatory effects and improve body weight in severe heart failure. *J. Heart Lung Transplant.* 25, 834–838

39 Busquets, S. *et al.* (2004) Anticachectic effects of formoterol: a drug for potential treatment of muscle wasting. *Cancer Res.* 64, 6725–6731

40 Lindholm, E. *et al.* (2004) Effects of recombinant erythropoietin in palliative treatment of unselected cancer patients. *Clin. Cancer Res.* 10, 6855–6864

41 Kanzaki, M. *et al.* (2005) Erythropoietin attenuates cachectic events and decreases production of interleukin-6, a cachexia-inducing cytokine. *Cytokine* 32, 234–239

42 Anker, S.D. *et al.* (2003) Prognostic importance of weight loss in chronic heart failure and the effect of treatment with angiotensin-converting-enzyme inhibitors: an observational study. *Lancet* 361, 1077–1083

43 Adigun, A.Q. and Ajayi, A.A. (2001) The effects of enalapril-digoxin-diuretic combination therapy on nutritional and anthropometric indices in chronic congestive heart failure: preliminary findings in cardiac cachexia. *Eur. J. Heart Fail.* 3, 359–363

44 Zhao, S.P. and Xie, X.M. (2001) Captopril inhibits the production of tumor necrosis factor-alpha by human mononuclear cells in patients with congestive heart failure. *Clin. Chim. Acta* 304, 85–90

45 Sanders, P.M. *et al.* (2005) Angiotensin II directly induces muscle protein catabolism through the ubiquitin-proteasome proteolytic pathway and may play a role in cancer cachexia. *Br. J. Cancer* 93, 425–434

46 Lainscak, M. *et al.* (2006) Body composition changes in patients with systolic heart failure treated with beta blockers: a pilot study. *Int. J. Cardiol.* 106, 319–322

47 Storer, T.W. *et al.* (2005) A randomized, placebo-controlled trial of nandrolone decanoate in human immunodeficiency virus-infected men with mild to moderate weight loss with recombinant human growth hormone as active reference treatment. *J. Clin. Endocrinol. Metab.* 90, 4474–4482

48 Evans, W. *et al.* (2007) Ostarine increases lean body mass and improves physical performance in healthy elderly subjects: implications for cancer cachexia patients. *ASCO Annual Meeting Proceedings Part I. Vol 25 J. Clin. Oncol.* (June 20 Supplement), 9119

49 McFarlane, C. *et al.* (2006) Myostatin induces cachexia by activating the ubiquitin proteolytic system through an NF-kappaB-independent, FoxO1-dependent mechanism. *J. Cell. Physiol.* 209, 501–514

50 Isfort, R.J. *et al.* (2005) Discovery of corticotropin releasing factor 2 receptor selective sauvagine analogues for treatment of skeletal muscle atrophy. *J. Med. Chem.* 48, 262–265

51 Argilés, J.M. *et al.* (2007) Effects of CRF2R agonist on tumour growth and cachexia in mice bearing the Lewis lung carcinoma. *Muscle Nerve* 2007 Oct 2; [Epub ahead of print]

52 Lee, D.H. and Goldberg, A.L. (1998) Proteasome inhibitors: valuable new tools for cell biologists. *Trends Cell. Biol.* 8, 397–403

53 von Haehling, S. *et al.* (2002) Cachexia: a therapeutic approach beyond cytokine antagonism. *Int. J. Cardiol.* 85, 173–183

54 Bodine, S.C. *et al.* (2001) Identification of ubiquitin ligases required for skeletal muscle atrophy. *Science* 294, 1704–1708

55 Mantovani, G. *et al.* (2006) A phase II study showing efficacy and safety in patients with cancer-related anorexia/cachexia and oxidative stress. *Cancer Epidemiol. Biomarkers Prev.* 15, 1030–1034

56 Argilés, J.M. *et al.* (2004) The pharmacological treatment of cachexia. *Curr. Drug Targets* 5, 265–277