

Targeting the GDF15-GFRAL Pathway in NSCLC Cachexia: From Stress Responses to Targeted Therapies

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Abstract

Cancer cachexia is a devastating, multifactorial wasting syndrome that significantly contributes to cancer-related mortality and drastically reduces patient quality of life. While numerous inflammatory cytokines drive this pathology, clinical trials targeting most of these factors have historically yielded limited success. Recently, growth differentiation factor 15 (GDF15) and its hindbrain-restricted receptor, glial cell-derived neurotrophic factor (GDNF) family receptor alpha-like (GFRAL), have emerged as critical mediators of cachexia, driving tissue wasting through both appetite suppression and active metabolic reprogramming. This review synthesizes the molecular biology, structural characteristics, and stress-induced regulatory mechanisms of the GDF15-GFRAL axis. We highlight paradigm-shifting preclinical findings—including our discovery that tumor-derived GDF15 dictates wasting in *STK11/LKB1*-mutant non-small cell lung cancer (NSCLC) cachexia. Furthermore, we evaluate the promising landscape of GDF15-GFRAL targeted therapeutics currently advancing through clinical trials. Finally, we propose that identifying early genetic biomarkers, such as *STK11/LKB1* mutations, is crucial for deploying these targeted interventions during the prodromal stages of cachexia, ultimately expanding the therapeutic window and improving patient survival.

Keywords: Cancer cachexia, GDF15-GFRAL axis, Targeted therapy, Biomarker.

Introduction

Cancer cachexia is a multifactorial wasting syndrome defined by unintentional body weight loss (greater than 5% over six months, or a body mass index under 20 kg/m² coupled with greater than 2% weight loss), primarily driven by the progressive depletion of skeletal muscle and/or adipose tissue. This devastating syndrome affects up to 80% of patients with advanced malignancies, accounts for at least 22% of all cancer-related mortality, and is strongly associated with reduced overall survival and diminished quality of life (Warren 1932; Argiles *et al.* 2018). Importantly, cachexia is not merely a late-stage consequence of tumor progression. Recent evidence indicates that significant weight loss can commence months prior to the formal diagnosis of malignancies, such as pancreatic cancer and non-small cell lung cancer (NSCLC) (Babic *et al.* 2023; Gilmore *et al.* 2025).

The pathophysiology of cancer cachexia is primarily driven by secreted factors that induce chronic inflammation, profound metabolic dysregulation, and suppressed appetite. Elevated levels of these mediators have been detected in both preclinical animal models and clinical cohorts, originating from the tumor, the host tissues, or a combination of both. Extensively studied cachexia factors include the interleukin-6 (IL-6) family of cytokines (IL-6, IL-8, IL-1 β , leukemia inhibitory factor/LIF), transforming growth factor-beta (TGF- β) superfamily proteins (TGF- β , GDF15, myostatin/GDF8, Activins, bone morphogenetic proteins/BMPs), tumor necrosis factor-alpha (TNF- α), parathyroid hormone-related protein (PTHrP), insulin-like growth factor-binding proteins (IGFBPs), and glucocorticoids (Ferrer *et al.* 2023; Hüllwegen *et al.* 2025). While these factors have been the subjects of numerous clinical trials over the past decades, the majority of targeted interventions have failed to completely reverse cachexia (Argiles *et al.* 2023), with the

notable exception of therapeutics directed against GDF15 (Groarke *et al.* 2024). In this review, we synthesize the current literature on the multifaceted role of GDF15 in cancer cachexia and provide a comprehensive overview of emerging therapeutic strategies targeting the GDF15 signaling pathway.

Molecular Biology of GDF15

Originally identified as macrophage inhibitory cytokine 1 (MIC-1), GDF15 is a divergent member of the TGF- β superfamily (Bootcov *et al.* 1997). The transcription of *GDF15* is primarily induced by cellular stress, tissue injury, and metabolic deficiencies, which activate convergent pathways governed by stress-response transcription factors, such as activating transcription factor 4-C/EBP homologous protein (ATF4-CHOP), p53, and early growth response transcription factor (EGR1) (Wang *et al.* 2021). p53 activation transcriptionally upregulates GDF15 through direct binding to a p53 response element in its promoter, resulting in GDF15 secretion in a human NSCLC cell line (Kannan *et al.* 2000; Tan *et al.* 2000). Similarly, EGR-1 binds the GDF15 promoter to transactivate its expression in a human colorectal carcinoma cell line (Baek *et al.* 2004). Beyond p53- and EGR1-mediated regulation, the integrated stress response (ISR)-ATF4-CHOP axis represents the most extensively characterized pathway driving GDF15 expression. Upon ISR activation, phosphorylation of the alpha subunit of eukaryotic translation initiation factor 2 (eIF2 α) promotes ATF4 nuclear translocation, where it partners with CHOP to transactivate *GDF15* transcription (Lockhart *et al.* 2020; Wang *et al.* 2021). Our group recently demonstrated that this pathway potently regulates GDF15 in cachexia driven by human NSCLC harboring loss-of-function mutations in serine/threonine kinase 11/liver kinase B1 (*STK11/LKB1*) (Figure 1) (Yu *et al.* 2026). Notably, the reconstitution of wild-type *STK11/LKB1* in these mutated tumors decreases eIF2 α

