Cachexia: A progressing systemic consequence of unresolved disease

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General introduction

The wasting condition, cachexia, is currently understood as a terminal systemic manifestation of unresolved disease, including cancer, organ failure, or infections, where it contributes to significant morbidity and mortality. In this setting, cachexia is characterized by end organ damage and overt loss of fat and muscle tissue that is refractory to therapeutic intervention. It remains unclear how the organism arrives at this state as the induction process and mechanistic progression of cachexia are under-researched stages in pathogenesis. Medical disciplines and basic research tend to lean towards identifying and targeting the localized root causes of disease and overlook the progressive systemic effects that ultimately cause death. Understanding the early processes by which an unresolved response to a perturbation or disease affects the whole organism may offer a novel paradigm that expands medical care to include holistic preservation and reconstitution of the host, in addition to treatment of the disease. Refocusing academic efforts away from terminal cachexia to the processes that lead to cachexia development may enable discoveries of new therapeutic approaches. In this review, we summarize the evidence for the progressive nature of cachexia, approaches to study cachexia, and make suggestions for a conceptual framework in which to develop cachexia-related discoveries and advance them to therapeutic interventions.

Epidemiology

With an estimated annual mortality of 2 million people worldwide, cachexia is one of the main contributors to morbidity and mortality (Farkas et al. 2013). When the term Cachexia ("*kakos hexis* = bad state") was first coined in early Greek literature, it was considered a consequence of disease or aging leading to a lack of physical "conditioning" and, therefore, of broad relevance across seemingly different underlying causalities (special interest box 1- history of cachexia). Recent epidemiological data continue to associate cachexia with several seemingly unrelated, but potentially converging conditions. Patients with cancer, such as lung, colon and pancreatic cancer have a high risk of developing cachexia, sometimes estimated to be as high as 90%. Cachexia is also common in patients with end-stage renal failure (ESRF)(25-50%), chronic obstructive pulmonary disease (COPD)(25%), chronic heart failure, AIDS, sepsis, and rheumatologic disorders (Bachmann et al. 2008; Dewys et al. 1980; Fearon et al. 2011; Monfared et al. 2009; Wagner 2008; Zanders et al. 2022). Given its incidence and prevalence, its universally negative impact on prognosis and quality of life (QoL), and the additional contribution to poor tolerance of and consequently reduced response to treatment, cachexia presents an area of major global public health burden and an urgent unmet need.

What patients with cachexia have in common is an unresolved underlying condition - a "wound that does not heal". They suffer from involuntary weight loss, more specifically muscle and fat loss, in the context of seemingly paradoxical anorexia, coupled with fatigue and anhedonia. The apparent multiplicity of conditions that lead to cachexia suggest that either multiple processes converge on a terminal state or multiple early diseases converge on a common pathway of disease progression to a terminal state. In both cases, an unresolved continued process consequential to one or several distinct disease-mediated systemic perturbations may drive a systemic effect that results in cachexia (Fig. 1) (special interest box 2- model of disease progression to cachexia). A lack of certainty about the underlying mechanisms driving

the process of cachexia requires additional work to identify the initiators and understand how they alter the communication and function within and among multiple organ systems in the body.

Diseased cell, tumor, and host-derived cachexia mediators

The process of inflammation has long been associated with cancer cachexia. We recognize that the term inflammation may have different meaning to different readers. Injury to a tissue from variety of insults (e.g., trauma, infection) result in the clinical phenotype of inflammation - features recognized since antiquity include red, hot, swollen, painful, and loss of function. The neuro-humoral output from a local injury, including a rapid elevation in circulating cytokines generated by the activated immune system can be transmitted systemically. This triggers broader molecular, cellular, neuronal and behavioral responses that result in a more systemic inflammatory phenotype.

As we highlight below, much evidence implicates a multiplicity of primarily immunologically-derived, pro-inflammatory circulating factors that serve as strong drivers of the systemic syndrome of cachexia. However, there are likely multiple other initiating factors that can cause or contribute to cancer cachexia. Some of the currently known initiating factors involve persistent and pathological inflammation, others involve an imbalance between circulating factors that maintain skeletal muscle mass, and another group seems primarily to affect the central nervous system (CNS).

The evidence that unresolved inflammation is a driver of one type of cachexia (DeBoer et al. 2009; Dusselier et al. 2019; Flint et al. 2016; Li and Reid 2000; Oldenburg et al. 1993; Schakman et al. 2012) spans a multiplicity of inflammatory factors detected in tissues and in the circulation of patients with cachexia (Fig. 2A) (Argilés et al. 2014; Biswas and Acharyya 2020b, 2020c; Fearon, Arends, and Baracos 2013). They have mostly been investigated at times when weight loss was detectable and their longitudinal trajectory frequently remained unclear. However, given that these factors can be produced directly by disease-driving cells (e.g., infected, damaged or cancerous cells), by cells recruited to the microenvironment of the cellular lesion (e.g., fibroblasts and/or immune cells), and/or by other tissues at organismal level (Fig. 2B), processes that may amplify each other, their changes will be dynamic, which is likely relevant to progression of disease to cachexia.

One of the first factors associated with cachexia, historically termed *cachexin*, was tumor necrosis factor alpha (TNF-alpha), a pro-inflammatory cytokine with muscle and fat tissue catabolic (Paval et al. 2022; Tisdale 2008) and anorexic (Sonti, Ilyin, and Plata-Salamán 1996) effects. TNF-alpha is associated with cancer cachexia and other cachexia-inducing inflammatory conditions such as rheumatoid arthritis. Trials in patients with cachexia either blocking the TNF-alpha receptor or neutralizing TNF-alpha itself (NCT00046904, NCT00060502, NCT00244192) have not detected clinical benefit (Wiedenmann et al. 2008).

Interleukin-6 (IL-6) superfamily members, including IL-6 and leukemia inducible factor (LIF), are among the most commonly reported cachectogenic factors. Elevated circulating levels of IL-6 and its upstream regulator interleukin 1 (IL-1), have been widely associated with cancer-associated cachexia in animal models and in humans (Paval et al. 2022; Rupert et al. 2021). In mice, IL-6 alters metabolic organ functions such as reducing the ketogenic capacity of the liver to respond to diminished food intake (Flint et al. 2016) and promoting adipose tissue browning (Petruzzelli et al. 2014). In non-cachectic conditions, IL-6 is

recognized to act on the brain (Erta, Quintana, and Hidalgo 2012) and influence energy balance (Wallenius et al. 2002). While reversibility of some of the IL-6 effects has been demonstrated in murine models, a clinical trial in patients with lung cancer and cachexia that blocked IL-6 signaling using ALD518, a humanized anti-IL-6 antibody (NCT00866970), showed only mild improvements, suggesting that late interventions may not be clinically beneficial in this case (Bayliss et al. 2011).

The chemokine CCL2 (monocyte chemoattractant protein-1; MCP-1) that directs CCR2-driven migration of macrophages and can be produced by endothelial cells, fibroblasts, and macrophages has also been linked to cachexia in mice (Burfeind et al. 2020). CCL2 promotes liver inflammation, neuroinflammation, weight loss, and metabolic changes in muscle and WAT (Bose and Cho 2013; Kanda et al. 2006; Luciano-Mateo et al. 2020; Obstfeld et al. 2010; Sell et al. 2006; Le Thuc et al. 2016; Weisberg et al. 2006). These reports indicate that persistent CCL2 production may sustain inflammatory changes, resulting in systemic metabolic alterations and reduced food intake that leads to cancer cachexia.

