

## Therapeutic strategies against cancer cachexia

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### Abstract

Cancer cachexia has two main components: anorexia and metabolic alterations. The main changes associated with the development of this multi-organic syndrome are glucose intolerance, fat depletion and muscle protein hypercatabolism. The aim of this paper is to review the more recent therapeutic approaches designed to counteract the wasting suffered by the cancer patient with cachexia. Among the most promising approaches we can include the use of ghrelin agonists, beta-blockers, beta-adrenergic agonists, androgen receptor agonists and anti-myostatin peptides. The multi-targeted approach seems essential in these treatments, which should include the combination of both nutritional support, drugs and a suitable program of physical exercise, in order to ameliorate both anorexia and the metabolic changes associated with cachexia. In addition, another very important and crucial aspect to be taken into consideration in the design of clinical trials for the treatment of cancer cachexia is to stage cancer patients in relation with the degree of cachexia, in order to start as early as possible this triple approach in the course of the disease, even before the weight loss can be detected.

**Key Words:** cancer cachexia, muscle wasting, treatment, multi-targeted approach

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Cachexia, according to an international consensus,<sup>1</sup> “is a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass. Anorexia, inflammation, insulin resistance and increased muscle protein breakdown are frequently associated with cachexia. Cachexia is distinct from starvation, age-related loss of muscle mass, primary depression, malabsorption and hyperthyroidism and is associated with increased morbidity”.<sup>1</sup> Although anorexia represents a very important event in the development of cachexia, it has been proven that total parenteral nutrition does not stop the loss of body weight. Therefore, it seems quite evident that metabolic alterations present in the patient (increased energy inefficiency, insulin resistance and abnormal carbohydrate metabolism, adipose tissue dissolution and hypertriglyceridemia, and muscle wasting) have a key role in the development of cachexia.<sup>2</sup> Moreover, some of the alterations are also a result of the chemotherapeutic treatment.<sup>3,4</sup> Bearing this in mind, the development of different therapeutic approaches has focused, either on increasing food intake or on reversing catabolism and increasing the anabolic drive of the cancer patient.

### Drugs modulating cytokine action

TNF- $\alpha$  (Tumor necrosis factor alpha), IL-1 (interleukin 1), IL-6 (interleukin 6) and interferon-gamma (IFN- $\gamma$ ) are the main cytokines implicated in cachexia. Interestingly, these cytokines share the same metabolic effects and their activities are closely interrelated. In many studies, they exhibit synergic effects when administered together. Therefore, therapeutic strategies have been based on either blocking their synthesis or their action. Weight loss in patients with esophageal tumors is related to the levels of the cytokines.<sup>5</sup> In fact, cytokines are able to act on multiple target sites such as bone marrow, myocytes, hepatocytes, adipocytes, endothelial cells and neurons, where they generate a complex cascade of responses leading to the wasting associated with cachexia. Using anti-TNF strategies such as etanercept (fusion protein directed against p75 TNF- $\alpha$  receptor) has led to a poor clinical outcome in cancer patients. However, a clinical pilot study with several advanced malignancies involving patients treated with etanercept combined with an antitumor agent (docetaxel),<sup>6</sup> showed less fatigue and improved tolerability of the antitumoral treatment.<sup>7</sup>

