Ther Adv Med Oncol
2017, Vol. 9(5) 369–382
DOI: 10.1177/1758834017698643

Cancer-induced muscle wasting: latest findings in prevention and treatment

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Abstract: Cancer cachexia is a severe and disabling clinical condition that frequently accompanies the development of many types of cancer. Muscle wasting is the hallmark of cancer cachexia and is associated with serious clinical consequences such as physical impairment, poor quality of life, reduced tolerance to treatments and shorter survival. Cancer cachexia may evolve through different stages of clinical relevance, namely pre-cachexia, cachexia and refractory cachexia. Given its detrimental clinical consequences, it appears mandatory to prevent and/or delay the progression of cancer cachexia to its refractory stage by implementing the early recognition and treatment of the nutritional and metabolic alterations occurring during cancer. Research on the molecular mechanisms underlying muscle wasting during cancer cachexia has expanded in the last few years, allowing the identification of several potential therapeutic targets and the development of many promising drugs. Several of these agents have already reached the clinical evaluation, but it is becoming increasingly evident that a single therapy may not be completely successful in the treatment of cancer-related muscle wasting, given its multifactorial and complex pathogenesis. This suggests that early and structured multimodal interventions (including targeted nutritional supplementation, physical exercise and pharmacological interventions) are necessary to prevent and/or treat the devastating consequences of this cancer comorbidity, and future research should focus on this approach.

Keywords: muscle wasting, cancer, cachexia, nutritional intervention, exercise, multimodal treatment

Received: 22 July 2016; revised manuscript accepted: 14 February 2017.

Introduction

Muscle wasting (with or without fat loss) is a pivotal feature of cancer cachexia, a multifactorial condition that negatively impacts patients' prognosis and quality of life.[1,2] The severity and phenotypic presentation of cancer cachexia may vary, and often muscle wasting may be an occult condition.[3] Regardless of body mass index (BMI), skeletal muscle depletion is considered a meaningful prognostic factor during cancer[4] and has been associated with higher incidence of chemotherapy toxicity, shorter time to tumor progression, poorer surgical outcome, physical impairment and shorter survival.[4–8]

Cancer cachexia may result from reduced nutrient intake and/or availability (secondary to anorexia, malabsorption or mechanical obstruction) and metabolic abnormalities, triggered by a complex network of cytokines, hormones and other tumor- and host-derived humoral factors. Apart from the consequences of cancer *per se*, the adverse effects of anti-neoplastic therapies may also contribute to exacerbation of this condition.[3,9,10]

The molecular mechanisms underlying cancer-related muscle wasting have not been fully elucidated. Available evidence suggests that a prominent role is played by increased muscle protein degradation, although impaired muscle protein synthesis and defective myogenesis may contribute as well. In addition, alterations in energy metabolism involving mitochondrial dysfunction have been implicated in the wasting

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process.[11,12] The prevalence of muscle loss has been reported as between 20% and 70%, depending on the type of tumor and the criteria used for assessment.[13] In advanced cancer patients the prevalence of muscle loss was found to be variable and dependent upon tumor type, stage and assessment tool. In early cancer patients undergoing curative treatment, prevalence of muscle loss ranged from 16% in breast,[14] to 33% in cholangiocarcinoma[15] and to 40.3% in hepatocellular carcinoma patients.[16] Loss of strength secondary to muscle loss is also frequent in cancer patients. Chemotherapy may induce fatigue and a severe decrease in muscle strength, especially in striated muscles,[17] which may be further aggravated by reduced physical activity. In patients not training and receiving chemotherapy for lymphoma, a decrease of up to 14.6% in muscle strength was reported.[18] The loss of contractile strength and function associated to muscle wasting and the onset of chronic fatigue may result in reduced physical activity, which in turn can further exacerbate muscle loss by instigating a vicious cycle.[19]

Although muscle mass depletion is a common feature of experimental and human cancer cachexia, discrepancies in the mechanisms underlying cancer-related muscle wasting have been reported between different experimental models as well as in patients with different tumor types, data available in human cancer cachexia still being scanty.[11,20] These diversities challenge the development of effective therapeutic strategies and underscore the need to implement research on patients and to design pre-clinical systems which as much as possible model the clinical scenario,[21] in order to identify the categories of patients who are more likely to respond to drugs targeting specific intracellular pathways.[20] Further, the development of effective treatments has been hampered by the high variability in clinical study design, including different patient selection criteria, clinical endpoints, analysis plans and definition of best supportive care.[22] Time of therapy administration is also critical: to date, most clinical trials on cancer cachexia have been conducted in patients very advanced in their disease trajectory, and experts have speculated that this could be a reason why many drugs, deemed effective at the pre-clinical phase, failed to show any benefits at the clinical evaluation.[23,24] Indeed, according to an international panel of experts, cancer cachexia may evolve in three stages of clinical relevance: pre-cachexia, cachexia and refractory cachexia. Although not all patients necessarily experience all of these stages, treatments should begin early in order to prevent or delay the progression to refractory cachexia.[1,2]

Despite these obstacles, several promising agents acting on specific molecular targets are currently under investigation. Results obtained so far suggest that a single therapy may be insufficient to counteract cancer cachexia and that early multimodal interventions (including targeted nutritional supplementation, physical exercise and pharmacological interventions) should be considered the best modality to manage the multifaceted aspects of this cancer comorbidity.[1,9,25,26]

The present article aims at reviewing the latest findings in the prevention and treatment of cancer-related muscle wasting that may represent the basis for the development of future cachexia therapies.

Options for prevention and treatment

The role of nutritional support

Nutritional interventions should be an essential part of the multimodal approach to cancer cachexia, as in the absence of an adequate energy and nutrient supply it is unlikely that muscle mass and body weight will be increased or stabilized. Since the reduction in food intake is an important yet reversible pathogenic mechanism accounting for cancer-related muscle wasting, the nutritional and metabolic support should be started early rather than delayed until there is an advanced degree of body weight loss.[1,2,27] This implies that when the diagnosis of cancer is made, any single patient should be nutritionally monitored in parallel with the oncologist by a clinical nutrition unit.[1] During this 'parallel pathway' continuous nutritional and metabolic support should be provided, which, accordingly to patients' needs, may include nutritional counseling, administration of oral supplements, nutraceuticals and artificial nutrition.[1]

Overcoming anabolic resistance: is it a clinical issue? A defining feature of cancer cachexia is that it cannot be fully reversed by *conventional* nutritional support.[2] Cancer cachexia, indeed, is different from simple starvation since, conceptually, both inflammation and metabolic abnormalities may alter the anabolic response of the skeletal muscle after meal ingestion. Recent evidence, however, suggests that cancer patients have an exploitable anabolic potential prior to reaching the

refractory phase of cachexia, thus creating a strong rationale for early nutritional interventions.[23,28,29] In this respect, a euglycemic, hyperinsulinemic clamp study in stage III and IV non-small cell lung cancer (NSCLC) patients showed a blunted whole-body anabolic response in conditions of iso-aminoacidemia, but a normal whole-body anabolic response to hyperaminoacidemia, suggesting that a significant protein intake is necessary to induce whole-body anabolism during cancer.[30] Consistently, another study reported that a high-protein formula containing high leucine levels, specific oligosaccharides and fish oil was able to stimulate muscle protein anabolism in advanced cancer patients compared to a conventional nutritional supplement.[31] In further support of a preserved anabolic potential, a recent study reported that the intake of 14 g of essential amino acids determined a high whole-body anabolic response in patients with stage III/IV NSCLC. Such effect was comparable to that observed in healthy matched controls and independent of recent weight loss, muscle mass, mild-to-moderate systemic inflammation and survival.[32] A comparable positive net balance during oral sip feeding of a commercially available formula was also observed in cachectic pancreatic cancer patients and controls, although with a different protein kinetic: indeed, while in cachectic patients only protein breakdown was reduced; in control patients both protein breakdown and synthesis were modulated.[33]

On the whole, these studies suggest that the failing anabolic response associated with cancer cachexia, if present, may be at least in part circumvented by providing an adequate nutritional support. Additional, *in vivo*, clinical investigations, however, are needed to determine to what extent in the long term cancer-related muscle wasting can be attenuated and reversed by an early and appropriate nutritional intervention, and to establish the optimal dose, timing and composition of the nutritional support.