phosphorylation, subsequently blunting the expression of both ATF4 and GDF15. However, *GDF15* transcription is not exclusively reliant on the ATF4 pathway in this system. The ablation of ATF4 does not completely abolish *GDF15* mRNA levels; this strongly suggests the existence of parallel regulatory mechanisms, either as part of the ISR (e.g., via ATF3) (Lee *et al.* 2010) or independent of it (Figure 1). AMP-activated protein kinase (AMPK), a central regulator of mitochondrial function, also modulates GDF15 expression. Pharmacological activation of AMPK increases GDF15 levels, an effect that is markedly attenuated in AMPK $\beta 1^{-/-}$ or CHOP $^{-/-}$ mice (Townsend *et al.* 2021). Because STK11/LKB1 is the principal upstream kinase driving AMPK phosphorylation and activation, its loss would be predicted to impair this axis and, in turn, reduce GDF15 production. Paradoxically, however, GDF15 is upregulated in *STK11/LKB1*-mutant NSCLC patient-derived xenografts (PDXs). This discrepancy may reflect several non-mutually exclusive possibilities: AMPK activation independent of STK11/LKB1, for instance via calcium/calmodulin-dependent protein kinase kinase 2 (CaMKK2) (Steinberg and Hardie 2023), which could sustain downstream GDF15 induction despite loss of the canonical kinase; a context-dependent uncoupling of AMPK's regulatory influence on GDF15 from its phosphorylation status; tissue-specific regulatory divergence; or mechanistic differences between human and murine model systems. Furthermore, while CREB was also reported as a transcriptional regulator of GDF15 in pancreatic cancer (Kalli *et al.* 2019; Shi *et al.* 2026), when we silenced it in *STK11/LKB1*-mutated NSCLC cells, we did not observe obvious change in the protein level of GDF15 (unpublished data).

Integrated Stress Response of *STK11/LKB1*-mutated NSCLC

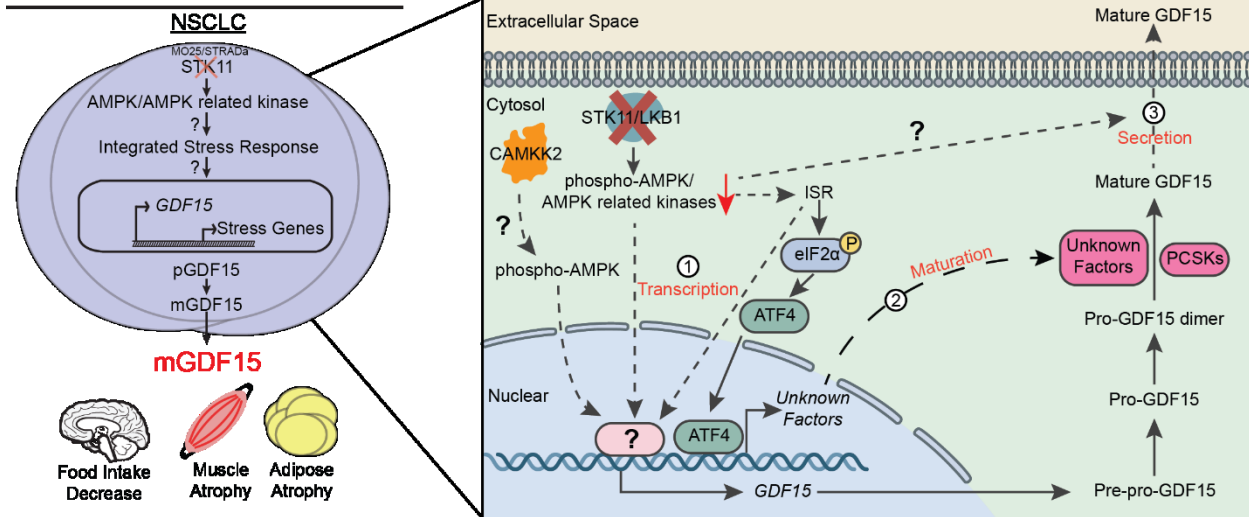


Figure 1 Proposed mechanisms of *STK11/LKB1*-driven GDF15 production and cancer cachexia.

STK11/LKB1 is a critical tumor suppressor and "master kinase" governing cellular energy metabolism. Its canonical functions are:

1. Forms a heterotrimeric complex with STRAD (STE20-related kinase adaptor) and MO25 (mouse protein 25) to activate AMPK and its 12 related kinases.
2. Consequence of loss-of-function mutations (in NSCLC): Abrogates this signaling network, inducing the integrated stress response (ISR) and driving robust GDF15 production.
3. Downstream effect: Elevated tumor-derived GDF15 triggers severe systemic cachexia, marked by suppressed food intake, adipose tissue wasting, and skeletal muscle atrophy.

Proposed mechanisms of GDF15 amplification following *STK11/LKB1* loss:

1. Transcriptional upregulation — mediated by the ISR and/or possibly parallel *STK11/LKB1*-dependent pathways.
2. Enhanced protein maturation/processing — driven by the *STK11/LKB1*–ISR–ATF4 axis via factors not yet characterized.
3. Open question — Whether *STK11/LKB1* mutations also regulate the secretion kinetics of mature GDF15 remains to be investigated.