Another phase II trial with infliximab - an anti-TNF- $\alpha$  monoclonal antibody - was unsuccessful in improving symptoms of cachexia (lean body mass) in pancreatic cancer patients.<sup>8</sup> Survival in cancer patients is inversely correlated with circulating IL-6 levels.<sup>9</sup> In a mouse model of cancer cachexia, tocilizumab, an IL-6 monoclonal antibody, improved cachexia.<sup>10</sup> A humanized monoclonal anti-IL-6 antibody increased hemoglobin levels and prevented muscle wasting in cancer patients.<sup>11</sup> In preclinical and in a Phase II trial, ALD518 targeting IL-6 appears well tolerated and ameliorates NSCLC-related anemia and cachexia.<sup>12</sup> On the same lines, a phase II clinical trial with Ruxolitinib - an inhibitor of Janus kinases (JAKs) activators of the STAT transcription factor - in patients with tumor-associated chronic wasting diseases is now on-going.<sup>13</sup> IL-6 intracellular signaling pathway takes place via activation of the Janus kinases. Targeting both TNF- $\alpha$  and IL-6 by means of a broad-spectrum peptide nucleic acid (OHR118, OHR Pharma), resulted in an increase in both body weight and physical performance in patients with advanced cancer in a phase II trial.<sup>14,15</sup> In a pre-clinical mouse model of pancreatic cancer cachexia, Greco et al. have described that blockade of TGF- $\beta$ , lessens cachexia, reducing mortality and metabolic alterations.<sup>16</sup> In fact, according to Waning, TGF- $\beta$  mediates muscle weakness associated with bone metastases in mice.<sup>17</sup> Indeed, during tumor-induced bone destruction, TGF- $\beta$  upregulates Nox4 - an NADPH oxidase - resulting in alterations in skeletal muscle proteins (oxidation). Among these proteins, the ryanodine receptor/calcium (Ca<sup>2+</sup>) release channel (RyR1) is oxidized. The altered RyR1 channels leak Ca<sup>2+</sup>, resulting in lower intracellular signaling required for adequate muscle contraction.<sup>17</sup> The production of the cytokines mentioned above, known as catabolic pro-inflammatory cytokines, is not the only factor involved in the metabolic changes associated with cancer cachexia. Indeed, the so-called anti-inflammatory cytokines, such as IL-4, -10 -12 and -15, are also involved. Indeed, IL-15 has been reported to be an anabolic factor for skeletal muscle.<sup>18,19</sup> IL-15 decreases protein degradation and DNA fragmentation while increases UCP3 (uncoupling protein-3) expression in skeletal muscle.<sup>18</sup> The action of the cytokine is directly upon skeletal muscle.<sup>20</sup> Pre-clinical studies indicate that IL-15 leads to an improvement of muscle mass and performance in tumor-bearing animals.<sup>19</sup> Martinez-Hernandez et al. have demonstrated a relevant association between serum IL-15 and changes in weight and muscle mass in cancer patients, suggesting a possible role of the cytokine as a body composition marker in weight-losing cancer patients.<sup>21</sup>

### Drugs modulating appetite

In humans, megestrol acetate - a synthetic, orally active derivative of the naturally occurring hormone progesterone - improves appetite, caloric intake and