Lipocalin-2 (LCN2), a glycopeptide involved in coordinating the host response to inflammation (Flo et al. 2004; Moschen et al. 2017) has been described in animal models as having an anorexigenic effect by acting through the central melanocortin system within the hypothalamus (Mosialou et al. 2021; Petropoulou et al. 2020). LCN2 plays a role in driving appetite suppression in pancreatic cancer cachexia (Olson et al. 2021). Melanocortin 4 receptor antagonists protect from the cachexia of chronic kidney disease and the melanocortin 3 receptor is relevant for lean body mass distribution (Lam et al. 2021), suggesting that these pathways may have translational potential for anabolic interventions in cachexia.

This selection of example inflammatory molecules illustrates that no single factor has emerged as the sole causative agent for cachexia. While some connectivity may be relevant, in that CCL2 activation of macrophages may drive IL-6 production or vice versa, and similar interactions are demonstrated for TNF-alpha, it is likely that there are several upstream inflammatory cascades that ultimately converge on the clinical phenotype of cachexia. In addition, no single cellular cause has emerged for cachexia. For example, tumor composition has proven to have a systemic effect in triggering cachexia. Changes in cancer-associated fibroblast (CAFs), such as loss of myofibroblastic CAFs (myCAFs) and enrichment of IL-6 producing CAFs (iCAFs), could lead to cachexia in mouse models of pancreatic cancer (Rhim et al. 2014; Steele et al. 2021). Since iCAFs are dependent on the activation of JAK/STAT signaling pathway for their formation in pancreatic ductal adenocarcinoma (PDAC), JAK/STAT inhibitors that cause loss of iCAFs may ameliorate the cachectic phenotype (Biffi et al. 2019). Similarly, depletion of fibroblast activation protein-α-positive (FAP+) stromal cells leads to loss of muscle mass and cachexia (Roberts et al. 2013; Tran et al. 2013), and genetic depletion of alpha-smooth muscle actin-positive (alphaSMA+) cells, which include myofibroblastic CAFs, following tumor formation leads to a reduction in body weight in mouse models of pancreatic cancer (Ozdemir et al. 2014).

Much research has been performed on circulating and local factors of muscle homeostasis. Activation of the activin receptor AcvR2B in skeletal muscle by agonists such as activin A or myostatin powerfully induces the catabolic process of autophagy and proteolysis of skeletal muscle cells (Aversa et al. 2012; Busquets et al. 2012; Walton et al. 2019). Treatment with a soluble Activin A decoy receptor has been

suggested as an intervention in preclinical work (Queiroz et al. 2022; Zhou et al. 2010). Follistatin deficiency secondary to fibroblast depletion in the muscle is a potent inducer of cachexia (Cite Roberts EW and Fearon DT JEM 2013).

Metabolic mediators may also drive inflammation-independent cachexia subtypes. For example, tumor-secreted insulin growth factor binding proteins (IGFBPs) can stimulate catabolism in nutrient-rich tissues by blocking insulin/IGF-1 signaling and promoting insulin resistance (Ding et al. 2021). Among individuals without cancer, insulin resistance reduces metabolic flexibility, impairs muscle protein synthesis, and increases energy expenditure (Klaman et al. 2000; Wang et al. 2006). In cross-sectional studies, patients with lung cancer often have insulin resistance (Winter, MacAdams, and Chevalier 2012). However, it is unknown how longitudinal changes in insulin resistance, metabolic flexibility, muscle protein synthesis, and energy expenditure relate to changes in muscle mass, muscle quality, and weight loss in patients with cancer.

Cancer also imposes systemic metabolic changes that have not yet been clearly linked to a specific factor. For example, lung cancer can induce diurnal and metabolic changes in the liver that promote gluconeogenesis and inhibit fatty acid metabolism (Goncalves et al. 2018; Masri et al. 2016; Verlande et al. 2021). These effects may be due to hepatic inflammation (Karsli-Uzunbas et al. 2013; Poillet-Perez et al. 2021), or could be secondary to elevated levels of catabolic hormones such as glucocorticoids (Keller 1993). Furthermore, unbiased metabolomic assessments have identified correlations between weight loss and plasma amino acids and phospholipids of unknown source (Cala et al. 2018; Miller et al. 2019; Yang et al. 2018).

Centrally acting circulating molecules such as GDF-15 have been shown to induce cachexia in a reversible manner. GDF-15 is produced in response to cell stress by epithelial and immune cells and may have evolved to mediate food aversion in response to toxin exposure (Patel et al. 2019). It binds exclusively to a small number of neurons in the brain stem, outside the blood brain barrier (Breen et al. 2021; Hsu et al. 2017; Lockhart, Saudek, and O'Rahilly 2020) that express its specific receptor GFRAL. In cancer, GDF-15 levels are elevated and associated with reduced food intake and body weight in humans and mice (Breit, Brown, and Tsai 2021; Lockhart et al. 2020). Moreover, GDF-15 potently activates the hypothalamic-pituitary adrenal (HPA) axis and increases circulating glucocorticoid levels (Cimino et al. 2021). Since glucocorticoids are powerfully anti-anabolic in skeletal muscle (Braun and Marks 2015), GDF-15 could, via the brain, contribute to the two key features of cachexia, i.e., reduced food intake and selective loss of skeletal muscle. Preclinical murine studies with GDF-15 blocking antibodies and GFRAL blockade protected against loss of food intake and weight and even produced reversal of cachexia (Suriben et al. 2020).

Reciprocal interactions between the cachexia-inducing disease and the host organ systems

The physiology of cancer progression may be seen as a continuously perturbed state that involves behavioral changes, dysregulation of the neuroendocrine system including changes in sleep and circadian rhythm, systemic immune dysregulation, and skeletal muscle and adipose tissue wasting, all of which occur in patients and model systems with cachexia (Fig. 1, Fig. 2A and B) (Masri et al. 2016; Verlande et

al. 2021). While the cachexia-inducing disease process may be locally confined, cachexia is a systemic disease manifestation affecting the whole organism. In fact, the defining features of cachexia, in particular weight loss, affect the host organism, irrespective of the underlying localized disease that is causally linked to the changes. Given that all hallmarks of cachexia are systemically mediated, the underlying mechanisms of cause and propagation likely involve modulation of networks that affect all body systems and inter-organ and organ-body communication. Molecular and cellular or inflammatory mediators, hormones, circulating metabolites and the peripheral nervous system are capable of systemic dissemination of signals, and are thus candidate main mediators of the whole-body signaling cascade leading to cachexia. It is likely and increasingly recognized that the response pattern of the host organism displays connectivity between organ systems and the underlying causative disease process. One way to approach this connectivity is from the perspective of the energetic imbalance, i.e., a relative lack of energy intake compared to energy expenditure of the system, that ultimately results in overt weight loss during terminal cachexia.