Can nutrients act as metabolic modulators in cancer cachexia? Besides providing energy and protein requirements, the nutritional intervention could also represent a potential strategy to counteract inflammation and interfere with molecular mechanisms involved in the pathogenesis of cancer cachexia through the use of specific nutrients/nutraceuticals.[34]

Many studies examined the effects of fish oil-derived fatty acids [either eicosapentaenoic acid (EPA) or docosahexaenoic acid] in the prevention and treatment of cancer cachexia, given their potential ability to modulate pro-inflammatory cytokines and increase insulin sensitivity.[35] As recently reviewed, although not all studies in the past reported a benefit of fish oil supplementation on cancer cachexia, promising results were obtained in recent trials.[36,37] Since it has been suggested that possible reasons for such inconsistencies among trials could be the variability in study design, compliance with the supplement, contamination between study arms and different methodologies used to evaluate body composition,[36] future well-designed trials are needed to clarify the therapeutic potential of n-3 fatty acids for cancer-related muscle wasting.

Branched chain amino acids (BCAAs) have been shown to attenuate muscle wasting in experimental cancer cachexia, possibly by stimulating protein synthesis and attenuating protein degradation.[38] Besides their proposed role in ameliorating cancer anorexia,[39] a few clinical studies seem to support the hypothesis that BCAAs can ameliorate muscle protein metabolism, but larger randomized, blind, placebo-controlled trials are needed to confirm the beneficial effects of BCAAs in cancer patients and indicate the optimal dosage.[26,28,40]

Beta-hydroxy-beta-methylbutyrate (HMB) is a metabolite of the BCAA leucine that, according to previous experimental studies, may attenuate muscle wasting during cancer cachexia by inhibiting protein degradation and/or stimulating protein synthesis.[41–43] The therapeutic role of HMB in human cancer cachexia, however, is still uncertain and deserves further investigation, as was noted in a recent systematic review on this topic.[44]

L-carnitine is an amino acid derivative involved in fatty acids metabolism and in energy production processes.[45,46] Carnitine supplementation has been proven beneficial in experimental cancer cachexia,[47,48] as well as in clinical trials on cancer patients, where it has been tested alone[49] or in combination with other drugs;[50] additional investigations are needed to clarify its therapeutic potential for cancer-related muscle wasting.

The role of physical exercise

In addition to nutritional interventions, physical exercise has been proposed as another crucial component of the multimodal approach to cancer

cachexia. Indeed, physical activity may modulate inflammation and skeletal muscle metabolism,[51] with substantial differences in relation to the exercise modality. In particular, while endurance training stimulates oxidative metabolic adaptations (with little effect on muscle mass), resistance training exerts an anabolic action resulting in muscle hypertrophy.[52] Moreover, exercise improves insulin sensitivity,[53] regulates cellular homeostasis by stimulating proteins and organelles turnover[54] and promotes myogenesis.[55] Particularly relevant, in this regard, is the ability of exercise to induce autophagy and mitophagy, enhancing the disposal of damaged/aged mitochondria, thus improving muscle energy balance.[56]

Experimental studies have shown that treadmill exercise training attenuates the initiation and progression of cancer cachexia in mice,[57] and that both endurance and resistance exercise can modulate the inflammatory response in tumor-bearing rats.[58,59] In addition, it has been recently reported that voluntary wheel running may prevent cachexia and increase survival in tumor-bearing mice,[60] and also alleviate cisplatin-induced muscle wasting in mice undergoing chemotherapy.[61]

Is physical exercise feasible in cancer patients? During cancer, exercise programs are frequently difficult to implement and factors limiting the exercise capacity (such as chronic fatigue, anemia, cardiac dysfunction and other comorbidities) should be carefully considered.[62] Indeed, in a recent experimental study, 2 weeks of low-intensity endurance exercise did not improve, and even worsened, muscle wasting in mice bearing the C26 carcinoma (an experimental model of cancer cachexia associated with anemia and cardiac dysfunction). Conversely, erythropoietin (EPO) treatment in combination with exercise normalized hematocrit rescued atrophy of oxidative myofibers, prevented the oxidative to glycolytic shift of muscle fibers and induced the expression of the peroxisome proliferator activated receptor (PPAR)-γ coactivator-1α (PGC-1α), a factor involved in mitochondrial biogenesis and function.[63] These results suggest that exercise could be an effective tool to be included in the multimodal approach to cancer cachexia, provided the exercise programs are adapted to the individual needs and that comorbidities such as anemia are promptly detected and appropriately treated.

Exercise and nutrition: a strategic interaction? Nutrient and energy availability play an important role in the modulation of acute and chronic adaptations to both endurance and resistance training,[64] suggesting that an adequate nutritional support should be provided to patients in order to preserve the potential benefits of exercise.[62] *Vice versa*, unloading blunts the amino acid-induced increase in myofibrillar protein synthesis, further supporting the concept that nutrition and exercise may have potential additive effects,[65] although this aspect deserves further investigation in cancer cachexia. It is important to investigate which nutrients/nutraceuticals could boost the effect of exercise in cancer-related muscle wasting. In this respect, EPA in combination with endurance exercise has been shown to improve muscle mass and strength in mice bearing the Lewis lung carcinoma (LLC).[66] Unfortunately, data in humans with cancer are not available.

Is exercise cost-effective? Available evidence suggests that physical exercise may have beneficial effects on cancer patients during and after active treatment, such as improving quality of life and reducing fatigue.[67–70] According to a recent systematic review, both aerobic and resistance exercise, or a combination, may contribute to improving muscle strength in cancer patients more than usual care, while muscle mass would seem to be more favorably affected by resistance exercise, although supporting evidence in this respect is still insufficient. Moreover, many of the studies included in this systematic review were conducted in patients with early-stage cancer (the majority with breast and prostate cancer, and only a few with other solid tumors) and conclusions cannot be extended to patients with advanced diseases.[71] Of note, a recent Cochrane review pointed out that evidences from randomized controlled trials proving the safety and effectiveness of exercise in patients with cancer cachexia are still lacking. Indeed, available data do not allow establishing whether cancer patients included in studies testing the effect of exercise were affected by pre-cachexia or cachexia. Ongoing clinical trials, however, are exploring the potential benefits of exercise for cancer cachexia within a multimodal approach.[72]

In summary, considering the heterogeneity of cancer cachexia and the possible presence of comorbidities limiting exercise capacity, additional investigation would be necessary to test the effects of personalized exercise programs, possibly designed according to the principles of

training,[73] in order to optimize the safety and effectiveness of exercise prescriptions within the multimodal approach to cancer cachexia.