nutritional status.<sup>22</sup> The mechanism that mediates the weight gain is mostly unknown, although it has been proposed that it may be partially mediated by neuropeptide Y (NPY), a potent central appetite stimulant. Interestingly, in experimental animals, megestrol acetate increases not only food intake but also lean mass and physical performance.<sup>23</sup> Nanocrystal suspensions of megestrol acetate are easy to use and represent an improvement in bioavailability.<sup>24</sup> Megestrol acetate is the standard drug in cancer cachexia treatment in many countries over the world.<sup>25</sup> The orexigenic mediator ghrelin, a novel endogenous ligand for the growth hormone secretagogue receptor, and secreted by the stomach and pancreas, has been reported as having a pivotal role in increasing appetite and, therefore, food intake. Besides, this peptide has important metabolic effects and regulates energy metabolism through growth hormone-dependent and -independent mechanisms.<sup>26</sup> Thus, administration of ghrelin constitutes a new therapeutic strategy for the treatment of cancer cachexia.<sup>27</sup> Pre-clinical studies have shown that ghrelin administration to cachectic tumor-bearing animals results in an improvement in both appetite and body weight, together with an improvement in lean body mass.<sup>28</sup> In addition, ghrelin administration to rats prevents cisplatin-induced mechanical hyperalgesia - increased pain sensitivity - and cachexia.<sup>29</sup> In fact, cisplatin-induced anorexia is mediated through reduced hypothalamic ghrelin secretion. In addition, ghrelin seems to attenuate gastrointestinal epithelial damage induced by doxorubicin.<sup>30</sup> These results support ghrelin as a protective factor against the toxic effects of chemotherapeutic agents. Several clinical trials with ghrelin or ghrelin mimetics have been performed or are currently ongoing. A couple of phase II randomized, placebo-controlled, double-blind studies using an oral ghrelin mimetic, anamorelin (Helsinn Therapeutics), a ghrelin receptor agonist that can be administered orally, have led to positive results in non-small cell lung cancer (NSCLC) patients showing an improvement in lean body mass, total body mass and hand grip strength.<sup>31</sup> However, two double-blinded phase II trials (ROMANA 1 & 2) in incurable stage II/IV NSCLC patients, showed that anamorelin (100 mg/day for 12 weeks) increased body weight, improved FAACT anorexia/cachexia scores,<sup>31,32</sup> but failed to improve handgrip strength.<sup>33</sup> In a *post hoc* analysis of the two phase II studies, Temel et al. concluded that anamorelin increased both lean and fat mass as well as decreased muscle fatigue.<sup>33</sup> Interestingly, Takayama et al. reported, in a phase-II randomized trial where NSCLC patients were daily given 100 mg of anamorelin, an increase in lean body mass, appetite, quality of life and performance status following anamorelin administration.<sup>34</sup> In addition, significant elevations in both IGF-1 and IGFBP-3 plasma concentrations were observed, suggesting an improvement in protein synthesis. Another appetite stimulant involved in clinical trials is AEZS-130 -

macimorelin -, an oral peptidomimetic growth hormone secretagogue (Aeterna Zentaris), now in phase II, and the endpoints of the trial being changes in body weight, IGF-1 levels and quality of life.<sup>35</sup> Finally, Asubio Pharmaceuticals is involved in a phase-II clinical trial with synthetic human ghrelin (SUN11031) in COPD patients.<sup>36</sup>

### Drugs acting on other metabolic targets

Pre-clinical studies using formoterol - a  $\beta_2$ -adrenergic agonist with low cardiac toxicity - have shown that the drug can reverse muscle wasting associated with cancer.<sup>37,38</sup> Essentially, formoterol treatment increases the rate of protein synthesis while inhibiting the rate of muscle proteolysis. Interestingly, this  $\beta_2$ -agonist is also able to diminish the increased rate of muscle apoptosis present in tumor-bearing animals, together with facilitating muscle regeneration by stimulating satellite cells.<sup>38,39</sup> A combination treatment of formoterol and soluble myostatin receptor ActRIIB has been able to completely reverse muscle wasting in tumor-bearing rats,<sup>40</sup> the results emphasizing the importance of combining drugs in the treatment of cancer cachexia. A phase-IIa study investigating the effects of a combination of formoterol and megestrol acetate (APD209) in 13 cachectic cancer patients has been undertaken by Acacia Pharma.<sup>41</sup> Six of the seven patients that completed the treatment period showed improved muscle size and strength, and three patients had improved levels of daily physical activity.<sup>41</sup> Erythropoietin (EPO) administration to cancer patients - with subnormal or even normal hemoglobin levels -- results in clinical benefit. Interestingly, Kanzaki et al. have shown that EPO --in a pre-clinical cancer cachexia model-- decreases the production of the pro-cachectic cytokine IL-6.<sup>42</sup> This may be linked with the attenuation of cachectic manifestations. EPO treatment also improves metabolic and exercise capacity via an increased erythrocyte count.<sup>42</sup> In a pre-clinical mouse model of cancer cachexia, the combination of EPO administration and aerobic exercise has led to a significant decrease of muscle wasting.<sup>43</sup> Patients with cancer cachexia have major abnormalities in heart mass and function, the so-called cardiac cachexia. In fact, cardiac arrest is the main cause of death - at autopsy - associated with cancer. From this point of view, several drugs have been used to counteract cardiac cachexia associated with cancer. Inhibitors of the angiotensin-converting enzyme (ACE) have been tested in preclinical models with success in increasing both muscle and fat mass.<sup>44,45</sup> Some evidence also exists concerning the potential of ACE inhibitors to ameliorate cancer cachexia in NSCLC patients.<sup>46</sup> Angiotensin receptor blockers can also be used in the treatment of cachexia. Thus, one of this compounds, Telmisartan, can be used as an add-on therapy with 5-fluorouracil,<sup>47</sup> or cisplatin,<sup>48</sup> or other traditional chemotherapeutic agents. Telmisartan inhibits TNF- $\alpha$ -induced IL-6 expression at the transcriptional level through the activation of PPAR- $\gamma$ .<sup>49</sup> NF- $\kappa$ B