AMPK paradox: CaMKK2 may compensate for *STK11/LKB1* loss by directly phosphorylating and activating AMPK, sustaining its activity through an *LKB1*-independent pathway.

pGDF15, pro-GDF15; mGDF15, mature GDF15.

Biologically, GDF15 functions as a ~ 25 kDa circulating homodimer synthesized as a 308-amino acid pre-pro-peptide, consisting of a signal peptide (residues 1-29), a pro-peptide (residues 30-196), and a C-terminal mature peptide (residues 197-308) (Bootcov *et al.* 1997). The signal peptide dictates intracellular trafficking, mediating transport into the endoplasmic reticulum (ER) prior to cleavage. Subsequently, the pro-peptide acts as a quality control determinant, directing improperly folded pro-GDF15 monomers toward proteasomal degradation (Bauskin *et al.* 2000). Proteolytic maturation occurs at an ¹⁹³RXXR¹⁹⁶ motif located between the pro-peptide and mature sequence, which is recognized and cleaved by enzymes such as proprotein convertase subtilisin/kexin (PCSK) family members or matrix metalloproteinase-26 (MMP-26), either intracellularly or within the extracellular matrix (Bauskin *et al.* 2005; Li *et al.* 2014; Li *et al.* 2018). The precise regulatory mechanisms governing GDF15 cleavage remain underexplored. We recently discovered that ATF4 knockout decreases intracellular mature GDF15 levels in *STK11/LKB1*-mutated NSCLC cells (Yu *et al.* 2026), which suggests that ATF4 participates in regulating the processing/maturation of GDF15 through unknown mechanisms in the cell (Figure 1). This implies that the loss of function of STK11/LKB1 may synergistically amplify GDF15 production by concurrently upregulating its transcription and post-translational processing through ISR or parallel pathways. Determining whether STK11/LKB1 actively regulates the secretion of mature GDF15 will require overexpressing the mature peptide in *STK11/LKB1*-mutated NSCLC cells.

Structurally, the mature GDF15 peptide harbors nine cysteine residues; eight participate in intra-chain disulfide bonds to stabilize the monomer, while the remaining cysteine (the sixth in the sequence) forms an inter-chain disulfide bridge with a corresponding cysteine on another pro-

GDF15 molecule within the ER, thus yielding the functional homodimer (Bootcov *et al.* 1997; Lockhart *et al.* 2020). Crystallographic analyses reveal that the three-dimensional structure of GDF15 features a unique adaptation of the classical TGF- β superfamily fold, dominated by two antiparallel β -sheets extending from a central core. The N-termini of the paired GDF15 monomers are fully exposed and similarly oriented, whereas the C-terminus of one monomer packs against a hydrophobic patch on its counterpart, with the terminal Isoleucine³⁰⁸ buried and sterically constrained by a disulfide bond between Cysteine³⁰⁷ and Cysteine²⁴⁴ (Xiong *et al.* 2017). Furthermore, Cysteine²¹¹ is critical for GDF15 secretion (Hsu *et al.* 2017; Fejzo *et al.* 2022; Fejzo *et al.* 2024), as individuals harboring a C211G variant exhibit undetectable circulating GDF15. Interestingly, individuals genetically deficient in GDF15 remain healthy and fertile (Gurtan *et al.* 2024), indicating that the cytokine may be largely dispensable under basal, non-stressed physiological conditions. Once secreted, GDF15 has an estimated circulating half-life of three hours in both mice and non-human primates (Xiong *et al.* 2017), though the specific mechanisms dictating its clearance require further elucidation.

GDF15-GFRAL Signaling Pathway

Recent large-scale population studies establishing normative serum GDF15 ranges indicate that median GDF15 concentrations in healthy young adults (under 30 years) are approximately 537 pg/mL, which progressively climb with advancing age to 2,152 pg/mL in those aged 80 and older (Welsh *et al.* 2022). Physiologically, significantly elevated GDF15 originating from the feto-placental unit is intimately linked to the maternal risk of nausea and vomiting during pregnancy (Fejzo *et al.* 2024). Furthermore, extensive plasma proteome profiling across diverse healthy and diseased adult cohorts has highlighted GDF15 as a paramount clinical biomarker. It

emerged as the top predictive protein for 200 distinct pathologies and the top diagnostic protein for 40 diseases (Deng *et al.* 2025). In the context of oncology, GDF15 levels can surge ten-fold or more in advanced cancer patients compared to healthy controls, strongly correlating with the onset and severity of cancer cachexia (Johnen *et al.* 2007; Lerner *et al.* 2015; Al-Sawaf *et al.* 2023; Abdelgalel *et al.* 2025; Hüllwegen *et al.* 2025; Levi *et al.* 2025). Notably, the feto-placental unit and tumors face an analogous immunological challenge — surviving as antigenically distinct tissue within a host capable of mounting a destructive immune response — and both appear to exploit GDF15 toward this end, with each context also marked by corresponding changes in feeding behavior. The placenta is the highest physiological source of GDF15, and reduced first-trimester levels have been linked to miscarriage, supporting a long-standing hypothesis that GDF15 helps protect the semi-allogeneic fetus from maternal immune attack (Wischhusen *et al.* 2020; Abd and Abd Ali 2026). Tumor-derived GDF15 achieves an analogous outcome by suppressing T-cell recruitment via the LFA-1/ICAM-1 axis, shielding malignant tissue from immune destruction and promoting progression (Bruzzese *et al.* 2014; Haake *et al.* 2023). The role of GDF15 in metabolic-related diseases, including obesity, diabetes, and cardiovascular disease, has been extensively reviewed elsewhere (Adela and Banerjee 2015; Wang *et al.* 2021; Iglesias *et al.* 2023; Sigvardsen *et al.* 2025).