The role of pharmacologic treatments

The development of pharmacologic therapies for muscle wasting effects of cancer cachexia have been focused on improving appetite, modulating inflammation and interfering with anabolic and catabolic pathways involved in the modulation of skeletal muscle. In addition, novel suitable therapeutic targets are continuously emerging at the experimental level. No single agent, however, has yet been proven to be completely effective, underscoring the need to integrate pharmacologic therapies into a multimodal approach able to cope with the complex pathogenesis of cancer cachexia.[74]

Appetite stimulants. Several potential appetite stimulants have been tested to counteract cancer anorexia. A recent Cochrane review analyzed data on megestrol acetate, and concluded that it improves appetite and body weight in cancer patients, although it is associated with adverse events.[75] In addition, weight gain is mostly due to an increase in fat and water rather than in lean body mass (LBM), although data in experimental cancer cachexia suggest a possible effect on skeletal muscle.[76]

Cannabinoids have also been evaluated. In this regard, a phase III trial on advanced cancer patients did not show any significant difference on appetite with respect to placebo,[77] while a pilot study suggested some potential beneficial effects that should be tested in larger trials.[78]

Agents targeting inflammation. Since inflammation is a major driver of cancer-related muscle wasting, many anti-inflammatory agents have been evaluated in the last few years.

Non-steroidal anti-inflammatory drugs (NSAIDs) have been tested alone or in combination, and a recent systematic review concluded that they may improve body weight or LBM, although the evidence to recommend NSAIDs outside clinical trials is still insufficient and deserves further investigations.[79] Interestingly, NSAIDs are currently being studied within a multimodal approach for cancer cachexia that includes exercise and nutrition. Preliminary results (presented as abstract) of a multi-center, randomized phase II trial (pre-MENAC [ClinicalTrials.gov identifier: NCT01419145]) suggest that a multimodal cachexia intervention (including exercise, NSAID, energy-dense nutritional supplements combined with dietary advice) may improve weight in patients with incurable lung or pancreatic cancer *versus* standard of care. Based on these findings, a phase III trial called MENAC [ClinicalTrials.gov identifier: NCT02330926] is currently enrolling patients.[80]

Corticosteroids are potent anti-inflammatory drugs frequently used in cancer patients; results obtained in two randomized, placebo-controlled trials suggest that in the short term they may improve fatigue and appetite.[81,82] Extended therapy with corticosteroids, however, is not recommended since they may cause side-effects including muscle wasting.[83,84]

Thalidomide, an agent with immunomodulatory and anti-inflammatory properties, has also been tested in the last few years, despite its serious side-effects, but evidence is still insufficient to recommend this agent for the clinical management of cancer cachexia.[85–87]

A more selective anti-inflammatory approach has been attempted using monoclonal antibodies targeting cytokines, but inconsistent results have been reported from different studies.[20,88] Such discrepancies could be due, at least in part, to the variety and heterogeneity of the cytokines involved in different types of cancer and patients.[20] Despite these limitations, targeting cytokines may have some potential therapeutic effects on cancer cachexia, as suggested by recent trials using new biological agents[89] such as MABp1 (a first-in-class true-human monoclonal antibody targeting IL-1α).[90] Further clinical investigation would therefore be necessary to clarify the role of anti-cytokine blockade in cancer-related muscle wasting within a multimodal approach.[74]

Agents targeting muscle catabolic pathways. Much attention in the last few years has been given to the development of agents targeting myostatin and the activin type II B receptor (ActRIIB) pathway, a negative regulator of muscle mass, which is activated upon binding of myostatin as well as other transforming growth factor-β (TGF-β) family members, including Activin A and growth differentiation factor 11 (GDF-11).[88] Modulation of myostatin signaling was described in both cancer-bearing animals and

patients.[91,92] Blockade of this pathway with the administration of ActRIIB decoy receptors in experimental cancer cachexia has been shown to counteract muscle wasting, improve muscle strength and prolong survival without influencing tumor growth.[93,94] Unfortunately, bleeding issues associated with the use of decoy receptors in initial clinical trials on patients with muscular dystrophy caused the termination of these studies. However, more selective anti-ActRIIB antibodies such as Bimagrumab (BYM338) are under development and being tested in patients with lung or pancreatic cancer [ClinicalTrials.gov identifier: NCT01433263]. Moreover, a phase II trial is testing the myostatin-specific mAb LY2495655 in patients with pancreatic cancer [ClinicalTrials.gov identifier: NCT01505530].[88]

Inhibition of proteolytic pathways (such as the ubiquitin proteasome system) has also been investigated as a possible therapeutic strategy. However, the administration of bortezomib, a potent reversible and selective proteasome and NF-κB inhibitor, has not so far showed a beneficial effect on cancer-related muscle wasting.[95–97] By contrast, MG132, a different proteasome inhibitor, improved body and muscle weight loss in tumor-bearing mice, possibly due to a different mechanism of action of this drug compared to bortezomib.[98] However, it should be recognized that in human muscle, evidence of increased ubiquitin-mediated proteolysis during cancer cachexia is not as robust as that seen in animal models – this is particularly true for NSCLC.[99] Moreover, it has been observed in gastrointestinal cancer that the well-documented upregulation of markers of ubiquitin proteasome system activity[100,101] may occur for only a small window during the progression of cachexia.[102] This could in part be responsible for why proteasome inhibitors have largely failed in clinical trials. Taken together, the available evidence suggests that further studies are needed before the ubiquitin proteasome system may be definitely identified as a possible therapeutic target for muscle wasting in cancer.

$Beta_2$-agonists have also been evaluated as a potential anti-catabolic therapy for cancer cachexia, although their possible cardiovascular effects have limited their application. Researchers focused in particular on formoterol, a β_2-agonist with a high degree of selectivity for skeletal muscle β_2-receptors and a relatively low toxicity. In experimental cancer cachexia, formoterol has been shown to ameliorate muscle wasting,[103–105] without negatively altering heart function.[106] Formoterol fumarate has been tested also in combination with megestrol acetate in a single-arm, uncontrolled pilot study on a small cohort of advanced cachectic cancer patients. Although some encouraging results were reported for those completing the 8-week course, further investigations in larger and controlled randomized trials are necessary to better assess this treatment in cancer cachexia.[107]

Agents targeting muscle anabolic pathways. Extensive efforts during the last few years have been directed toward the study of anamorelin, an oral selective agonist of the ghrelin receptor GHSR-1a (growth hormone segretagogue receptor) with orexigenic and anabolic effects.[108,109] Ghrelin induces the release of growth hormone (GH), stimulates appetite, regulates energy homeostasis and decreases inflammation.[110,111] Based on the promising results obtained in several phase II studies,[112–114] anamorelin was recently tested in two large double-blind, phase III trials (ROMANA 1, $n = 484$; ROMANA 2, $n = 495$). In these trials, patients with incurable stage III/IV NSCLC and cachexia were randomized 2:1 to receive anamorelin 100 mg or placebo over 12 weeks. In both studies, anamorelin significantly improved LBM, body weight and anorexia-cachexia-related symptoms, but failed to significantly improve handgrip strength, a co-primary endpoint of the study.[115] In this regard, the lack of effect of anamorelin on muscle strength in face of improved LBM might reflect the not necessarily linear relationship between skeletal muscle mass and strength, the latter also depending on myofiber quality.[116,117] Moreover, in these studies food intake was not recorded and it is not known whether the improvement in anorexia translated into an adequate nutritional intake, which is likely to be important to support (and maybe enhance) the anabolic action of anamorelin.[118]

Patients who completed ROMANA 1 or ROMANA 2 trials had the option to continue their assigned treatment for another 12 weeks to further evaluate efficacy and safety of anamorelin (ROMANA 3 [ClinicalTrials.gov identifier: NCT01395914]). In this extension study, anamorelin treatment over 24 weeks was well tolerated and the incidence of adverse events was similar in both anamorelin- and placebo-treated patients.[119]

Besides anamorelin, other novel ghrelin agonists (such as macimorelin) are currently under investigation.[120]