signaling plays an important role during skeletal muscle atrophy and fat lipolysis. On these lines, pyrrolidine dithiocarbamate (PDTC, an inhibitor of the transcription factor) is able to attenuate cancer cachexia symptom in C26 tumor-bearing mice models in vivo without influencing tumor volume interfering with muscle atrophy and fat lipolysis.<sup>50</sup> Beta-blockers can reduce body energy expenditure and improve the efficiency of substrate utilization. Some of them do combine many different pharmacological effects. Espindolol (MT-102, PsiOxus Therapeutics) is a non-specific  $\beta_1/\beta_2$  adrenergic receptor antagonist that exhibits effects through  $\beta$  and central 5-HT $1\alpha$  receptors to demonstrate pro-anabolic, anti-catabolic, and appetite-stimulating actions.<sup>51</sup> The ACT-ONE trial showed that espidolol 10 mg twice daily was able to revert weight loss, improve fat-free mass, and maintain fat mass and improve handgrip strength in cachectic patients with non-small cell lung cancer or colorectal cancer.<sup>52</sup> VT-122 combines a non-selective beta-blocker, propranolol - used in controlling high blood pressure - and etodolac, a COX-2 inhibitor. Data from a phase II clinical study clearly show an improvement in lean body mass in non-small cell lung cancer patients.<sup>53</sup> Even though derivatives of gonadal steroids have important side effects, such as masculinization, fluid retention and hepatic toxicity, treatment with these drugs facilitates nitrogen protein accumulation, therefore counteracting the progressive nitrogen loss associated with muscle wasting. In fact, non-steroidal selective androgen receptor modulators (SARMs) hold promise as a new class of function promoting anabolic therapies for several clinical conditions that manifest muscle wasting. In a phase IIb, double-blind, placebo-controlled study, involving non-small-cell lung cancer (NSCLC), colorectal cancer, non-Hodgkin's lymphoma, chronic lymphocytic leukemia, or breast cancer patients, Enobosarm treatment led to significant improvements in lean body mass, physical function, and quality of life.<sup>54</sup> These positive results have led to the design of phase III trials. On these lines, Crawford et al. reported a study design and rationale for the phase III clinical development program of Enobosarm, for the prevention and treatment of muscle wasting in oncology patients (POWER Trials).<sup>55</sup> To assess enobosarm's effect on both prevention and treatment of muscle wasting, in each pivotal POWER trial, subjects will receive placebo or Enobosarm 3 mg orally once daily for 147 days. Physical function will be assessed as stair climb power, and lean body mass assessed by dual-energy X-ray absorptiometry (DXA), these being the co-primary efficacy endpoints in both trials assessed at day 84.<sup>55</sup> Preliminary data report an increase in lean body mass and improvement in SCP (POWER1). POWER2 also shows an increase in lean body mass, while no clinical improvement in the stair climb power test and handgrip strength is seen.<sup>56</sup> Myostatin, a TGF- $\beta$  super-family member, is a negative regulator of muscle growth and development. In fact,