The central nervous system (CNS) has primacy for the control of energy homeostasis and the hypothalamus is emerging as an area of inflammation sensing with potential relevance to cachexia-inducing disease. The central melanocortinergic system of the hypothalamus, and specifically MC3R, play a role in sensing the nutritional status of the body and co-coordinating the acquisition and retention of calories and their disposition into processes such as growth, reproduction and the acquisition of lean mass (Lam et al. 2021). Lack of an appropriate response to peripheral inputs leads to diminished appetite and promotes catabolic stimuli (i.e., reduced energy intake, increased energy expenditure, increased muscle proteolysis, and adipose tissue wasting). Moreover, the CNS regulates endocrine organ function through the release of hormones. Systemic release of glucocorticoids is a well described event in cachexia that occurs in response to the activation of the hypothalamic–pituitary–adrenal (HPA) axis by stressors and induces skeletal muscle atrophy and catabolism (Braun et al. 2011, 2013). Malfunction of the hypothalamic–pituitary–gonadal (HPG) axis significantly decreases testosterone levels, contributing to several cachexia symptoms like fatigue, weight loss and muscle catabolism (Burney and Garcia 2012).

In the periphery, hepatic inflammation and/or activation of the acute phase response are biosynthetically and bioenergetically costly, and when left unresolved this contributes to the systemic metabolic and energetic imbalance. All aspects of intermediary metabolism are affected including carbohydrate, protein, fat, and energy metabolism. Elevated levels of glucocorticoids and increased gluconeogenesis, but inhibited fatty acid metabolism and suppressed ketogenesis in the liver are other examples of cancer-induced metabolic changes (Cala et al. 2018; Goncalves and Farooki 2022; Masri et al. 2016; Miller et al. 2019; Verlande et al. 2021; Yang et al. 2018). Insulin resistance is often a feature of cachexia, leading to reduced metabolic flexibility, impaired muscle protein synthesis, and increased energy expenditure (Biolo, Fleming, and Wolfe 1995; Blonk et al. 1994; Galgani, Moro, and Ravussin 2008; Petersen and Shulman 2018; Ravussin et al. 1985; Smith et al. 2018; Weyer, Bogardus, and Pratley 1999; Wong, McAuley, and Trinh 2018). Skeletal muscle (SkM) and white adipose tissue (WAT) are the body's main reservoirs for amino acids and lipids, respectively, and both inflammation and imbalances of factors that maintain muscle mass can increase rates of protein breakdown (MacDonald et al. 2015). During times of stress when food intake is low and nutrient demands increase, such as in starvation associated with cancer cachexia, SkM and WAT activate catabolic processes and distribute stored nutrients to the rest of the body

so that they can then be used for energy generation and promote survival. If left unresolved, however, progressive catabolism of SkM and WAT leads to physical deterioration, and death. Tumors seemingly alter host nutrient availability, exchange, and use to favor their own metabolic demands. Identifying the fundamental nature of this tumor-mediated host metabolic reprograming will reveal new tools for the diagnosis and treatment of cancer cachexia.

Members of the intestinal microbiota can coordinate hormonal communication between adipose tissue and skeletal muscle to protect from cachexia during inflammatory and infection settings (Schieber et al. 2015). Furthermore, changes in the intestinal microbiome ecology, known as dysbiosis, has been shown to influence cachexia due to gut barrier dysfunction (Ni et al. 2021), and intestinal pathogens can limit the cachectic response by controlling inflammatory signaling along the gut-brain axis to regulate feeding behavior (Rao et al. 2017). Thus, manipulation of beneficial bacteria in the gut microbiota has been explored as treatment (Varian et al. 2016). Since the circadian clock plays an important role in modulating fat metabolism, its disruption in the context of cachexia is associated with lipid metabolism imbalance (Tsoli et al. 2014).

This suggests a potential sequence of events which lends itself to systematic scientific study: a local insult promotes a persistent systemic response if the original insult is not cleared. This response promotes central reduction in nutrient intake behavior and altered peripheral nutrient processing, leading to changes in body composition, fatigue and functional decline, which in turn diminishes tolerance to therapeutic interventions targeting the underlying disease, and ultimately to death.

Host and iatrogenic contributors to cachexia

The interaction between cachexia molecular drivers and organ responsiveness occurs in a host organism. Individuals may have genetic or acquired characteristics that protect from or predispose to cachexia. This is an important dimension for understanding cachexia, because genetic or acquired cachexia related traits will synergize or antagonize with the progression of disease-induced cachexia. Modestly powered studies have, so far, not identified genetic loci that predispose to cachexia. However, experiments in cachectic animals treated with dextran sulfate sodium to cause intestinal injury have demonstrated that strains purchased from different suppliers or vivarium rooms have more or less rapid onset of body weight loss and variations in the degree of skeletal muscle atrophy (Schieber et al. 2015). Variations in the intestinal microbiota ecology were demonstrated to be sufficient for these differences, while the contribution of genetic differences remains unknown.

Sexual dimorphism

Distinct body composition, fat distribution, insulin sensitivity, glucose and lipid metabolism, and energy substrate utilization are fundamental biological differences in the metabolism of males and females. Innate metabolic divergences such as these may well influence the susceptibility and development of metabolic syndromes such as cachexia. Nevertheless, much of the preclinical and clinical research of cachexia has focused on its consequences in skeletal muscle tissue. Muscle depletion is more prevalent in males than in females with cancer (Baracos et al. 2010; Wallengren et al. 2015) and cachectic male patients have increased muscle fatigue and decreased handgrip strength compared to cachectic female

patients (Norman et al. 2012; Stephens et al. 2012). This difference could be attributed to estrogen status, since estrogen signaling is a regulator of muscle contractility and anabolism (Pöllänen et al. 2010), and can impact morphology, fatigability and function of myofibers. Furthermore, strength loss of postmenopausal females can be recovered with hormone replacement therapy (Phillips et al. 1993), and hypogonadism has been associated to cachexia development (Del Fabbro et al. 2010). In addition, estrogens modulate inflammation (Li et al. 2022), and while pro-inflammatory cytokines such as IL-6 induce and accelerate cachexia in tumor-bearing male mice, IL-6 does not impact tumor-bearing female mice (Hetzler et al. 2015; White et al. 2011). Estrogens have a direct effect on hypothalamic neurons regulating physical activity and energy expenditure in females (Krause et al. 2021; van Veen et al. 2020). Future studies must identify the precise immune factors and molecules that are influenced by biological sex with the long-term goal of personalizing treatment of cachexia.

However, different cachexia susceptibility in males and females may also be due to sexually dimorphic distribution and metabolic preference of muscle fiber types. Type II muscle fibers account for the majority of male muscle mass and have a glycolytic phenotype, whereas females have predominantly Type I muscle fibers that are oxidative (Staron et al. 2000). Data from preclinical models and patients with cancers suggests that Type II glycolytic myofibers are more sensitive to cancer-induced muscle wasting than Type I myofibers (Wang and Pessin 2013). Thus, this inherent fiber difference is associated with differential fatigue susceptibility in males and females, and although direct causality has not been established it may drive some of the sex-dependent differential responses during muscle wasting and cachexia.
Sex-driven differences lead to treatment effectiveness being limited to males or females in preclinical models (Queiroz et al. 2022) and are potentially relevant for differential outcome in clinical interventions in patients with cancer. A better understanding of the role of sexual dimorphism in cachexia is needed and would benefit the development of therapeutics that improve quality of life and survival.