Other emerging anabolic agents for the prevention and treatment of cancer-related muscle wasting are the selective androgen receptor modulators (SARM), a new class of non-steroidal, tissue-specific, anabolic drugs that can increase muscle mass and ameliorate physical function without the side-effects commonly associated with testosterone or other nonselective, synthetic anabolic steroids.[121] In particular, Enobosarm, an orally bioavailable SARM, was recently tested in a double-blind, randomized, controlled phase II trial on cancer patients who had at least 2% weight loss in the previous 6 months. Results obtained showed a significant increase, compared with baseline, in total LBM and in mean stair-climb power among patients who received enobosarm 1 mg and 3 mg, while no significant changes were observed for handgrip strength.[121] The 3 mg dose of enobosarm was next evaluated in two placebo-controlled, double-blind, phase III clinical trials, named POWER 1 and POWER 2 [ClinicalTrials.gov identifiers: NCT01355484, NCT01355497], in which stage III or IV NSCLC have been randomized to receive for 5 months an oral daily dose of enobosarm 3 mg or placebo at the initiation of first-line chemotherapy (platinum + taxane in POWER 1; platinum + non-taxane in POWER 2).[122] Preliminary results reported that enobosarm treatment was associated with an increase in LBM and stair-climb power (co-primary endpoints) in the POWER 1 trial, while in the POWER 2 trial there was only a significant increase in LBM.[123]

Many drugs, however, may affect both anabolism and catabolism. Espindolol (MT-102), for example, may decrease catabolism (through nonselective β-blockade), reduce fatigue and thermogenesis (through central 5-HT1a antagonism) and increase anabolism (through partial β_2-receptor agonism). The ACT-ONE phase II trial in stage III/IV NSCLC or colorectal cancer patients showed that espindolol 10 mg twice daily improved body weight, LBM and handgrip strength.[124]

New scenarios in pharmacological treatment. Insights into the molecular basis of cancer cachexia suggest that counteracting intracellular kinases such as the mitogen-activated protein kinase (MEK), the extracellular signal protein kinase (ERK) and the Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway,[125–127] could represent a promising approach. In experimental cancer cachexia, administration of PD98059, a MEK inhibitor able to block ERK activation, has been shown to restore myogenesis and attenuate muscle depletion and weakness.[125] Consistently, selumetinib, an MEK inhibitor with tumor-suppressive activity and inhibitory effects on IL-6 production, in a phase II trial induced gain of skeletal muscle in cholangiocarcinoma patients.[127] Pharmacologic or genetic inhibition of the JAK/STAT3 pathways has been reported to reduce muscle wasting in experimental cancer cachexia.[126] Ruxolitinib is an oral, potent and selective JAK1/2 inhibitor; use in a clinical trial on patients with myelofibrosis has been associated with an increase in body weight.[128] Currently, an open-label phase II trial [ClinicalTrials.gov identifier: NCT02072057] is investigating the safety and efficacy of ruxolitinib for the treatment of cachexia in patients with tumor-associated chronic wasting diseases.[26,120] Sunitinib, a tyrosine kinase inhibitor used for the treatment of renal cell carcinoma, has been shown to prevent experimental cancer cachexia by inhibiting STAT3 activation and muscle RING Finger 1 protein (MuRF1) upregulation in the skeletal muscle.[129] More controversial results are available for sorafenib, a multi-kinase inhibitor that has been proven effective in attenuating experimental cancer cachexia by inhibiting both STAT3 and ERK activity in the skeletal muscle,[129,130] but shown to cause muscle wasting in patients with advanced renal cell carcinoma.[131]

Targeting the alterations in fat and energy metabolism underlying cancer cachexia is also gaining attention as a potential therapeutic strategy. Recently, pharmacological inhibition of fatty acid oxidation by etoxomir (a specific inhibitor of carnitine palmitoyltransferase-1) has been shown to rescue muscle wasting in experimental cancer cachexia.[132] Inhibition of white adipose tissue browning, a process involved in increasing energy expenditure and thermogenesis, has also been shown to ameliorate experimental cancer cachexia.[133] Consistently, treatment with an antibody neutralizing the parathyroid-hormone-related protein (PTHrP), a tumor-derived factor promoting thermogenic gene expression, prevented adipose tissue loss and browning as well as muscle wasting and dysfunction in LLC-bearing mice.[134] Similar results were recently obtained by implanting the LLC in mice with fat-specific knockout of PTHR (the receptor for parathyroid hormone and PTHrP).[135]

Besides the aforementioned approaches, targeting mitochondrial dysfunction is emerging as another potential therapeutic opportunity to

normalize energy metabolism in catabolic conditions, but available data are still scanty.[136]

Exercise is an important regulator of mitochondrial dynamics and skeletal muscle metabolism, but training programs are not always easy to implement, therefore scientists are working on the development of exercise mimetics.[137] In this regard, the administration of the exercise mimetic 5-aminoimidazole-4-carboxamide-1-beta-D-ribofuranoside (AICAR), an adenosine monophosphate-activated protein kinase (AMPK) activator, has been shown to counteract cachexia and restore the autophagic flux in the skeletal muscle of C-26 bearing mice, similarly to rapamycin (an mTOR inhibitor able to trigger autophagy) and voluntary wheel running.[60]

Other novel agents targeting different molecular mechanisms are also currently under investigation in experimental cancer cachexia, and very promising results were recently reported for the administration of the histone deacetylase (HDAC) inhibitor AR-42[138] and the antibodies targeting the fibroblast growth factor-inducible 14 (Fn-14), a member of the TNF family.[139] Both treatments indeed prevented cancer cachexia and prolonged survival in tumor-bearing mice. It should be noted, however, that not all HDAC inhibitors share the same ability to treat cancer cachexia,[138,140] suggesting that AR-42 beneficial effects are presumably mediated by specific effects intrinsic to this drug, which at the moment are only partially understood.

Finally, modulation of gut microbiota has been recently proposed as a potential therapeutic opportunity to counteract cancer-related muscle wasting, but data available are still scarce and more insights on the mechanisms linking skeletal muscle homeostasis to gut microbiota are necessary to ascertain whether this could represent a suitable therapeutic target.[141]

Overall, experimental studies seem to indicate a vast array of promising therapeutic opportunities for cancer-related muscle wasting, but additional investigations are needed to better understand the therapeutic potential of all these new pharmacological approaches.

Conclusions and perspectives

No effective therapy against cancer cachexia is available at present. For this reason, it is mandatory to implement strategies aimed at preventing or at least delaying this condition. In this regard, the increasing knowledge about the molecular mechanisms underlying cancer-related muscle wasting has allowed the identification of several potential therapeutic targets and the development of many promising drugs, some of which reached the clinical trial phase. At the same time, however, it is becoming clear that a multimodal approach is mandatory to successfully manage patients with cancer cachexia. Another crucial point is the early recognition and treatment of the nutritional and metabolic alterations occurring during cancer. Several evidences, indeed, suggest that cancer patients have an exploitable anabolic potential. For this reason, adequate nutritional support should be provided to slow the wasting process. Along this line, exercise training, compatible with the exercise capacity of cancer patients, could represent another important tool to boost the anabolic effects of the nutritional support and to prevent the detrimental consequences of physical inactivity on muscle mass and function.

Additional clinical trials are therefore necessary in the next few years to optimize multimodal interventions to counteract cancer cachexia and deliver the best of care to patients.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Conflict of interest statement

The authors declare that there is no conflict of interest.