myostatin inhibitors induce muscle hypertrophy specially through effects on myofibrillar protein synthesis rather than through an stimulation of satellite cell proliferation.<sup>57,58</sup> Bearing this in mind, anti-myostatin strategies have been used in clinical trials involving cachectic patients. From this point of view, a phase II study in sarcopenic patients has been undertaken using AMG745, a peptibody against myostatin.<sup>59</sup> Similarly, Acceleron Pharma has performed a phase I study with ACE031, a soluble Activin receptor type IIB.<sup>60</sup> Bimagrumab or BYM338, an activin II receptor antibody, has also been studied in relation with cachexia in patients with inclusion myositis.<sup>61</sup> BYM338 is able to bind ActRIIB 200-times better than ActRIIA, promoting skeletal muscle hypertrophy when administered *in vivo*. When administered in association with glucocorticoids, BYM338 was able to prevent skeletal muscle mass loss and preserved muscle function, facilitating the recovery from muscle atrophy.<sup>62</sup> A humanized monoclonal antibody LY2495655 has been used in sarcopenic patients in a phase II trial, involving subjects who recently reported falls and low muscle strength and power.<sup>63</sup> Patients receiving the antibody showed an increase in lean mass and a significant improvement of muscle power expressed as improved stair-climbing time, fast gait speed, and chair rise with arms. A phase II study is now being held in pancreatic cancer patients although no results are yet available.<sup>64</sup> Increased proteolysis in skeletal muscle during cachexia involves activation of the ubiquitin/proteasome system in muscle.<sup>2</sup> Taking this into consideration, inhibitors of this proteolytic system such as peptide aldehyde, lactacystin and  $\beta$ -lactone – which effectively can block up to 90% of the degradation of normal proteins and short-lived proteins in the cells - could be potential drugs for the treatment of muscle wasting.<sup>65</sup> However, the toxicity of such compounds is fairly high, since they are not specific inhibitors of the proteolytic system in muscle tissue. Bearing this in mind, a drug that could specifically block myofibrillar protein degradation is still waiting to be found. Inhibitors of the proteasome have been used as anti-cancer drugs - since the proteasome has a main role in cell division - in multiple myeloma patients. The use of these drugs has led to contradictory results in the treatment of muscle wasting in pre-clinical models. Thus, bortezomib did not show any significant effects in the treatment of cancer cachexia in rats bearing the cachectic Yoshida hepatoma AH-130 ascites tumor model.<sup>66</sup> Conversely, carfilzomib inhibits skeletal muscle proteolysis and apoptosis reducing cachexia in a pre-clinical mouse model.<sup>67</sup> A phase Ib investigation showed promising results with the MEK inhibitor binimetinib in patients with advanced or metastatic biliary tract cancer.<sup>68</sup> Cancer cachexia and type II diabetes share common metabolic characteristics, including weight loss, insulin resistance and increased hepatic gluconeogenesis. From this point of view, recent interest has developed around anti-diabetic drugs - such as metformin - for the

treatment of muscle wasting in cancer. An interesting study reveals that metformin improves protein metabolism in skeletal muscle in tumor-bearing rats.<sup>69</sup> A very innovative and revolutionary strategy to fight muscle wasting in cancer is the use of stem cells with the aim of replacing degenerated muscle tissue.<sup>70</sup> While adult stem cells are tissue-specific and have limited capacity to be expanded, *ex vivo* pluripotent stem cells can differentiate into any cell type while possessing unlimited *in vitro* self-renewal. Scott et al. described a methodology for large-scale isolation of satellite cells from skeletal muscle<sup>70</sup>, which could then be applied as a therapeutic strategy to stimulate muscle regeneration.<sup>71</sup> Another interesting approach that has led to promising results in pre-clinical models of cancer cachexia is the use of statins such as simvastatin. Indeed, in a study involving the cachectic Yoshida AH-130 ascites hepatoma has shown that simvastatin attenuated body weight loss and preserved muscle mass.<sup>72</sup>