Aging
A gradual decrease in muscle mass and strength is estimated to start at the age of 30, with the rate of decline increasing after 60 years of age, and by the age of 80, 30% of muscle mass is estimated to be lost (Frontera et al. 2000; Lexell 1995). Moreover, decrease in appetite and anhedonia are associated with aging and could be explained by changes in various neurotransmitters and brain circuitry, and hormones, which may then result in the frequently observed food intake decline (Lampe, Kahn, and Heeren n.d.; Leibowitz 1988; Rolls 1992).

A major feature of aging is a loss of physiological reserve and coordinated tuning of the organism, which would synergize with the predisposition to cachexia (special interest box 2). This is perhaps also captured in the concept of "Inflammaging", the sustained increased levels of circulating pro-inflammatory molecules, which is associated with diminishing organ function, and progressive sarcopenia (loss of muscle: from Greek *sarx*: flesh, *penia*: poverty). In murine models, aging causes an energetic imbalance towards catabolism that interferes with homeostatic signaling, and ultimately causes high susceptibility to chronic morbidity, disability, frailty, and premature death (Ferrucci and Fabbri 2018). Data from the Rotterdam Study demonstrates that the neutrophil-to-lymphocyte ratio (NLR) is an independent risk indicator for survival in the elderly, and even in the general population over the age of 45 (Fest et al. 2019).

This highlights the clinical value of NLR as an early marker of disease progression (Petruzzelli and Ferrer et al. 2022) and suggests that it may be a proxy measure of the aging process. Recent studies link metabolic dysregulation and chronic aging-associated inflammation in a reversible manner (He et al. 2020; Minhas et al. 2021), opening new interventional avenues for anti-aging treatments.

Other factors, including reduced peripheral or central responsiveness for nutritional and lean body homeostasis may synergize with disease processes in aging and cachexia. Altogether, the phenotype and processes associated with old age mirrors those observed in patients with end-stage cachexia, pointing to converging biological phenomena and underlying mechanisms that occur at different rates and may potentiate each other, an area that warrants further research.

Anti-cancer therapy-induced cachexia
Anatomical obstructions of the gastrointestinal tract secondary to tumor progression, malabsorption due to infections or treatment side effects, surgical- or radiotherapy-induced alterations of the digestive system that result in strictures or removal of organ parts that aid nutrient uptake may all contribute to the whole-body susceptibility of significant wasting due to caloric deficiency. These may negatively synergize with the molecular mechanisms that cause cachexia. Some anti-cancer treatments, such as chemotherapy, can cause muscle wasting, weakness, and fatigue in patients, thus exacerbating cachexia and worsening prognosis (Mitsunaga, Kasamatsu, and Machii 2020; da Rocha et al. 2019). Mechanisms underlying the cachectogenic effect of chemotherapeutic drugs may include upregulation of ERK1/2 and p38 MAPKs (Barreto et al. 2016; Murphy et al. 2022), loss of molecular motor protein MyHC-II (Amrute-Nayak et al. 2021), production of reactive oxygen species (ROS) that impair myotube morphometry (Rybalka et al. 2018), systemic inflammation and production of pro-inflammatory cytokines that induce skeletal muscle atrophy (Braun et al. 2011), and glucocorticoid release (Braun et al. 2014). In fact, Dexamethasone, a synthetic glucocorticoid used as a supportive care co-medication for patients with cancer, induces muscle atrophy and dysfunction when used long-term (Cea et al. 2016; Ma et al. 2003). Chemotherapy-induced increase in circulating GDF-15 peptide causes anorexia, nausea and emesis (Breen et al. 2020). These symptoms may be exacerbated by an underlying decreased glomerular filtration rate (GFR) in chronic kidney disease (CKD), or organ failure in the elderly. For example, endogenous formaldehyde toxicity induced GDF-15 production in the proximal renal tubule and thereby cachexia in a murine model of Cockayne syndrome A (Mulderrig et al. 2021). Moreover, symptoms of emesis may be treated/prevented with Dexamethasone, as it is a well-established effective antiemetic drug for patients receiving chemotherapy, and thus induce a positive feedback loop that accelerates wasting. However, administration of Dexamethasone reduces IL-6 secretion, ameliorates inflammation in muscle cells, and promotes appetite (Chang et al. 2021; Quante et al. 2008). This warrants further investigation, as glucocorticoids may have a dose-dependent and dose scheduling dependent effect on skeletal muscle and the cachectic phenotype.

Early disease progression to terminal cachexia

To date, perhaps led by the literal interpretation of *hexis* (state), definitions and research of cachexia focus on contrasting health with end-stage (terminal) cachexia. More recently, the pre-cachectic state has been

recognized. However, in principle a successive chain of events must occur that connects the healthy state with terminal cachexia. As listed above, molecular, organ, and host level contributory factors and aspects are emerging. A better understanding of the exact hierarchical sequence of events and functional roles are necessary to guide the attempts to treat cachexia successfully or prevent its onset. For example, the early dynamics of tumor-host interaction, the pattern of change for circulating cachectogenic factors and metabolites, and the organ-specific changes should be causally resolved over time (Figure 3).

In the clinic and in mice, evidence of activation of the liver acute phase response can be detected long before overt weight loss and development of cachexia is observed (Li et al. 2018). In some, but not all patients who eventually develop cachexia, elevations of circulating C-reactive protein (CRP), a key marker of systemic inflammation and a response gene of IL-6, is detected at earlier stages of cancer and shows a strong relationship with functional decline in patients with cachexia (Laird et al. 2011). Likewise, an elevated Neutrophil-to-Lymphocyte ratio (NLR) is an early biological event in cancer, and neutrophilia may play an adaptive role in host metabolic homeostasis during cancer progression and directly influence weight loss (Petruzzelli and Ferrer et al. 2022).

Modest increases in glucose oxidation and desensitization to insulin have also been frequently observed in patients with cancer and can become more notable with cancer progression towards cachexia. These processes are driven by cytokines such as TNF-alpha, IL-1 and IL-6, and hormones such as glucocorticoids, which accelerate whole-body catabolism and lead to changes in body composition (Hansell, Davies, and Burns 1986; Keller 1993).

The patterns of progression for inflammation-independent cachexia are not established. However, they are likely to contribute to the increase over time of fatigue, depression and anhedonia, a cluster of symptoms and behavioral changes in the cachectic syndrome that contribute to diminished wellbeing in patients (Laird et al. 2011). Understanding the progressive sequence of events that lead to cachexia, their relationship to the normal biology of the body, their dynamics, and their effect on the causal disease state are essential for diagnosis, stratification, prevention, and therapy of cachexia.

Prevention and reversal of cachexia

Cachexia is preventable and reversible. Patients with early-stage cancer or with infections do not develop cachexia if they are cured. In murine models, excision of cachexia-inducing tumors at the stage of systemic cachexia leads to recovery of the mice. Case reports of patients with cachexia, who respond strongly to treatment of the underlying disease (infection or cancer), demonstrate recovery of lean body mass. However, as seen in the case of the clinical trials to date (special interest box 4 - The clinical trial landscape in cachexia), reversibility of cachexia, especially if the treatment is aimed at preventing the end organ damage of body fat loss and skeletal muscle atrophy, is a great challenge.