Historically, host-derived GDF15 was presumed to be the primary driver of GDF15-associated wasting, particularly during platinum-based chemotherapy (Hsu *et al.* 2017; Breen *et al.* 2020). Clinical data from the TRACERx study confirmed elevated serum GDF15 levels in cachectic NSCLC patients relative to non-cachexia counterparts (Al-Sawaf *et al.* 2023). Interestingly, this study found no significant association between tumor GDF15 gene expression

or copy-number alterations and systemic serum GDF15 levels, indirectly suggesting that circulating GDF15 might predominantly originate from the host. We recently established robust GDF15-induced cancer cachexia models through the engraftment of human GDF15-producing, patient-derived *STK11/LKB1*-mutant NSCLC cell lines into immunodeficient mice. By utilizing CRISPR/Cas9 to selectively silence tumor cell-derived GDF15, we observed that these NSCLC lines lost the ability to induce cachexia, proving that the tumor cells themselves — not the host — are the critical cellular source of GDF15 in these specific models (Yu *et al.* 2026). The TRACERx findings raise the possibility of additional host-derived GDF15 sources, potentially from immune cells, that could not be assessed in the immunodeficient model. Therefore, further investigations utilizing immunocompetent mice and single cell studies are necessary to fully dissect the complex interplay between host and tumor GDF15 in *STK11/LKB1*-mutant NSCLC cancers.

Following its discovery, GDF15 was attributed a versatile array of biological functions. It should be noted that some early conflicting findings regarding its functional pleiotropy may have stemmed from TGF- β contamination in commercially available recombinant GDF15 preparations (Olsen *et al.* 2017). Nevertheless, the indispensable role of GDF15 in driving cancer cachexia has been unequivocally validated through both antibody-mediated neutralization and genetic silencing approaches (Johnen *et al.* 2007; Kim-Muller *et al.* 2023; Groarke *et al.* 2024; Yu *et al.* 2026), which have been comprehensively documented in several excellent reviews (Baek and Eling 2019; Lockhart *et al.* 2020; Wang *et al.* 2021; Ferrer *et al.* 2023; Breit and Tsai 2025; Sigvardsen *et al.* 2025).

Early mechanistic studies demonstrated that the administration of recombinant GDF15 activates c-Fos expression in the area postrema (AP) of the brainstem, implicating this neural

nucleus in mediating GDF15-induced anorexia and subsequent cachexia (Johnen *et al.* 2007). However, the specific receptor for GDF15 remained elusive until 2017, when four independent research groups utilized orphan ligand-receptor capture technologies and cDNA library screening to identify GFRAL as the bona fide, high-affinity receptor for GDF15 (Emmerson *et al.* 2017; Hsu *et al.* 2017; Mullican *et al.* 2017; Yang *et al.* 2017). The physiological relevance of this discovery was profound: GFRAL knockout mice proved completely refractory to both exogenous GDF15 administration and chemotherapy-induced GDF15 surges, failing to exhibit characteristic anorexia, weight loss, or brainstem signaling activation even at supraphysiological doses. Consequently, these knockout animals are fully protected against wasting in GDF15-overexpressing tumor models, establishing GFRAL as the exclusive metabolic receptor mediating the catabolic effects of this cytokine.

Initial characterizations indicated that GFRAL expression is strictly anatomically restricted to the hindbrain's AP and the nucleus tractus solitarius (NTS)—regions uniquely positioned outside a complete blood-brain barrier. While some immunohistochemical studies have reported GFRAL detection in various cancer and peripheral tissues (Laurens *et al.* 2020; Zhao *et al.* 2020; Buchholz *et al.* 2021; Fichtner *et al.* 2024), recent highly specific murine in situ hybridization studies failed to detect *Gfral* mRNA outside the AP/NTS (Hes *et al.* 2025). Notably, these hybridization models were limited to healthy subjects; thus, further investigations during disease states are necessary to provide a comprehensive understanding. It has been postulated that an alternative splice variant of GFRAL lacking the transmembrane domain might be secreted into circulation (Li *et al.* 2005) that may cross-react with peripheral immunohistochemical probes. Although GFRAL expression is generally considered restricted to the hindbrain, recurring reports

of peripheral expression highlight the need for tissue-specific knockout studies to definitively resolve this discrepancy.