References

1. Muscaritoli M, Molfino A, Gioia G, *et al.* The "parallel pathway": a novel nutritional and metabolic approach to cancer patients. *Intern Emerg Med* 2011; 6: 105–112.
2. Fearon K, Strasser F, Anker SD, *et al.* Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol* 2011; 12: 489–495.
3. Fearon KC, Glass DJ and Guttridge DC. Cancer cachexia: mediators, signaling, and metabolic pathways. *Cell Metab* 2012; 16: 153–166.
4. Martin L, Birdsell L, Macdonald N, *et al.* Cancer cachexia in the age of obesity: skeletal

muscle depletion is a powerful prognostic factor, independent of body mass index. *J Clin Oncol* 2013; 31: 1539–1547.

5. Prado CM, Lieffers JR, McCargar LJ, *et al*. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. *Lancet Oncol* 2008; 9: 629–635.
6. Prado CM, Baracos VE, McCargar LJ, *et al*. Sarcopenia as a determinant of chemotherapy toxicity and time to tumor progression in metastatic breast cancer patients receiving capecitabine treatment. *Clin Cancer Res* 2009; 15: 2920–2926.
7. Tan BH, Birdsell LA, Martin L, *et al*. Sarcopenia in an overweight or obese patient is an adverse prognostic factor in pancreatic cancer. *Clin Cancer Res* 2009; 15: 6973–6979.
8. Lieffers JR, Bathe OF, Fassbender K, *et al*. Sarcopenia is associated with postoperative infection and delayed recovery from colorectal cancer resection surgery. *Br J Cancer* 2012; 107: 931–936.
9. Muscaritoli M, Bossola M, Aversa Z, *et al*. Prevention and treatment of cancer cachexia: new insights into an old problem. *Eur J Cancer* 2006; 42: 31–41.
10. Fearon K, Arends J and Baracos V. Understanding the mechanisms and treatment options in cancer cachexia. *Nat Rev Clin Oncol* 2013; 10: 90–99.
11. Johns N, Stephens NA and Fearon KC. Muscle wasting in cancer. *Int J Biochem Cell Biol* 2013; 45: 2215–2229.
12. Argilés JM, Busquets S, Stemmler B, *et al*. Cancer cachexia: understanding the molecular basis. *Nat Rev Cancer* 2014; 14: 754–762.
13. Ryan AM, Power DG, Daly L, *et al*. Cancer-associated malnutrition, cachexia and sarcopenia: the skeleton in the hospital closet 40 years later. *Proc Nutr Soc* 2016; 75: 199–211.
14. Villasenor A, Ballard-Barbash R, Baumgartner K, *et al*. Prevalence and prognostic effect of sarcopenia in breast cancer survivors: the HEAL Study. *J Cancer Surviv* 2012; 6: 398–406.
15. Otsuji H, Yokoyama Y, Ebata T, *et al*. Preoperative sarcopenia negatively impacts postoperative outcomes following major hepatectomy with extrahepatic bile duct resection. *World J Surg* 2015; 39: 1494–1500.
16. Harimoto N, Shirabe K, Yamashita YI, *et al*. Sarcopenia as a predictor of prognosis in patients following hepatectomy for hepatocellular carcinoma. *Br J Surg* 2013; 100: 1523–1530.
17. Gilliam LA and St Clair DK. Chemotherapy-induced weakness and fatigue in skeletal muscle: the role of oxidative stress. *Antioxid Redox Signal* 2011; 15: 2543–2563.
18. Vermaete N, Wolter P, Verhoef G, *et al*. Physical activity and physical fitness in lymphoma patients before, during, and after chemotherapy: a prospective longitudinal study. *Ann Hematol* 2014; 93: 411–424.
19. Biolo G, Cederholm T and Muscaritoli M. Muscle contractile and metabolic dysfunction is a common feature of sarcopenia of aging and chronic diseases: from sarcopenic obesity to cachexia. *Clin Nutr* 2014; 33: 737–748.
20. Mueller TC, Bachmann J, Prokopchuk O, *et al*. Molecular pathways leading to loss of skeletal muscle mass in cancer cachexia - can findings from animal models be translated to humans? *BMC Cancer* 2016; 16: 75.
21. Penna F, Busquets S and Argilés JM. Experimental cancer cachexia: evolving strategies for getting closer to the human scenario. *Semin Cell Dev Biol* 2016; 54: 20–27.
22. Fearon K, Argiles JM, Baracos VE, *et al*. Request for regulatory guidance for cancer cachexia intervention trials. *J Cachexia Sarcopenia Muscle* 2015; 6: 272–274.
23. Prado CM, Sawyer MB, Ghosh S, *et al*. Central tenet of cancer cachexia therapy: do patients with advanced cancer have exploitable anabolic potential? *Am J Clin Nutr* 2013; 98: 1012–1019.
24. Martin L and Sawyer MB. Cancer cachexia: emerging pre-clinical evidence and the pathway forward to clinical trials. *J Natl Cancer Inst* 2015; 107: djv322.
25. Muscaritoli M, Molfino A, Lucia S, *et al*. Cachexia: a preventable comorbidity of cancer. A T.A.R.G.E.T. approach. *Crit Rev Oncol Hematol* 2015; 94: 251–259.
26. Madeddu C, Mantovani G, Gramignano G, *et al*. Advances in pharmacologic strategies for cancer cachexia. *Expert Opin Pharmacother* 2015; 16: 2163–2177.
27. Martin L, Senesse P, Gioulbasanis I, *et al*. Diagnostic criteria for the classification of cancer-associated weight loss. *J Clin Oncol* 2015; 33: 90–99.
28. Chevalier S and Winter A. Do patients with advanced cancer have any potential for protein anabolism in response to amino acid therapy?

Curr Opin Clin Nutr Metab Care 2014; 17: 213–218.