### The use of nutrition

Nutrition is an essential element in cancer care, and patients report a high interest and need; however, a recent study has shown that many patients do not have access to high-quality nutrition therapy either during or after cancer treatment.<sup>73</sup> While some studies demonstrate a beneficial effect for nutritional advice,<sup>74,75</sup> other studies shown - a two-year randomized controlled trial - that early dietary counseling was efficient in increasing intake but had no beneficial effect on mortality or secondary outcomes.<sup>76</sup> While standard nutrition supplements have not led to positive results in cancer cachexia, the use of nutrients in combination with nutraceuticals - the so-called specialized nutrition - has given more positive results. Omega3-polyunsaturated fatty acids (PUFA), present in large amounts in fish oil, have been proposed as very active in reducing either tumor growth or muscle wasting. An improvement in the lean body mass and improved quality of life was observed in a randomized doubled blind trial using a protein and energy dense omega3-fatty acid-enriched oral supplement,<sup>77</sup> provided that its consumption was equal or superior to 2.2 g eicosapentaenoic acid (EPA)/day. However, data arising from a large, multicentre, double-blind placebo-controlled trial indicate that EPA administration alone is not successful in the treatment of weight losing patients with advanced gastrointestinal or lung cancer.<sup>78</sup> Moreover, a meta-analysis based on five trials concluded that there were insufficient data to establish whether oral EPA was better than placebo.<sup>79</sup> Comparisons of EPA combined with a protein energy supplementation versus a protein energy supplementation (without EPA) in the presence of megestrol acetate provided no evidence that EPA improves symptoms associated with the cachexia syndrome often seen in patients with advanced cancer.<sup>80</sup> In spite of this, several recent trials suggest that EPA-enriched nutrition results in positive outcomes in cancer patients.<sup>81-83</sup>

### A multitarget approach including physical exercise

During the last years, it has become apparent that a combination of nutrition, nutraceuticals and drugs is a much-preferred therapeutic approach than just looking for a single drug "magic bullet". In fact, the treatment of cancer cachexia has to involve, not only drugs and/or nutrients, but also a possibilistic program of physical exercise<sup>84-86</sup>. Indeed, in cancer patients - either suffering from cachexia or not - an exercise program can improve their quality of life.<sup>87,88</sup> This is accomplished by inducing metabolic alterations that result in changes in body composition. A study has shown clear benefits - on cachectic cancer (head and neck) patients - of an exercise program (12 weeks: 2-3 sets of 8-15 repetition maximum of seven conventional exercises).<sup>89</sup> Indeed, with an increase of 4.2% of lean body mass, enhanced muscle strength and quality of life were observed.<sup>89</sup> Similarly, in the same type of cancer patients, McNeely et al. demonstrated improved shoulder muscle function following resistance exercise training.<sup>90</sup> Exercise programs have also been able to increase muscle strength and endurance, the six-minute walk distance, up-and-go time, the number of arm curls, and the number of chair stands, in lung cancer patients.<sup>91</sup> A systematic review reports beneficial effects for breast cancer survivors.<sup>92</sup> Concerning the mechanisms involved in the effects of exercise training programs, it seems very clear that an anti-inflammatory status is accomplished with decreases in pro-inflammatory cytokines - such as TNF- $\alpha$  - and increases in IL-10, a clear anti-inflammatory cytokine.<sup>87</sup> The decrease in inflammatory status is accompanied by a reduction in oxidative stress.<sup>87</sup> Elevations in IGF-1 and PGC-1  $\alpha$  in skeletal muscle have also been associated with the beneficial effects of exercise on cancer.<sup>87</sup> Muscaritoli et al. have defined the so-called TARGET approach, which is a good way of interpreting the multimodal approach.<sup>93</sup> It actually integrates active interventions and research programs related to the onset and progression of cancer cachexia. This approach includes Teaching (nutrition, metabolic alterations in cancer), Awareness (of the negative impact of cancer cachexia), Recognition (diagnosis and staging), Genetics (inherited susceptibility), Exercise (physical activity) and Treatment.<sup>93</sup> The MENAC (Multimodality Exercise/Nutrition Anti-inflammatory treatment for Cachexia) trial,<sup>94</sup> represents an excellent example of a multimodal approach. This on-going phase III trial is enrolling both lung, cholangio- and pancreatic carcinoma cancer patients and includes nutritional counseling, oral nutrition supplementation (including EPA), a physical exercise program and an anti-inflammatory (ibuprofen) treatment.<sup>95</sup> A combined multitargeted approach in a randomized placebo-controlled trial, using celecoxib, L-carnitine, curcumin and lactoferrin, was able to improve the nutritional and immunometabolic alterations of cachexia, ameliorate the patient quality of life and correct cancer-related anemia.<sup>96</sup> Practical (individual reports) multimodal care programs for cancer cachexia have been