An argument can be made for early intervention because cachexia prevents patients with advanced cancer from getting adequate treatments (Biswas and Acharyya 2020a). Most patients with terminal cachexia are too weak to tolerate standard doses of anticancer therapies and instead, succumb to accelerated death resulting from respiratory and cardiac failure due to weakened diaphragm and cardiac muscles. As a consequence, a substantial portion of deaths in advanced cancer stem not necessarily from

cancer itself, but from cachexia (Baracos et al. 2018) (Figure 2). Anti-cachexia treatments may synergize with cancer-directed treatments to the benefit of patients. A specific therapeutic example could be the synergy of patient reconditioning and normalization of HPA axis function in the context of cancer immunotherapy, for example by administration of anti-GDF15 treatment.

The multiple triggers of cancer cachexia and the amalgam of metabolic conditions that result from a tumor-initiated imbalance in whole body metabolism also suggest some value in exploring diet. Clinical guidelines for nutrition support during cachexia mostly focus on the latter and end stages of disease (Arends et al. 2021) and research approaches to nutrition and cachexia typically test a defined meal or supplement strategy (Nakajima 2021). A better understanding of the early dynamics in tumor versus host metabolism is thus vital to the design of optimally targeted nutrition support earlier in disease process. Blunt nutritional interventions, such as a ketogenic diet (Barrea et al. 2020), may disrupt tumor metabolism and/or synergize with chemotherapy (Wallace et al. 2019), but on the other hand may challenge the host metabolism (Flint et al. 2016). Total parental nutrition has had minimal or no effect in delaying cachexia in small trials (Amano et al. 2021; Grubbs, Rogers, and Cameron 1979), perhaps indicating that nutrient utilization is impaired in addition to nutrient uptake. Additional clarity with respect to nutrient-gene interactions, the gut microbiota, the circadian clock, and biological rhythms in feeding and metabolism must also be considered.

Dimensions for enhanced cachexia research and care

The underlying mechanisms that drive the multifactorial processes involved in the development, as well as the longitudinal timeline of cachexia are poorly understood, hence limiting the identification of treatments directed to prevent and reverse cachexia. Clinical trials evaluating treatments for cachexia to date have faced discrepancies in recognition of clinically relevant outcomes and have had to make assumptions with regard to time of enrollment of patients, which usually are in very advanced stages of the disease. Generalizability of therapeutic approaches that do not consider disease site or specific weight loss criteria may also lead to lack of power to detect the impact and effect size necessary to achieve clinical benefit.

Glaring gaps in our understanding of disease mechanism and longitudinal course are likely to be the root of suboptimal endpoints, enrolment and dosing of patients in failed clinical trials. Compounding this further, as cachexia manifests non-uniformly across all patients, there may be multiple cachexia subtypes. Moreover, the general lack of mechanistic knowledge with paired biomarkers is a barrier to linking the right patient to the most effective clinical trial and potential treatment. It is also not clear if all disease mechanisms that trigger cachexia (e.g., cancer, infection etc.) do so the same way. It is also curious and perhaps informative that not every cancer patient develops cachexia. Given the urgent necessity of a deeper and appropriate interpretation of phased disease progression into cachexia in order to refine the design of clinical trials, preclinical guidance of clinical research is essential. Mechanistic biomarker-driven patient stratification, better longitudinal understanding of the process leading to end stage cachexia and refined trial design may improve therapeutic developments (Supplement Table 1).

In addition to longitudinal tracking of circulating molecules and underlying disease with repeat sampling, the distribution and utilization of nutrients and the composition of lean body mass and organs can be monitored longitudinally in pre-clinical and clinical research using radiological methods. Utilizing this approach for research and care in cancer cachexia is prudent, because in the clinic, computed tomography (CT) is used for routine surveillance of tumor burden in cancer care. From these routine scans, cross sectional muscle area size at the height of third lumbar vertebra (L3) correlate with whole-body muscle and adipose tissue volumes and their analyses can be automated for reproducible routine measurement in trials and care (Cespedes Feliciano et al. 2020; Faron et al. 2019; Mourtzakis et al. 2008; Shen et al. 2004). Dynamic metabolic tracking offered by magnetic resonance imaging (MRI) and by positron emission tomography (PET) offers further research and care advances: for example, functional MRI of the brain has been used to demonstrate that pre-treatment dysfunction in executive networks is associated with post-treatment fatigue and cognitive dysfunction more strongly than receipt of chemotherapy (Askren et al. 2014). MRI and PET have also been used to track choline and glucose uptake in the brain and lungs and depletion of triglycerides as well as altered liver gluconeogenesis in murine cancer models. In patients, tumor glucose uptake positively correlates with energy expenditure (Mitamura et al. 2011) and weight loss (Grabinska et al. 2015), while low liver uptake of glucose associates with poor cachexia-associated survival (Nakamoto et al. 2019). New and sensitive (x40 fold improvement) total-body PET scanners that can image the full body in a single scan and measure multiple metabolic substrates bring new possibilities to image dynamic metabolic networks and identify interactions between organs, with examples including tumor-liver-muscle or brain-gut axes, as well as to image other metabolic pathways such as beta-oxidation in BAT, fatty acid synthesis in the tumor and liver, and the Cori and Cahill cycles in the liver and muscle (Cherry et al. 2018; Witney and Lewis 2017). Radiological imaging, therefore, has potential for early detection of the metabolic alterations that precede changes in body composition. These new imaging approaches may also be applied to monitoring the effectiveness of new interventions in cachexia.

More specific and concrete categorization of cachexia populations, a deeper understanding of the molecular and physiologic underpinnings of each cachexia subtype, and evidence of how clinical and functional metrics change over time are urgently needed to advance the field. Large prospective observational trials in the clinic and correlative deep phenotyping and mechanistic sequential research in pre-clinical models, both focused on understanding the natural trajectory of cachexia, would meet this unmet need and inform more targeted, more precise, and hopefully more positive cachexia clinical trials of the future (Figure 4).

At a patient care level, the view of cachexia as a unique entity that can be treated with one standard approach is oversimplified. The current definition of cachexia is sensitive but not specific (Fearon et al. 2011), which leads to ineffective enrolment in clinical trials. Data from cross-sectional and retrospective studies suggest that distinct subtypes of cachexia with variable clinical phenotypes exist (K. C. Fearon, Voss, and Hustead 2006; Kays et al. 2018; Laird et al. 2011). Moreover, cachexia may appear indistinguishable from other clinical entities, such as unexplained weight loss, malnutrition, sarcopenia, or frailty. These conditions are often overlapping in an individual. More specific and concrete categorization of cachexia populations, a deeper understanding of the molecular and physiologic

underpinnings of each cachexia subtype (genetic, microenvironment and histologic), and evidence of how clinical and functional metrics change over time are urgently needed to advance the field. Rather than broadening the scope of cachexia trials, cachexia intervention trials should be more focused in terms of the target population and trial endpoints.