29. Engelen MP, van der Meij BS and Deutz NE. Protein anabolic resistance in cancer: does it really exist? *Curr Opin Clin Nutr Metab Care* 2016; 19: 39–47.
30. Winter A, MacAdams J and Chevalier S. Normal protein anabolic response to hyperaminoacidemia in insulin-resistant patients with lung cancer cachexia. *Clin Nutr* 2012; 31: 765–773.
31. Deutz NE, Safar A, Schutzler S, *et al*. Muscle protein synthesis in cancer patients can be stimulated with a specially formulated medical food. *Clin Nutr* 2011; 30: 759–768.
32. Engelen MP, Safar AM, Bartter T, *et al*. High anabolic potential of essential amino acid mixtures in advanced nonsmall cell lung cancer. *Ann Oncol* 2015; 26: 1960–1966.
33. van Dijk DP, van de Poll MC, Moses AG, *et al*. Effects of oral meal feeding on whole body protein breakdown and protein synthesis in cachectic pancreatic cancer patients. *J Cachexia Sarcopenia Muscle* 2015; 6: 212–221.
34. Laviano A, Seelaender M, Sanchez-Lara K, *et al*. Beyond anorexia-cachexia. Nutrition and modulation of cancer patients' metabolism: supplementary, complementary or alternative anti-neoplastic therapy? *Eur J Pharmacol* 2011; 668(Suppl. 1): S87–S90.
35. Dewey A, Baughan C, Dean T, *et al*. Eicosapentaenoic acid (EPA, an omega-3 fatty acid from fish oils) for the treatment of cancer cachexia. *Cochrane Database Syst Rev* 2007; CD004597.
36. Pappalardo G, Almeida A and Ravasco P. Eicosapentaenoic acid in cancer improves body composition and modulates metabolism. *Nutrition* 2015; 31: 549–555.
37. Sánchez-Lara K, Turcott JG, Juárez-Hernández E, *et al*. Effects of an oral nutritional supplement containing eicosapentaenoic acid on nutritional and clinical outcomes in patients with advanced non-small cell lung cancer: randomised trial. *Clin Nutr* 2014; 33: 1017–1023.
38. Eley HL, Russell ST and Tisdale MJ. Effect of branched-chain amino acids on muscle atrophy in cancer cachexia. *Biochem J* 2007; 407: 113–120.
39. Laviano A, Muscaritoli M, Cascino A, *et al*. Branched-chain amino acids: the best compromise to achieve anabolism? *Curr Opin Clin Nutr Metab Care* 2005; 8: 408–414.
40. Bozzetti F and Bozzetti V. Is the intravenous supplementation of amino acid to cancer patients adequate? A critical appraisal of literature. *Clin Nutr* 2013; 32: 142–146.
41. Smith HJ, Mukerji P and Tisdale MJ. Attenuation of proteasome-induced proteolysis in skeletal muscle by {beta}-hydroxy-{beta}-methylbutyrate in cancer-induced muscle loss. *Cancer Res* 2005; 65: 277–283.
42. Aversa Z, Bonetto A, Costelli P, *et al*. β-hydroxy-β-methylbutyrate (HMB) attenuates muscle and body weight loss in experimental cancer cachexia. *Int J Oncol* 2011; 38: 713–720.
43. Mirza KA, Pereira SL, Voss AC, *et al*. Comparison of the anticatabolic effects of leucine and Ca-β-hydroxy-β-methylbutyrate in experimental models of cancer cachexia. *Nutrition* 2014; 30: 807–813.
44. Molfino A, Gioia G, Rossi Fanelli F, *et al*. Beta-hydroxy-beta-methylbutyrate supplementation in health and disease: a systematic review of randomized trials. *Amino Acids* 2013; 45: 1273–1292.
45. Stephens FB, Constantin-Teodosiu D and Greenhaff PL. New insights concerning the role of carnitine in the regulation of fuel metabolism in skeletal muscle. *J Physiol* 2007; 581: 431–444.
46. Silvério R, Laviano A, Rossi Fanelli F, *et al*. L-Carnitine induces recovery of liver lipid metabolism in cancer cachexia. *Amino Acids* 2012; 42: 1783–1792.
47. Laviano A, Molfino A, Seelaender M, *et al*. Carnitine administration reduces cytokine levels, improves food intake, and ameliorates body composition in tumor-bearing rats. *Cancer Invest* 2011; 29: 696–700.
48. Busquets S, Serpe R, Toledo M, *et al*. L-Carnitine: an adequate supplement for a multi-targeted anti-wasting therapy in cancer. *Clin Nutr* 2012; 31: 889–895.
49. Kraft M, Kraft K, Gärtner S, *et al*. L-Carnitine-supplementation in advanced pancreatic cancer (CARPAN)-a randomized multicentre trial. *Nutr J* 2012; 11: 52.
50. Madeddu C, Dessì M, Panzone F, *et al*. Randomized phase III clinical trial of a combined treatment with carnitine + celecoxib ± megestrol acetate for patients with cancer-related anorexia/cachexia syndrome. *Clin Nutr* 2012; 31: 176–182.
51. Gould DW, Lahart I, Carmichael AR, *et al*. Cancer cachexia prevention via physical exercise: molecular mechanisms. *J Cachexia Sarcopenia Muscle* 2013; 4: 111–124.

52. Camera DM, Smiles WJ and Hawley JA. Exercise-induced skeletal muscle signaling pathways and human athletic performance. *Free Radic Biol Med* 2016; 98: 131–143.
53. Mann S, Beedie C, Balducci S, *et al.* Changes in insulin sensitivity in response to different modalities of exercise: a review of the evidence. *Diabetes Metab Res Rev* 2014; 30: 257–268.
54. Vainshtein A, Grumati P, Sandri M, *et al.* Skeletal muscle, autophagy, and physical activity: the ménage à trois of metabolic regulation in health and disease. *J Mol Med* 2014; 92: 127–137.
55. Snijders T, Nederveen JP, McKay BR, *et al.* Satellite cells in human skeletal muscle plasticity. *Front Physiol* 2015; 6: 283.
56. Vainshtein A and Hood DA. The regulation of autophagy during exercise in skeletal muscle. *J Appl Physiol* (1985) 2016; 120: 664–673.
57. Puppa MJ, White JP, Velázquez KT, *et al.* The effect of exercise on IL-6-induced cachexia in the Apc (Min/+) mouse. *J Cachexia Sarcopenia Muscle* 2012; 3: 117–137.
58. Donatto FF, Neves RX, Rosa FO, *et al.* Resistance exercise modulates lipid plasma profile and cytokine content in the adipose tissue of tumour-bearing rats. *Cytokine* 2013; 61: 426–432.
59. Lira FS, Antunes Bde M, Seelaender M, *et al.* The therapeutic potential of exercise to treat cachexia. *Curr Opin Support Palliat Care* 2015; 9: 317–324.
60. Pigna E, Berardi E, Aulino P, *et al.* Aerobic exercise and pharmacological treatments counteract cachexia by modulating autophagy in colon cancer. *Sci Rep* 2016; 31; 6: 26991.
61. Hojman P, Fjelbye J, Zerahn B, *et al.* Voluntary exercise prevents cisplatin-induced muscle wasting during chemotherapy in mice. *PLoS One* 2014; 9: e109030.
62. Argilés JM, Busquets S, López-Soriano FJ, *et al.* Are there any benefits of exercise training in cancer cachexia? *J Cachexia Sarcopenia Muscle* 2012; 3: 73–76.
63. Pin F, Busquets S, Toledo M, *et al.* Combination of exercise training and erythropoietin prevents cancer-induced muscle alterations. *Oncotarget* 2015; 6: 43202–43215.
64. Smiles WJ, Hawley JA and Camera DM. Effects of skeletal muscle energy availability on protein turnover responses to exercise. *J Exp Biol* 2016; 219: 214–225.
65. Glover EI and Phillips SM. Resistance exercise and appropriate nutrition to counteract muscle wasting and promote muscle hypertrophy. *Curr Opin Clin Nutr Metab Care* 2010; 13: 630–634.
66. Penna F, Busquets S, Pin F, *et al.* Combined approach to counteract experimental cancer cachexia: eicosapentaenoic acid and training exercise. *J Cachexia Sarcopenia Muscle* 2011; 2: 95–104.
67. Speck RM, Courneya KS, Mâsse LC, *et al.* An update of controlled physical activity trials in cancer survivors: a systematic review and meta-analysis. *J Cancer Surviv* 2010; 4: 87–100.
68. Mishra SI, Scherer RW, Geigle PM, *et al.* Exercise interventions on health-related quality of life for cancer survivors. *Cochrane Database Syst Rev* 2012; 8: CD007566.
69. Mishra SI, Scherer RW, Snyder C, *et al.* Exercise interventions on health-related quality of life for people with cancer during active treatment. *Cochrane Database Syst Rev* 2012; 8: CD008465.
70. Puetz TW and Herring MP. Differential effects of exercise on cancer-related fatigue during and following treatment: a meta-analysis. *Am J Prev Med* 2012; 43: e1–e24.
71. Stene GB, Helbostad JL, Balstad TR, *et al.* Effect of physical exercise on muscle mass and strength in cancer patients during treatment–a systematic review. *Crit Rev Oncol Hematol* 2013; 88: 573–593.
72. Grande AJ, Silva V, Riera R, *et al.* Exercise for cancer cachexia in adults. *Cochrane Database Syst Rev* 2014; 11: CD010804.
73. Sasso JP, Eves ND, Christensen JF, *et al.* A framework for prescription in exercise-oncology research. *J Cachexia Sarcopenia Muscle* 2015; 6: 115–124.
74. Molfino A, Formiconi A, Rossi Fanelli F, *et al.* Cancer cachexia: towards integrated therapeutic interventions. *Expert Opin Biol Ther* 2014; 14: 1379–1381.
75. Ruiz Garcia V, López-Briz E, Carbonell Sanchis R, *et al.* Megestrol acetate for treatment of anorexia-cachexia syndrome. *Cochrane Database Syst Rev* 2013; 3: CD004310.
76. Argilés JM, Anguera A and Stemmler B. A new look at an old drug for the treatment of cancer cachexia: megestrol acetate. *Clin Nutr* 2013; 32: 319–324.
77. Strasser F, Luftner D, Possinger K, *et al.* 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* 2006; 24: 3394–3400.

