

Commentary

Targeting the Upstream Driver of Cancer Cachexia

Lingbing Zhang¹, Jeffrey A Norton^{2,*}¹Yinuo Ltd., Changchun 130012, China²Department of Surgery, School of Medicine, Stanford University, Stanford, CA 94305, USA

***Correspondence:** Jeffrey A Norton, Department of Surgery, School of Medicine, Stanford University, Stanford, CA 94305, USA, E-mail: janorton@stanford.edu; DOI: 10.1042/JCTCS.9.3.0065

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Description

The review by Zhang and Norton, "Cancer Cachexia Research and Drug Development: Lessons from Failures and the Promise of Immunomodulation," reassesses how cancer cachexia was studied and treated [1]. The authors argue that cachexia is not primarily a nutritional complication of advanced cancer. It is a systemic immune-metabolic syndrome arising from interactions among the tumor, the immune system and the body. This interpretation has important consequences for drug development. Cachexia impairs physical function, reduces tolerance of anticancer treatment, diminishes quality of life, and increases mortality [2, 3]. Earlier therapies concentrated on caloric intake and appetite stimulation. Agents such as megestrol acetate and corticosteroids may improve appetite or produce modest weight gain, but they do not necessarily restore skeletal muscle or function. Nutritional support is helpful, yet it cannot reverse the inflammatory process that drives the wasting.

The history of drug development for cancer cachexia explains why rational single-target strategies have often disappointed. After tumor necrosis factor alpha, interleukin-1, and interleukin-6 were implicated, individual cytokines became attractive targets. Clinical studies nevertheless failed to produce consistent improvements in muscle mass, function, or survival [4]. These outcomes do not show that inflammatory cytokines are not important. They show that inflammatory networks are redundant and adaptive, allowing parallel or compensatory pathways to remain active when one cytokine is blocked.

The ROMANA trials provide another lesson that targeting mechanisms of single symptoms may not work. Anamorelin increased body weight and lean body mass in patients with non-small cell lung cancer but did not significantly improve hand grip strength [5]. Increasing tissue quantity does not necessarily restore tissue quality or patient function. Body weight and lean mass are informative, but they cannot substitute strength, mobility, treatment tolerance, quality of life, or survival.

Zhang and Norton do not advocate combining treatments aimed at separate downstream symptoms. They call for a more fundamental change: identify and target the upstream driver of the syndrome [1]. Systemic inflammation, altered metabolism, muscle degradation, adipose tissue loss, anorexia, and impaired regeneration may be interconnected consequences of tumor-induced immune dysregulation [6]. Targeting one downstream pathway may provide partial or temporary benefit while leaving the underlying disorder intact. Restoring immune homeostasis could influence several downstream processes simultaneously and thus permit more meaningful and durable reversal of cachexia.

Immunomodulation is therefore distinct from neutralizing a single inflammatory molecule. Its objective is to restore functional balance across interacting immune cells and signaling pathways while avoiding broad immunosuppression [6]. R-ketorolac is presented as an emerging example. In tumor-bearing animal models, it reduced weight loss and muscle wasting, modified immune and inflammatory abnormalities, and prolonged survival [7]. These effects occurred independently of food intake or tumor size, supporting an action on the host response rather than an indirect effect of appetite stimulation or tumor reduction.

The evidence for R-ketorolac remains preclinical. Clinical translation will require careful assessment of pharmacokinetics, dose response, safety, immunomodulation effects, and interactions with chemotherapy or immunotherapy. Mechanistic biomarkers may be needed to confirm target engagement and identify patients most likely to benefit. Candidate measures include inflammatory cytokines, immune-cell profiles, and metabolic signatures, although each requires prospective validation [8].

Future trials should enroll patients by cachexia stage and evidence of immune dysregulation. Intervention during early cachexia stage may

offer a better opportunity for recovery than treatment after severe tissue loss or organ damage. Endpoints should include body composition, muscle strength, physical performance, patient-reported outcomes, treatment tolerance, and survival. Nutrition, symptom control, and exercise should remain part of routine care [9], while experimental therapy is judged by its ability to reverse the syndrome by acting on upstream drivers.

The review's main contribution is to challenge the downstream and single-pathway approach to cancer cachexia and redirect research toward the upstream biology that initiates and sustains the syndrome. Cachexia is a biologically active and treatable disorder that accelerates patient decline and interferes with effective anticancer therapies. Future studies should determine whether targeting upstream immune dysregulation can improve physical function, treatment tolerance, and survival. Success would demonstrate cachexia is reversible and establish cachexia treatment as a central component of advanced cancer care.

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