In terms of trial operation, most cachexia clinical trial programs enroll patients who have experienced >5% body weight loss (Garcia et al. 2015; Temel, Abernethy, et al. 2016). Weight loss, however, does not fully correlate with skeletal muscle loss (Roeland et al. 2017), nor does it fully characterize the effect of cachexia on physical functioning, quality of life, and overall survival (K. C. Fearon et al. 2006). Moreover, weight loss is a late-onset manifestation of cachexia, therefore, the whole-body metabolism is likely to have already been reprogrammed at the time of enrolment (Caro et al. 1987; Faubert, Solmonson, and DeBerardinis 2020; Groop et al. 1989; Hardee, Montalvo, and Carson 2017; Pereira et al. 2013). Interventions most likely to succeed have to be delivered promptly at cancer diagnosis when patients are in the early stages of cachexia; however, there continues to be no effective biomarkers for this state.

Though important efforts, trials evaluating multimodal interventions are difficult to conduct, onerous to patients in regard to adherence, and difficult to interpret measured benefits and/or risks of each intervention. Large prospective longitudinal trials focused on understanding the natural trajectory of cachexia would meet this unmet need and inform more targeted, more precise cachexia clinical trials of the future. Currently underway, the REVOLUTION study is a longitudinal observational study recruiting patients from a palliative care service with advanced cancer following changes in body composition, function, quality of life and inflammatory markers (Patton et al. 2021).

There is a lack of agreement on the endpoints for clinical trials on cancer cachexia treatments (Crawford 2017). It remains uncertain if bodyweight per se represents an endpoint that is sufficiently clinically meaningful (Roeland et al. 2020; Solheim et al. 2018). Notably, in one study using computerized tomography (CT), the traditional definition of >5% body weight loss underestimated cachexia at 56.6% while CT based body composition analysis detected tissue loss of >5% in 81% of patients (Kays et al. 2018). Endpoints that directly reflect how patients feel, function, or survive are most informative (Kluetz et al. 2016). Historically, regulatory agencies have required co-primary endpoints that quantify lean tissues and objectively measured physical functioning for cancer cachexia treatment indications (Crawford et al. 2016). Enobosarm and anamorelin (Temel, Abernethy, et al. 2016) are examples of drugs that showed improved lean body mass but no changes in physical function and were consequently not approved by the FDA (Dobs et al. 2016). Recently, a composite endpoint approach has been adopted that combines a measure of body habitus (e.g., body weight or body composition) with a patient-reported outcome (NCT03743964)(Hickish et al. 2017). Such a composite endpoint approach could enable the quantification of clinical benefit across various types of interventions (e.g., lifestyle, pharmacotherapy, etc.) in a clinically meaningful manner.

Robustly addressing these challenges will reduce common barriers to developing and approving effective interventions for cachexia prevention and treatment (Figure 4). These discoveries would dramatically enhance the provision of evidence-based, patient-oriented cancer care. The foundation research is

instrumental, but outcome work in chronic disease management has demonstrated the benefit from the involvement of an informed care team in patient support. A cachexia-focused clinical effort should thus not be solely focused on interventions. Education of a multidisciplinary team, awareness of malnutrition and other conditions that could "mask" as cachexia, and close collaborations with the teams that address the relevant driver condition of cachexia are essential for best care. This should also consider the involvement and support of patient caregivers and social networks.

Conclusion

While some aspects of cachexia have been illuminated, much work remains in understanding the molecular, cellular, tissue, and organism mechanistic sequences that lead from health to such an advanced systemic condition. Understanding this process is expected to bring health benefits impacting many diseases. The combination of pre-clinical and clinical research and the understanding of unifying and distinct processes that drive the initiation and progression of cachexia will enable better clinical intervention and patient-centered care in the years to come.

SPECIAL INTEREST BOXES:

1. Historic perspective of cachexia

Early references to hexis (condition) can be found in Xenophon's Memorabilia 3.12 and Plato's Gorgias 450a6, both dated to the first half of the 4th century BCE, where athletic and military fitness are discussed and euexia ("good condition") is contrasted to kachexia ("bad condition" from now on spelled cachexia). The Corpus Hippocraticum (earliest texts from the 5th century BCE) gives a description of the characteristic wasting in combination with ascites: "flesh is consumed and becomes water….the abdomen fills with water; the feet and legs swell; the shoulders, clavicles, chest, and thighs melt away" and also lists kachexia as afflicting old people (aphorismoi 3.31.3). Aristoteles names kachexia as a reason for loose flesh (Ethica Nicomachea 1129a20, 4th century BCE) and identifies the cachectic state as a consequence of a progressive failure to distribute nutriment and blood (de partibus animalium 668b5) as well as a consequence of disease (Topica 113b36: Topica 157b20) leading to "lack of strength" (Divisiones Aristoteleae 61.23). Further references can be found in Diocles, Med. Fragmenta 43b.5 (=Pseudo-Plutarch, Placita philosophorum 5.13) and Theophrastus, Fragmenta 9.5.6; 9.6.5; 9.15.2; 9.17.2 (4./3. C. BCE) and extensive consideration regarding hexis (here understood as the muscular composition of the body) including connections to diet form part of Galen's Art of Medicine (2nd c. CE).

Additional connections to disease in the form of "consumption" are found in the 1st century AD to describe cachexia secondary to terminal tuberculosis (Aretaeus of Cappadocia) and in writings by Celsus who identifies different categories, for example one where "the body is not nourished, and since something is naturally ever leaving it, while nothing succeeds in its place, a most extreme emaciation takes place"; and another that "the Greeks call cachexia, where the condition of the body is bad; and on this account all the nutriment becomes putrid"(Bennani-Baiti and Walsh 2009). During the romantic period of the 19th century TB-induced cachexia became widely recognized with specialist sanatoriums that focused on supportive care. William Cullen Bryant captured the terminal diagnosis in his poem "Consumption" (1867). This disease association of cachexia to cancer was extended to cancer by Butler (1906), who describes "cancer cachexiae" as characterized by "debility, emaciation, anemia, and a dirty yellowish-brown or brown-green complexion"(Bennani-Baiti and Walsh 2009). The similarities were by Taylor (1915) "There is however, nothing that is distinctive about cancerous cachexia. Any of the known changes and a similar picture may be produced by other diseases… The symptoms of the cachexia are gradual but progressive…The emaciation is a late symptom…with the loss of appetite, and nausea"(Bennani-Baiti and Walsh 2009). A graphic description (albeit without use of the term) associated with terminal cancer can be found in the poem "Mann und Frau gehen durch die Krebsbaracke" by the physician Gottfried Benn (1912).

In summary, cachexia is historically understood as a group of conditions characterized by progressive loss of lean body mass that can be caused by disease or aging, an understanding that is partially reflected in the most recent consensus definition for cancer cachexia: a multifactorial syndrome characterized by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support"(Fearon et al. 2011).

2. Mathematical model of disease associated conditional changes that lead to terminal illness/cachexia

Here we consider a simple abstract model for cachexia that focuses on the interaction between biological perturbation of physiology and patient condition. The model attempts to account for both the observed dynamics of recovery from a perturbation in the context of generally good condition (perturbed healthy organism) and the abrupt worsening of condition frequently observed in terminal cachexia (perturbed already deconditioned organism).