Structurally, in contrast to other GDNF family receptors that are typically glycosylphosphatidylinositol (GPI)-anchored, GFRAL is a single-pass type I transmembrane protein. The binding of a GDF15 homodimer to a GFRAL homodimer induces the recruitment of the transmembrane co-receptor rearranged during transfection (RET), culminating in a heterohexameric complex assembled in a strict 2:2:2 stoichiometry (Figure 2) (Hsu *et al.* 2017; Li *et al.* 2019). The formation of this complex triggers the trans-autophosphorylation of specific intracellular tyrosine residues on RET, primarily Tyrosine¹⁰⁶², effectively igniting the downstream signaling cascade (Hsu *et al.* 2017; Mullican *et al.* 2017; Yang *et al.* 2017).

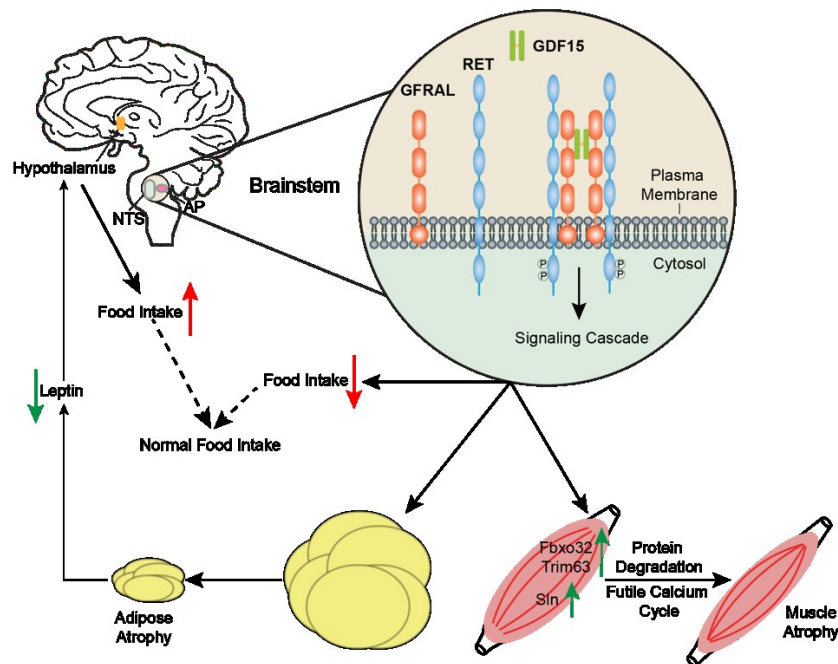


Figure 2 The GDF15-GFRAL-RET signaling axis and downstream mechanisms of cancer cachexia.

1. Receptor complex assembly: Circulating GDF15 (green) reaches the area postrema (AP) and nucleus tractus solitarius (NTS) within the brainstem, where it binds a GFRAL homodimer (orange) at the plasma membrane, recruiting the co-receptor RET (blue) to form a heterohexameric signaling complex. This triggers RET trans-autophosphorylation and initiates an intracellular signaling cascade.
2. Peripheral wasting: Downstream signaling drives both muscle atrophy and adipose wasting. In muscle, GDF15-GFRAL signaling upregulates sarcolipin (*Sl*), promoting a futile calcium cycle that increases energy expenditure, alongside induction of E3 ubiquitin ligase Fbxo32 (Atrogin-1) and Trim63 (MuRF1), which drive protein degradation.
3. Neuroendocrine counter-regulation: GDF15-GFRAL-RET signaling in the brainstem suppresses food intake, while fat wasting lowers leptin levels, reducing leptin's appetite-suppressive signaling in the hypothalamus, which may counterbalance GDF15-driven food intake decrease.

The GDF15-GFRAL Axis: Mechanisms of Cancer Cachexia

Initially, the GDF15-GFRAL axis was viewed simply as a hindbrain-restricted signaling loop that drives body weight loss primarily through appetite suppression. However, recent advances have significantly broadened this paradigm, revealing that GDF15 drives cachexia through a coordinated, multipronged pathology encompassing food intake-dependent mechanisms and food intake-independent pathways, and complex neuroendocrine counter-regulations.

Food intake-dependent mechanisms (anorexia and visceral malaise): The profound suppression of caloric intake remains a central, devastating pillar of GDF15-induced cachexia (Emmerson *et al.* 2017; Hsu *et al.* 2017; Mullican *et al.* 2017; Yang *et al.* 2017; Groarke *et al.* 2024). Importantly, GDF15-GFRAL signaling does not merely induce normal postprandial satiety; rather, it triggers an aversive feeding response. Preclinical models demonstrate that elevated GDF15 induces conditioned taste aversion and visceral illness behaviors. In non-human primates and clinical populations, this pathway is intimately linked to the emetic neurocircuitry (Breen *et al.* 2020; Engström Ruud *et al.* 2024). This mirrors its physiological role in driving hyperemesis

gravidarum during pregnancy (Fejzo *et al.* 2024). Mechanistically, while the area postrema (AP) acts as the primary sensory node for receiving this circulating signal, mapping of the downstream architecture has identified brain-derived neurotrophic factor (BDNF)-expressing neurons in the medial NTS (mNTS) as an obligatory convergence hub for processing this GDF15-mediated anorexia (Figure 2) (Feetham *et al.* 2024). Ultimately, this centrally mediated malaise effectively abolishes the patient's hedonic and homeostatic drives to eat, driving a severe, intractable negative energy balance.