78. Brisbois TD, de Kock IH, Watanabe SM, *et al.* Delta-9-tetrahydrocannabinol may palliate altered chemosensory perception in cancer patients: results of a randomized, double-blind, placebo-controlled pilot trial. *Ann Oncol* 2011; 22: 2086–2093.

79. Solheim TS, Fearon KC, Blum D, *et al.* Non-steroidal anti-inflammatory treatment in cancer cachexia: a systematic literature review. *Acta Oncol* 2013; 52: 6–17.

80. Kaasa S, Solheim T, Laird BJA, *et al.* A randomised, open-label trial of a Multimodal Intervention (Exercise, Nutrition and Anti-inflammatory Medication) plus standard care versus standard care alone to prevent / attenuate cachexia in advanced cancer patients undergoing chemotherapy. *J Clin Oncol* 2015; 33(Suppl.): abstract 9628.

81. Yennurajalingam S, Frisbee-Hume S, Palmer JL, *et al.* Reduction of cancer-related fatigue with dexamethasone: a double-blind, randomized, placebo-controlled trial in patients with advanced cancer. *J Clin Oncol* 2013; 31: 3076–3082.

82. Paulsen O, Klepstad P, Rosland JH, *et al.* Efficacy of methylprednisolone on pain, fatigue, and appetite loss in patients with advanced cancer using opioids: a randomized, placebo-controlled, double-blind trial. *J Clin Oncol* 2014; 32: 3221–3228.

83. Fardet L, Flahault A, Kettaneh A, *et al.* Corticosteroid-induced clinical adverse events: frequency, risk factors and patient's opinion. *Br J Dermatol* 2007; 157: 142–148.

84. Hasselgren PO, Alamdari N, Aversa Z, *et al.* Corticosteroids and muscle wasting: role of transcription factors, nuclear cofactors, and hyperacetylation. *Curr Opin Clin Nutr Metab Care* 2010; 13: 423–428.

85. Reid J, Mills M, Cantwell M, *et al.* Thalidomide for managing cancer cachexia. *Cochrane Database Syst Rev* 2012; 4: CD008664.

86. Davis M, Lasheen W, Walsh D, *et al.* A phase II dose titration study of thalidomide for cancer-associated anorexia. *J Pain Symptom Manage* 2012; 43: 78–86.

87. Yennurajalingam S, Willey JS, Palmer JL, *et al.* The role of thalidomide and placebo for the treatment of cancer-related anorexia-cachexia symptoms: results of a double-blind placebo-controlled randomized study. *J Palliat Med* 2012; 15: 1059–1064.

88. Cohen S, Nathan JA and Goldberg AL. Muscle wasting in disease: molecular mechanisms and promising therapies. *Nat Rev Drug Discov* 2015; 14: 58–74.

89. Ma JD, Heavey SF, Revta C, *et al.* Novel investigational biologics for the treatment of cancer cachexia. *Expert Opin Biol Ther* 2014; 14: 1113–1120.

90. Hong DS, Hui D, Bruera E, *et al.* MABp1, a first-in-class true human antibody targeting interleukin-1α in refractory cancers: an open-label, phase 1 dose-escalation and expansion study. *Lancet Oncol* 2014; 15: 656–666.

91. Costelli P, Muscaritoli M, Bonetto A, *et al.* Muscle myostatin signalling is enhanced in experimental cancer cachexia. *Eur J Clin Invest* 2008; 38: 531–538.

92. Aversa Z, Bonetto A, Penna F, *et al.* Changes in myostatin signaling in non-weight-losing cancer patients. *Ann Surg Oncol* 2012; 19: 1350–1356.

93. Zhou X, Wang JL, Lu J, *et al.* Reversal of cancer cachexia and muscle wasting by ActRIIB antagonism leads to prolonged survival. *Cell* 2010; 142: 531–543.

94. Benny Klimek ME, Aydogdu T, Link MJ, *et al.* Acute inhibition of myostatin-family proteins preserves skeletal muscle in mouse models of cancer cachexia. *Biochem Biophys Res Commun* 2010; 391: 1548–1554.

95. Jatoi A, Alberts SR, Foster N, *et al.* Is bortezomib, a proteasome inhibitor, effective in treating cancer-associated weight loss? Preliminary results from the North Central Cancer Treatment Group. *Support Care Cancer* 2005; 13: 381–386.

96. Chacon-Cabrera A, Fermoselle C, Urtreger AJ. Pharmacological strategies in lung cancer-induced cachexia: effects on muscle proteolysis, autophagy, structure, and weakness. *J Cell Physiol* 2014; 229: 1660–1672.

97. Penna F, Bonetto A, Aversa Z, *et al.* Effect of the specific proteasome inhibitor bortezomib on cancer-related muscle wasting. *J Cachexia Sarcopenia Muscle* 2016; 7: 345–354.

98. Zhang L, Tang H, Kou Y, *et al.* MG132-mediated inhibition of the ubiquitin-proteasome pathway ameliorates cancer cachexia. *J Cancer Res Clin Oncol* 2013; 139: 1105–1115.

99. Op den Kamp CM, Langen RC, Minnaard R, *et al.* Pre-cachexia in patients with stages I-III

non-small cell lung cancer: systemic inflammation and functional impairment without activation of skeletal muscle ubiquitin proteasome system. *Lung Cancer* 2012; 76: 112–117.

100. Bossola M, Muscaritoli M, Costelli P, *et al.* Increased muscle ubiquitin mRNA levels in gastric cancer patients. *Am J Physiol Regul Integr Comp Physiol* 2001; 280: R1518–R1523.

101. Bossola M, Muscaritoli M, Costelli P, *et al.* Increased muscle proteasome activity correlates with disease severity in gastric cancer patients. *Ann Surg* 2003; 237: 384–389.

102. Khal J, Hine AV, Fearon KC, *et al.* Increased expression of proteasome subunits in skeletal muscle of cancer patients with weight loss. *Int J Biochem Cell Biol* 2005; 37: 2196–2206.

103. Busquets S, Figueras MT, Fuster G, *et al.* Anticachectic effects of formoterol: a drug for potential treatment of muscle wasting. *Cancer Res* 2004; 64: 6725–6731.

104. Busquets S, Toledo M, Sirisi S, *et al.* Formoterol and cancer muscle wasting in rats: effects on muscle force and total physical activity. *Exp Ther Med* 2011; 2: 731–735.

105. Toledo M, Busquets S, Penna F, *et al.* Complete reversal of muscle wasting in experimental cancer cachexia: additive effects of activin type II receptor inhibition and β-2 agonist. *Int J Cancer* 2016; 138: 2021–2029.

106. Toledo M, Springer J, Busquets S, *et al.* Formoterol in the treatment of experimental cancer cachexia: effects on heart function. *Cachexia Sarcopenia Muscle* 2014; 5: 315–320.

107. Greig CA, Johns N, Gray C, *et al.* Phase I/II trial of formoterol fumarate combined with megestrol acetate in cachectic patients with advanced malignancy. *Support Care Cancer* 2014; 22: 1269–1275.