The model considers the interaction of two idealized variables x, denoting the physiological deconditioning of the patient (where we use the convention that larger values indicate worse condition), and y, which indicates the degree of perturbation and response to the perturbation induced. We assume that the normal equilibrium condition of the patient is governed by a balance between some constant process of deconditioning and a homeostatic mechanism that attempts to restore healthy condition, but that the ability of this homeostatic mechanism to promote recovery lessens as a function of worsening condition. Thus, at sufficiently poor condition, these normally homeostatic mechanisms become counter-productive and serve only to further worsen condition. We assume that the organism's response to a perturbation also worsens condition, and that the equilibrium level of response to the perturbation is governed by the balance between a basal homeostatic activity and a response that clears the causes of perturbation (healing or recovery) at a certain rate. These assumptions can be encapsulated in the following system of equations:

$$\frac{dx}{dt} = 1 - rx\left(1 - \frac{x}{d}\right) - y$$
$$\frac{dy}{dt} = b(c - y)$$

where the parameter $r>0$ controls the strength of homeostatic reconditioning (and deconditioning), $d>0$ determines the point beyond which homeostatic mechanisms further degrade condition, $b>0$ sets the time scale over which a transient perturbation resolves, and $c>0$ controls the basal level of homeostasis.

This system of equations displays two different sets of qualitative behaviors depending on the basal level of homeostatic activity, c (e.g., inflammation). For low basal inflammation levels, c< (r d)/4 -1, the system behaves much as one would expect in a healthy individual. The dynamics show two fixed points (potential equilibria), Fig. 5A (left). The first of these fixed points is a stable equilibrium that displays low values for x and y, and corresponds to a stable set-point that the system will tend to return to under moderate perturbations. Figure B (left) shows the trajectory after a perturbation of this type, where a sudden increase in biological response such as inflammation (e.g., due to infection or a cancer that is cured) decays rapidly and produces a transient worsening of condition followed by a complete recovery. In this regime, there is all a second fixed point, which is a saddle point (a type of unstable fixed point). This saddle point lies on the dividing line between perturbations to condition and/or inflammation that result in a successful recovery (i.e., which result in a return to the stable point), versus trajectories with ever worsening condition corresponding death.

As c increases, we see that the basal level of responsiveness, for example in the form of inflammation, at the stable fixed point also increases, and that the stable fixed point and the saddle point move closer together, Fig. 5A (center), until at the critical value c =(r d)/4 -1 the stable fixed point and the saddle point

collide and annihilate each other in what is known as a saddle-node bifurcation (Strogatz 1994). As a result, for c >(r d)/4 -1, the dynamics have no stable fixed point, so that all trajectories ultimately lead to a continuing worsening of condition, corresponding to terminal cachexia, Fig. 5A (right).

Fig. 5B (right) explores the predictions of this model for cancer-induced cachexia. Specifically, we model cancer-induced perturbation as a linearly increasing value for the basal level of perturbation, c. As c increases, the observed level of the relevant perturbation slowly increases and condition slowly worsens until c reaches the critical value (vertical dashed line), after which there is a sudden rapid worsening of condition. Importantly, the degree of perturbation-induced response due to infection, cancer, or aging that is sufficient to induce terminal cachexia (Fig. 5B, right), may often be well-tolerated in a healthy individual if only experienced transiently (Fig. 5B, left). Factors that lead to perturbation could also be stresses such as chemotherapy, surgery, or starvation, in concordance with the clinical observation that low performance status (a clinical consensus approach to capture condition in a set of categorical variables) is a contraindication for such interventions.

3. Established model systems for cachexia research

While human sampling can't capture the gradual transition, research using pre-clinical models can be used for that purpose. Well-characterized animal models are needed to demonstrate the efficacy of prospective treatments and to continue to explore etiologies of disease, potentially identifying new therapeutic targets (Figure 6).

Thus far *in vivo* pre-clinical models of cachexia have been of use to investigate multiple aspects of disease, such as higher energy expenditure, which has been extensively described in the C26 mouse model of colorectal cancer cachexia (Tsoli et al. 2012); and brown adipose tissue (BAT) thermogenic activity, which, despite being present in only 7% of patients with cancer (Becher et al. 2021), is greater in cachectic rats with Yoshida sarcoma (Oudart et al. 1995). Browning of white adipose tissue (WAT) has been described in multiple mouse models, including genetically engineered mouse models (GEMMs) of lung, pancreatic and skin cancer, diethylnitrosamine (DEN)-induced model of liver cancer, and subcutaneous models of melanoma (B16), lung (LLC) and colorectal (C26) cancers. IL-6 inhibition prevents browning and weight loss in the K5-SOS and the C26 model (Kir et al. 2014; Molfino et al. 2022; Petruzzelli et al. 2014). Measurements of glucose uptake flux by tumors and tissues in the MAC16 model led to identification of the tumor as the second major consumer of glucose, only after the brain. MAC16 tumors also have a higher cycling flux through the triglyceride-fatty acid cycle, but protein synthesis rates are unchanged (Beck and Tisdale 2004; Mulligan and Tisdale 1991; Plumb et al. 1991). These findings demonstrate a direct impact of the tumor on major nutrition in the host.

Studies in various *in vivo* models describe severe systemic hypoglycemia, impaired hepatic ketogenesis, increased plasma triglycerides, VLDL and LDL, and modified ceramides as the main metabolic consequences of cancer cachexia in the host, making them potential therapeutic targets for prevention and reversal of cancer cachexia (Das et al. 2011; Flint et al. 2016; López-Soriano et al. 1997; McDevitt and Tisdale 1992; Morigny et al. 2020; O'Connell et al. 2008; Tanaka et al. 1990).

The fruit fly *Drosophila* has emerged as an attractive model to address some of the outstanding questions in cachexia research because of 1) The conservation of signaling pathways and hormonal control of metabolism (Leopold and Perrimon 2007); 2) The tools available (Ugur, Chen, and Bellen 2016); and 3) The availability of organ wasting/cachexia models (Bilder et al. 2021; Dionne, Ghori, and Schneider 2003; Liu et al. 2022). A wealth of genetic tools is available for *Drosophila* studies of organ wasting. In particular, new cachectic factors can be identified using genome-wide tissue-specific RNAi or CRISPR screens. In addition, tissue-specific proximity labeling methods using biotin ligases can identify secreted factors from various tissues (Droujinine et al. 2021). Importantly, several Drosophila tumor models, based on the expression of oncogenes or loss of tumor suppressors in tissues such as the gut, imaginal discs, in either larvae and adults, are available (Bilder et al. 2021; Liu et al. 2022). Already, studies of these models have identified tumor-derived factors involved in wasting and have provided insights into their roles in tumor-induced metabolic dysregulation. Among them are insulin-binding protein (ImpL2), receptor tyrosine kinase ligands (Pvf1/PDGF-VEGF, Bnl/FGF), Matrix Metallopeptidase (MMP1), and inflammatory cytokines (Unpaireds/IL-6, Eiger/TNF-alpha)(Bilder et al. 2021; Liu et al. 2022). Studies from flies support the emerging concept that cachexia is more than one disease as the nature of cachectic factors in many cases

depend on the type of tumors analyzed. Moving forward, the fly models will not only help obtain a system level understanding of cachectic factors throughout the entire organism, but also allow various studies such as characterization of the role of microbiota in cachexia and how tumors affect feeding, olfactory and gustatory behaviors.