Food intake-independent mechanisms (systemic energy expenditure): Despite the consistent finding that acute administration of recombinant GDF15 causes decreased food intake and body weight loss, emphasizing anorexia as the sole driver of wasting drastically oversimplifies the pathology. In fact, a vast body of clinical and experimental evidence highlights non-anorexia mechanisms during chronic diseases and pathological states. Clinically, Garcia and colleagues observed that serum GDF15 is significantly elevated in cancer patients (36% are lung cancer) with weight loss compared to weight-stable cancer patients and healthy controls; however, the cachectic cohort exhibited no significant differences in food intake as judged by appetite scores (Lerner *et al.* 2015). This clinical disconnect is mirrored in preclinical oncology. For instance, mice bearing GDF15-dependent HT1080 tumors undergo severe cachexia without significant decreases in food intake compared to non-tumor-bearing controls. Furthermore, while the administration of a GFRAL neutralizing antibody rescued adipose and muscle wasting in these animals, it did not alter their feeding behavior (Suriben *et al.* 2020). Similarly, we observed no significant food intake differences in mice bearing STK11/LKB1-mutant NSCLC patient-derived xenografts (PDXs)

when compared to mice bearing GDF15-silenced tumors or those treated with a GDF15 neutralizing antibody (Yu *et al.* 2026).

Mechanistically, this food intake-independent weight loss is largely driven by a pathological surge in skeletal muscle energy expenditure. In models of metabolic dysfunction-associated steatohepatitis (MASH), recombinant GDF15 induces weight loss where reduced food intake accounts for only half of the body weight reduction, as proven by pair-fed cohorts (Wang *et al.* 2023). Further investigations revealed that GDF15 administration induces massive muscle energy expenditure through the upregulation of muscle sarcolipin (*Sln*). We recently validated this axis in *STK11/LKB1*-mutant NSCLC cachexia, observing that expression of *Sln* and established protein degradation markers (*Fbxo32* and *Trim63*) negatively correlates with body weight. *STK11/LKB1*-mutant NSCLC tumor-bearing mice exhibited significantly higher *Sln* mRNA levels in both the gastrocnemius and soleus muscles compared to controls; critically, silencing tumor GDF15 abrogated this *Sln* induction (Figure 2) (Yu *et al.* 2026). Consistent with this, the PolgD257A/D257A mouse model of primary mitochondrial myopathy — which harbors an elevated mitochondrial DNA mutation rate leading to defective mitochondrial proteins and consequent loss of muscle mass, strength, and exercise capacity — phenocopies key metabolic and muscle wasting features of this pathway. The mice show elevated GDF15, and antibody-mediated GDF15 neutralization rescues the wasting phenotype, concordant with reduced *Sln* expression in gastrocnemius muscle (Flaherty *et al.* 2025). Furthermore, acute activation of GFRAL-expressing neurons precipitates a hypometabolic, torpor-like state characterized by hypothermia and a rapid hepatic shift toward ketogenesis and lipid oxidation (Engström Ruud *et al.* 2024). Collectively, these findings underscore that GDF15-mediated cachexia is an active, maladaptive metabolic

reprogramming rather than passive starvation. Definitively confirming *Sln*-mediated energy expenditure as the primary effector of this wasting will warrant future studies utilizing muscle-specific *Sln* silencing.

Neuroendocrine counter-regulation (the leptin compensatory axis): Beyond direct energy expenditure, secondary neuroendocrine feedback loops likely obscure the acute anorexic effects of GDF15 during chronic disease, explaining the inconsistent feeding behaviors observed across prolonged cachexia studies. Food intake is tightly regulated by a variety of non-GDF15 hormonal signals, with leptin being a paramount regulator of long-term energy balance (Woods *et al.* 2000; Bruning and Fenselau 2023). We previously reported that tumor-secreted cachexia factors, such as leukemia inhibitory factor (LIF), cause significant adipose loss and anorexia (Arora *et al.* 2018; Gandhi *et al.* 2022). However, wild-type mice administered LIF experience only a transient state of hypophagia that rapidly returns to normophagia. This behavioral recovery is driven by a compensatory plunge in circulating leptin secondary to the initial adipose depletion. In leptin-deficient (*ob/ob*) or leptin receptor-deficient (*db/db*) mice, this counterbalance is absent, leading to perpetual hypophagia (Arora *et al.* 2018).

We have now observed a parallel compensatory axis in GDF15-driven cachexia. Mice bearing subcutaneous and orthotopic *STK11/LKB1*-mutant NSCLC tumors exhibited a severe cachectic phenotype accompanied by a significant decrease in serum leptin levels compared to non-tumor-bearing mice. When *GDF15* was genetically silenced or pharmacologically neutralized, the cachexia phenotype was rescued, and serum leptin levels were restored (Yu *et al.* 2026). These data consistently suggest that the progressive drop in leptin serves as a potent counterbalance to

the anorexic signals induced by cancer cachexia factors (Figure 2). Ultimately, this compensatory rescue of appetite masks the initial GDF15-driven hypophagia, driving the "normophagic wasting" frequently observed in the clinic. To fully dissect the interplay between GDF15 and this neuroendocrine feedback loop, future investigations employing *ob/ob* and *db/db* cachexia models are highly warranted.