108. Esposito A, Criscitiello C, Gelao L, *et al.* Mechanisms of anorexia-cachexia syndrome and rational for treatment with selective ghrelin receptor agonist. *Cancer Treat Rev* 2015; 41: 793–797.

109. Zhang H and Garcia JM. Anamorelin hydrochloride for the treatment of cancer-anorexia-cachexia in NSCLC. *Expert Opin Pharmacother* 2015; 16: 1245–1253.

110. Molfino A, Formiconi A, Rossi Fanelli F, *et al.* Ghrelin: from discovery to cancer cachexia therapy. *Curr Opin Clin Nutr Metab Care* 2014; 17: 471–476.

111. Reano S, Graziani A and Filigheddu N. Acylated and unacylated ghrelin administration to blunt muscle wasting. *Curr Opin Clin Nutr Metab Care* 2014; 17: 236–240.

112. Garcia JM, Friend J and Allen S. Therapeutic potential of anamorelin, a novel, oral ghrelin mimetic, in patients with cancer-related cachexia: a multicenter, randomized, double-blind, crossover, pilot study. *Support Care Cancer* 2013; 21: 129–137.

113. Garcia JM, Boccia RV, Graham CD, *et al.* Anamorelin for patients with cancer cachexia: an integrated analysis of two phase 2, randomised, placebo-controlled, double-blind trials. *Lancet Oncol* 2015; 16: 108–116.

114. Temel J, Bondarde S, Jain M, *et al.* Efficacy and safety results from a phase II study of anamorelin HCl, a ghrelin receptor agonist, in NSCLC patients (Abstract 5e01). *J Cachexia Sarcopenia Muscle* 2013; 4: 295–343.

115. Temel JS, Abernethy AP, Currow DC, *et al.* Anamorelin in patients with non-small-cell lung cancer and cachexia (ROMANA 1 and ROMANA 2): results from two randomised, double-blind, phase 3 trials. *Lancet Oncol* 2016; 17: 519–531.

116. Mitchell WK, Williams J, Atherton P, *et al.* Sarcopenia, dynapenia, and the impact of advancing age on human skeletal muscle size and strength; a quantitative review. *Front Physiol* 2012; 3: 260.

117. Chen L, Nelson DR, Zhao Y, *et al.* Relationship between muscle mass and muscle strength, and the impact of comorbidities: a population-based, cross-sectional study of older adults in the United States. *BMC Geriatr* 2013; 13: 74.

118. Muscaritoli M. Targeting cancer cachexia: we're on the way. *Lancet Oncol* 2016; 17: 414–415.

119. Currow D, Temel J, Fearon K, *et al.* A safety extension study of anamorelin in advanced non-small cell lung cancer patients with cachexia: ROMANA 3. *J Clin Oncol* 2015; 33(Suppl.): abstract e20715.

120. Dingemans AM, de Vos-Geelen J, Langen R, *et al.* Phase II drugs that are currently in development for the treatment of cachexia. *Expert Opin Investig Drugs* 2014; 23: 1655–1669.

121. Dobs AS, Boccia RV, Croot CC, *et al.* Effects of enobosarm on muscle wasting and physical function in patients with cancer: a double-blind, randomised controlled phase 2 trial. *Lancet Oncol* 2013; 14: 335–345.

122. Crawford J, Prado CM, Johnston MA, *et al.* Study design and rationale for the phase 3 clinical development program of enobosarm, a selective androgen receptor modulator, for the

prevention and treatment of muscle wasting in cancer patients (POWER Trials). *Curr Oncol Rep* 2016; 18: 37.

123. Crawford J, Johnston MA, Taylor RP, *et al.* Enobosarm and lean body mass in patients with non-small cell lung cancer. *J Clin Oncol* 2014; 32(Suppl. 5): abstract 9618.

124. Stewart Coats AJ, Ho GF, Prabhash K, *et al.* Espindolol for the treatment and prevention of cachexia in patients with stage III/IV non-small cell lung cancer or colorectal cancer: a randomized, double-blind, placebo-controlled, international multicentre phase II study (the ACT-ONE trial). *J Cachexia Sarcopenia Muscle* 2016; 7: 355–365.

125. Penna F, Costamagna D, Fanzani A, *et al.* Muscle wasting and impaired myogenesis in tumor bearing mice are prevented by ERK inhibition. *PLoS One* 2010; 5: e13604.

126. Bonetto A, Aydogdu T, Jin X, *et al.* JAK/STAT3 pathway inhibition blocks skeletal muscle wasting downstream of IL-6 and in experimental cancer cachexia. *Am J Physiol Endocrinol Metab* 2012; 303: E410–E421.

127. Prado CM, Bekaii-Saab T, Doyle LA, *et al.* Skeletal muscle anabolism is a side effect of therapy with the MEK inhibitor: selumetinib in patients with cholangiocarcinoma. *Br J Cancer* 2012; 106: 1583–1586.

128. Harrison C, Kiladjian JJ, Al-Ali HK, *et al.* JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis. *N Engl J Med* 2012; 366: 787–798.

129. Pretto F, Ghilardi C, Moschetta M, *et al.* Sunitinib prevents cachexia and prolongs survival of mice bearing renal cancer by restraining STAT3 and MuRF-1 activation in muscle. *Oncotarget* 2015; 6: 3043–3054.

130. Toledo M, Penna F, Busquets S, *et al.* Distinct behaviour of sorafenib in experimental cachexia-inducing tumours: the role of STAT3. *PLoS One* 2014; 9: e113931.

131. Antoun S, Birdsell L, Sawyer MB, *et al.* Association of skeletal muscle wasting with treatment with sorafenib in patients with advanced renal cell carcinoma: results from a placebo-controlled study. *J Clin Oncol* 2010; 28: 1054–1060.

132. Fukawa T, Yan-Jiang BC, Min-Wen JC, *et al.* Excessive fatty acid oxidation induces muscle atrophy in cancer cachexia. *Nat Med* 2016; 22: 666–671.

133. Petruzzelli M, Schweiger M, Schreiber R, *et al.* A switch from white to brown fat increases energy expenditure in cancer-associated cachexia. *Cell Metab* 2014; 20: 433–447.

134. Kir S, White JP, Kleiner S, *et al.* Tumour-derived PTH-related protein triggers adipose tissue browning and cancer cachexia. *Nature.* 2014; 513: 100–104.

135. Kir S, Komaba H, Garcia AP, *et al.* PTH/PTHrP receptor mediates cachexia in models of kidney failure and cancer. *Cell Metab* 2016; 23: 315–323.

136. Attaix D, Pichard C and Baracos VE. Muscle wasting: is mitochondrial dysfunction a key target? *Curr Opin Clin Nutr Metab Care* 2015; 18: 213–214.

137. Penna F, Pin F, Ballarò R, *et al.* Novel investigational drugs mimicking exercise for the treatment of cachexia. *Expert Opin Investig Drugs* 2016; 25: 63–72.

138. Tseng YC, Kulp SK, Lai IL, *et al.* Preclinical investigation of the novel histone deacetylase inhibitor AR-42 in the treatment of cancer-induced cachexia. *J Natl Cancer Inst* 2015; 107: djv274.

139. Johnston AJ, Murphy KT, Jenkinson L, *et al.* Targeting of Fn14 prevents cancer-induced cachexia and prolongs survival. *Cell* 2015; 162: 1365–1378.

140. Bonetto A, Penna F, Minero VG, *et al.* Deacetylase inhibitors modulate the myostatin/follistatin axis without improving cachexia in tumor-bearing mice. *Curr Cancer Drug Targets* 2009; 9: 608–616.

141. Varian BJ, Goureshetti S, Poutahidis T, *et al.* Beneficial bacteria inhibit cachexia. *Oncotarget* 2016; 7: 11803–11816.