Observations of animal responses to non-cancer-associated cachexia have informed our understanding of the pathophysiology of this wasting syndrome, highlighting inflammation as one of the most relevant aspects of cachexia. Preclinical models of acute or chronic inflammation, such as injection of lipopolysaccharide (LPS) or specific inflammatory cytokines (TNF-α, IL-6 or IL-1) exhibit an intense decrease in food intake and increase in resting energy expenditure as seen in disease-associated cachexia (Figure 3). Cardiac cachexia is a frequent comorbidity in heart failure patients, partly caused by the release of inflammatory mediators in response to bacterial toxins absorbed through an edematous bowel wall. The use of surgical techniques either to cause infarction of cardiac muscle or to limit left ventricular output allow for the replication of the main clinical findings of cardiac cachexia. Alike to heart failure, cachexia in patients with chronic kidney disease (CKD) is thought to be due to increased inflammation. Animal models of CKD focus on surgical approaches that increase uremia as a means of inducing changes in food intake and body composition. Models of both cardiac cachexia and cachexia associated with CKD, as well as models of radiation- and chemotherapy-induced cachexia, have been used to demonstrate efficacy of melanocortin-inhibitors and ghrelin on improving appetite, weight gain and lean body mass (Akashi et al. 2009; Cheung et al. 2007; Liu et al. 2006).

4. The clinical trial landscape in cachexia

Cachexia therapeutic development is at a critical juncture. Despite 60 years of investigation, there are no effective U.S Food and Drug Administration (FDA)-approved treatments for cachexia (von Haehling and Anker 2014; Tomasin, Martin, and Cominetti 2019). Early cachexia clinical trials focused on evaluating drugs that simply stimulated appetite, but did not significantly improve other aspects of this wasting syndrome (K. C. H. Fearon et al. 2006; Jatoi et al. 2002; Leśniak et al. 2008; Loprinzi et al. 1999). The past decade has seen advances in the pathophysiologic understanding of cachexia, which has resulted in the development of drugs targeting mechanisms of cachexia rather than just appetite and weight. Unfortunately, these more recent strategies have proven to be only partially effective or led to unsuccessful clinical trials. An extended list of current and completed clinical trials for patients with cachexia is shown in Table 2.

Phase 2 clinical trials conducted evaluating enobosarm (Dobs et al. 2016), and anamorelin (Garcia et al. 2015), demonstrated improvements in body and lean mass, and physical function. These smaller trials led to the largest phase 3 cachexia intervention trials conducted this century: the POWER (enobosarm) and ROMANA (anamorelin) trials. Though both studies were able to demonstrate improvements in lean body mass with these agents, neither reached the FDA-mandated dual primary endpoints of improving both mass and physical function (Ebner and von Haehling 2016; Temel, Shaw, and Greer 2016). Anamorelin has been approved for use in treating cancer cachexia in Japan (Katakami et al. 2018) but not in the U.S., and continues to be evaluated in Phase 3 clinical trials (NCT03743064 and NCT03743051) though its primary endpoints have shifted to focus more on weight and anorexia.

A Phase 2 clinical trial assessing the efficacy of lenalidomide, an immunomodulatory drug, on lean body mass and handgrip strength in advanced solid tumor patients with inflammatory cachexia showed no treatment response on muscle mass nor muscle strength (NCT01127386) (Blum et al. 2022). The JAK 1/2 inhibitor ruxolitinib is currently in a Phase 2 (NCT04906746) clinical trial to assess the efficacy of targeting inflammatory signaling pathways activated in cachexia.

Most recently, antibody-mediated blockade of the GDF15-GFRAL pathway has been reported to be efficient in reversing cancer-associated cachexia (Suriben et al. 2020). The role Growth Differentiation Factor 15 (GDF-15) plays in anorexia, lipolysis, and muscle wasting has provided a strong rationale to study anti-GDF-15 agents in ongoing human clinical trials (NCT04803305, NCT04068896, NT04725474).

Building on a Phase 2 feasibility trial (Solheim et al. 2017), the MENAC trial (NCT02330926) is an active Phase 3 randomized-controlled trial (RCT) investigating the use of a home-based exercise routine, nutritional supplementation, and anti-inflammatories (EPA/NSAID).

Patients with cancer have been traditionally dichotomized into either presence or absence of cachexia. However, the view that all cachexia can be treated with one standard approach is likely oversimplified. Data from cross-sectional and retrospective studies suggest that distinct subtypes of cachexia with variable clinical phenotypes exist (Kays JS, 2018; Laird BJ, 2011). Recently, Gagnon et al. demonstrated that there are at least two subtypes of cancer cachexia, based on each patient's inflammation and anorexic symptoms. The Inflammatory-Necrotic/Anorexic group had shorter median survival (13.9 vs. 27.7 months) than the Non-Inflammatory/Non-Anorexic group. Several other studies have used clustering

approaches to describe body composition changes observed in patients with cachexia (Jin et al. 2022; Kays et al. 2018), and three distinct clusters were found: muscle and fat wasting, fat wasting alone, and no wasting. In all three studies, those with no wasting had the best survival outcomes, followed by those with fat wasting alone. Those with both muscle and fat wasting had the least favorable outcomes.

Display items

Figure 1. Interconnected causes and consequences of disease/cancer associated cachexia at organ level. Examples of host cell contributors to and organ level consequences of cachexia inducing inflammatory processes are illustrated.

Figure 2. Sources and targets of known cancer cachexia mediators. (A) Effect organ matrix for cachexia mediators. (**B**) Venn diagram of tumor- or host-derived cachexia mediators.

Figure 3. Longitudinal progression of biological phenomena and clinical observations from early cancer (disease) to terminal cachexia.

Figure 4. Potential and established contributory areas for the advancement of cachexia research and care. Selected aspects relating to the full translational research enterprise from pre-clinical mechanistic work to clinical team building and trial design are listed.

Figure 5. A dynamic systems theory model of health, disease, and cachexia

Dynamical interactions between biological perturbation and homeostatic response, and patient loss and recovery of condition. (A) Stream diagrams showing the interaction between both parameters under our mathematical model. Flow plots illustrate system trajectories at specific points of the underlying vector field. (B) Specific patient trajectories for either a sudden perturbation and response that is cleared in an otherwise normal patient (left) and slowly increasing biological perturbation for example secondary to chronic inflammation due to a growing cancer (right). The dashed vertical line indicates the time when the critical value is reached, resulting in the loss of any stable fixed point. Parameters are $d=30$, $r=2$, and $b=1$, for all panels so that the saddle-node bifurcation occurs at $c=14$. For (A) $c=1$, 10, 15 from left to right. For (B, left) $c=1$ and the system starts at $x=1$, $y=15$. For (B, right) $c=1+.2\,t$ and the system starts at $x=1$, $y=1$.

Figure 6. Key examples of established pre-clinical model systems for systemic inflammation predisposing or leading to cachexia. (**A**) Venn diagram of physiological cachexia defining aspects of different cancer and non-cancer model systems. (**B**) Summary categorization of model systems.

Table 1. Selected ongoing and completed clinical trials for patients with cachexia.

Supplement Table 1. Monitoring and measuring pathophysiological parameters in cachexia

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