GDF15-GFRAL Axis as a Therapeutic Target for Cancer Cachexia and Advanced Cancer

The clinical translation of targeting the GDF15-GFRAL axis represents a watershed moment in supportive oncology, catalyzing a paradigm shift from non-specific nutritional supplementation to the precise molecular targeting of the cachectic drive. Decades of preclinical promise have now culminated in definitive human proof-of-concept: the phase 2 PROACC-1 trial ([NCT05546476](#)) evaluating ponesimab, Pfizer's GDF15 neutralizing antibody, demonstrated robust, dose-dependent weight gain and functional improvement in patients with non-small cell lung, pancreatic, and colorectal cancers exhibiting elevated circulating GDF15 (≥ 1500 pg/mL) (Groarke *et al.* 2024). It is important to note, however, that circulating GDF15 sequestered by ponesimab can accumulate to extraordinarily high levels that may eventually overwhelm the antibody's binding capacity (Crawford *et al.* 2024), suggesting that prolonged treatment regimens might necessitate progressive dosage escalation.

Alternatively, directly targeting the GFRAL receptor offers distinct theoretical pharmacokinetic advantages. NGM120, a first-in-class anti-GFRAL antibody, successfully promoted gains in body weight and lean mass in both preclinical models and advanced solid tumor patients during a phase 1/2 trial ([NCT04068896](#)) (Suriben *et al.* 2020; Jain *et al.* 2021), paving the

way for an ongoing phase 2 trial ([NCT07033026](#)) specifically in cachectic colorectal cancer patients. Furthermore, as our molecular understanding of cancer cachexia deepens, it is increasingly apparent that the syndrome is rarely driven by a solitary cytokine. Consequently, a clinical trial ([NCT06898255](#)) investigating GFS202A, a novel bispecific antibody engineered to simultaneously target GDF15 and IL-6, has been initiated for advanced solid tumor patients presenting with pre-cachexia or cachexia. The rationale for this dual targeting is strongly supported by recent findings demonstrating that IL-6 can penetrate the brainstem AP to activate local neurons and induce a cachexia phenotype, with brain-restricted IL-6 neutralization sufficient to attenuate this wasting (Sun *et al.* 2024). Separately, cachexia-associated apathy and effort-sensitivity arise from a brainstem-to-basal ganglia circuit that senses IL-6 and suppresses mesolimbic dopamine, and targeting this circuit—via anti-IL-6 treatment, brainstem ablation, or dopamine restoration—reversed these behavioral symptoms (Zhu *et al.* 2025). Together, these findings establish the brainstem as a convergence point for IL-6-driven physical wasting and behavioral/affective symptoms, paralleling the mechanistic depth described above for GDF15-GFRAL signaling and reinforcing the rationale for the bispecific GDF15/IL-6 targeting strategy.

Beyond its established role as a metabolic driver of cachexia, GDF15 also functions as a potent immunosuppressor by inhibiting the leukocyte function-associated antigen (LFA-1)/intercellular adhesion molecule (ICAM)-1 axis in T cells and T cell migration into tumor tissue, facilitating tumor progression (Haake *et al.* 2023). Blocking GDF15 has been shown to rejuvenate tumor immune cell infiltration and augment the efficacy of immune checkpoint blockade therapy across multiple malignancies (Wischhusen *et al.* 2021; Haake *et al.* 2023; Hong *et al.* 2023). Leveraging this dual mechanism, CatalYm's visugromab is currently under investigation in the GDFATHER

trial ([NCT04725474](#)), pioneering a "dual-benefit" clinical paradigm. This approach has demonstrated that GDF15 neutralization can re-sensitize refractory tumors to anti-PD-1 or anti-PD-L1 therapies while concurrently mitigating cachectic weight loss (Melero *et al.* 2025). Similarly, combining the anti-GFRAL antibody NGM120 with standard chemotherapy ([NCT04068896](#)) yielded encouraging disease control rates in advanced pancreatic cancers (Hendifar *et al.* 2022). Building on these successes, the pivotal Phase 2b/3 trial ([NCT06989437](#)) evaluating ponesimab in combination with chemotherapy for metastatic pancreatic ductal adenocarcinoma (PDAC) will critically assess whether reversing cachexia directly translates into enhanced chemotherapy tolerance and improved overall survival. AVEO's V-380 ([NCT05865535](#)) is employing comparable strategies in metastatic cancer patients presenting with elevated GDF15 levels. Unlike historical cachexia therapies that primarily tried to supplement more nutrients, GDF15-GFRAL inhibitors appear to fundamentally reset the pathological catabolic state while simultaneously lifting local immune suppression, presenting a highly plausible, multipronged therapeutic strategy.