recently published.<sup>97</sup> Another critical factor that may positively contribute to cancer cachexia treatment is a proper staging of the cachectic condition in cancer patients.<sup>27</sup> This would allow for adequate treatment at the different phases of cachexia.<sup>98</sup> Timing is very important and has to be carefully considered when designing the therapeutic approach. Any nutritional/metabolic/pharmacological support should be started early in the course of the disease, before severe weight loss occurs, and appropriate treatment should be applied at every phase of the cachectic syndrome. More research should also be devoted to finding new biomarkers for cancer cachexia. Indeed, many cancer patients are treated only when a significant amount of weight loss is detected, or when the patients suffer from certain limitations in their daily living activities. Biomarkers may serve to detect the changes before any clinical manifestations arise, facilitating treatment and, possibly, improving prognosis. Progress has undoubtedly been made involving biomarkers,<sup>99</sup> but more research is needed in this field to find an easily measurable - either plasmatic or urinary - early and specific muscle-wasting biomarker. Another key aspect to consider is the design of appropriate trials. Indeed, on-going trials have a rather heterogeneous design and include an excessively wide span of different types of tumors with different degrees of cachexia. In fact, a unified approach is requested in a recent consensus document.<sup>100</sup> Many of the most promising drug candidates are entirely new molecules and, therefore, particular attention has to be focused on safety issues and not just side effects, but also long-term treatment associated problems, together with the issue of interaction with other drugs. This last point is particularly relevant since, as we have mentioned, the ideal treatment for cancer cachexia is multimodal, involving different drugs and nutraceuticals. Endpoints - particularly primary ones - are also essential. Lean body mass or, even better, muscle mass, together with a measurement of function, such as total daily physical activity are good candidates.

In conclusion, the future multimodal treatment of the cachectic syndrome will no doubt combine different approaches to efficiently counteract metabolic alterations while improving the energy intake of the patients. Defining this therapeutic multimodal combination of factors is an exciting project that will stimulate many scientific efforts.

### List of acronyms

ACE - angiotensin-converting enzyme  
BYM338 - Bimagrumab  
COPD - chronic obstructive pulmonary disease  
DXA - dual-energy X-ray absorptiometry  
EPA - eicosapentaenoic acid  
EPO - Erythropoietin  
FAACT - Functional Assessment of Anorexia Cachexia Therapy  
IFN- $\gamma$  - interferon-gamma

IL-1 - interleukin 1  
 IL-6 - interleukin 6  
 IL-10 - interleukin 10  
 MENAC - Multimodality Exercise/Nutrition Anti-inflammatory treatment for Cachexia  
 NPY - neuropeptide Y  
 NSCLC - non-small cell lung cancer  
 PDTC - pyrrolidine dithiocarbamate  
 PUFA - polyunsaturated fatty acids  
 SARM - selective androgen receptor modulators  
 TNF- $\alpha$  - Tumor necrosis factor alpha  
 UCP3 - uncoupling protein-3

#### Author's contributions

Each author has participated sufficiently, intellectually or practically, in the work to take public responsibility for the content of the article, including the conception and design. JMA, FJL-S, BS, SB conceived the content of the review, drafted the manuscript and revised critically it. All authors have read and approved the final manuscript.

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#### Conflict of Interest

All authors of this research have not conflict of interest related with employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or other funding.

#### Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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