While GDF15-GFRAL inhibitors are proving to be highly effective therapeutic tools, current clinical trials predominantly enroll patients with advanced-stage cancers or exceptionally high circulating GDF15 (≥ 1500 pg/mL), inherently restricting access for early-stage patients. Compellingly, our recent data demonstrated that both patient-derived and engineered murine *STK11/LKB1*-mutant NSCLC cells, which secrete similar or only slightly elevated levels of GDF15 compared to control wild-type cells, are still fully capable of driving profound cachexia in vivo. Importantly, both tumor genetic silencing and antibody-mediated neutralization of GDF15 in these models successfully rescued the cachectic phenotype (Yu *et al.* 2026). These findings

strongly advocate for expanding the clinical application of GDF15-GFRAL inhibitors to NSCLC cachexia patients irrespective of absolute systemic GDF15 thresholds, utilizing *STK11/LKB1* loss-of-function mutations as an actionable early diagnostic biomarker. To fully realize this personalized medicine approach, future translational studies must systematically define the specific oncogenic mutations and transcriptional networks that pathologically upregulate GDF15 across diverse tumor types, thereby identifying robust genetic biomarkers that enable earlier, more effective clinical interventions.

Conclusion and Perspective

The clinical recognition of cachexia dates back to ancient Greece, where Hippocrates aptly described it as a severe wasting condition where “the flesh is consumed and becomes water”. Despite this millennia-old clinical awareness, there are currently no globally approved targeted therapies specifically for this syndrome. This glaring therapeutic void stems historically from viewing cachexia merely as a terminal, inevitable complication of advanced malignancy, a perspective that severely underestimated its active, destructive role in patient mortality.

Fortunately, clinical paradigms are shifting. Recent epidemiological data highlight unintentional weight loss as a potent harbinger of undiagnosed malignancies, noting that individuals presenting with unexplained weight loss have a significantly higher incidence of subsequent cancer diagnoses or more advanced diseases at cancer diagnosis (Nicholson *et al.* 2022; Wang *et al.* 2024; Gilmore *et al.* 2026). In fact, the metabolic prodrome of cachexia can commence up to 12 months prior to a formal clinical cancer diagnosis (Gilmore *et al.* 2025). Long before measurable morphological or functional decline is evident, tumor-derived factors initiate a cascade

of metabolic alterations and inflammation that inexorably drive skeletal muscle and adipose catabolism. Consequently, the identification of these early tumor-derived cachexia factors and metabolic signatures provides a critical, untapped window for early oncological diagnosis and intervention. Detecting cachexia in its latent, prodromal state empowers clinicians to deploy targeted therapies before patients enter the unmanageable, refractory stage, effectively widening the therapeutic window for definitive anti-cancer treatment. Therefore, the rigorous clinical monitoring of body weight trajectories and the validation of early detection biomarkers for cachexia remain paramount.

Inhibitors targeting the GDF15-GFRAL axis represent the first truly promising, targeted intervention for cancer cachexia, while their strategic combination with first-line chemotherapy or immune checkpoint inhibitors offers a synergistic approach to comprehensive cancer care. However, because current clinical evaluation is heavily focused on advanced-stage disease with significant GDF15 elevations, the discovery of highly sensitive, early predictive biomarkers represents the field's most urgent unmet need. Our recent discovery positioning tumor-derived GDF15 as an indispensable mediator and prime therapeutic target in *STK11/LKB1*-mutant NSCLC-associated cachexia — regardless of circulating GDF15 concentrations (Yu *et al.* 2026), provides a compelling blueprint for such biomarker-driven stratification. Whether oncologists can successfully expand the application of GDF15-GFRAL axis inhibitors to the approximately 15% of NSCLC patients harboring *STK11/LKB1* mutants awaits validation in prospective clinical trials.

However, it is crucial to recognize that GDF15 may not be the exclusive driver of *STK11/LKB1*-mutant NSCLC-associated cachexia. Our lab and others have observed significant

elevations of IL-6 family cytokines in both *STK11/LKB1*-mutant NSCLC PDX and genetically engineered *Stk11/Lkb1*-mutant mouse models, and pharmacological inhibition of the downstream JAK/STAT pathway using ruxolitinib or pacritinib has demonstrated protective effects against fat mass loss (Iyengar *et al.* 2023; Dantas *et al.* 2025). Whether the IL-6 family cytokine and GDF15 pathways interact cooperatively or operate independently warrants further investigation. Ultimately, identifying comprehensive multi-omic signatures will be equally critical to stratify patients whose cachexia is driven by multiple overlapping factors, ensuring they are directed toward the most appropriate alternative or combinatorial therapeutic strategies. Collectively, these inspiring molecular insights should catalyze intensive preclinical efforts to identify specific genetic alterations and dysregulated signaling nodes that uncouple the GDF15-GFRAL axis in cancer, transforming these molecular signatures into the next generation of early, predictive biomarkers for cachexia intervention.

Acknowledgement

We used Google Gemini and Claude to increase the readability of the manuscript.

This work was supported by grants from the Burroughs Wellcome Fund Career Awards for Medical Scientists (1019692, REI); American Cancer Society Grant (133889-RSG-19-195-01-TBE, REI); Cancer Prevention and Research Institute of Texas (RP230140 (REI/PI); and National Institutes of Health grants (1R01CA266900 (REI/PI), 1R01DK128166 (REI/PI), 1P30DK127984 (REI), P30CA142543 (REI), and P50CA070907 (REI).

Compliance with Ethics Guidelines

Conflict of interest

All authors acknowledge no conflicts of interest related to this work except REI who maintains collaborative cancer cachexia research projects with Pfizer Inc., Incyte and NGM Biopharmaceuticals.

Human and animal rights and informed consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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