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Immunology of Cancer Cachexia

Lingbing Zhang*

Editorial

Cancer cachexia - a syndrome defined by severe weight loss, muscle wasting, and metabolic dysfunction [1] - afflicts up to 80% of advanced cancer patients, undermining their quality of life and treatment prospects. For over 15 years, I have studied this condition, initially at Stanford and later through my work in industry, and I have come to see it not merely as a metabolic byproduct of malignancy, but as a profound immunological disorder. While metabolic dysregulation is undeniable, I argue that the immune system's role, including its chronic inflammation, cellular dysfunction, and systemic ripple effects, deserves equal footing in our understanding and approach to cachexia.

The roots of cachexia lie in a relentless inflammatory state, sparked by cytokines like tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), interleukin-1β (IL-1β), growth differentiation factor 15 (GDF-15) and many others. These molecules, intended as immune sentinels, turn destructive when unchecked. TNF-α, once called "cachectin," degrades muscle proteins via the ubiquitin-proteasome pathway and dampens appetite through hypothalamic signaling. IL-6 shifts amino acid resources from muscle to liver acute-phase proteins, starving skeletal tissue. My 2024 collaboration with Dr. Philip D. Bonomi illuminated how these cytokines hijack pathways like JAK/STAT and NF-κB to drive wasting - a framework I've spent years refining through preclinical models [2].

My investigations have also spotlighted immune cells as key players. Myeloid-derived suppressor cells (MDSCs), abundant in tumor-bearing hosts, bring damage by massive infiltration to vital organs (e.g., liver and lung), and secreting pro-inflammatory factors that erode muscle and fat. In my studies, MDSCs emerged as dual agents - suppressing anti-tumor immunity while fueling systemic catabolism. This insight reshapes cachexia as a fallout of immune dysregulation. I've also explored adaptive immunity's role, particularly T-cell dynamics. While activated CD8+ T cells, spurred by tumor antigens and IFN-γ, may inadvertently target muscle fibers, a significant feature of the adaptive immunity I have observed under cancer cachexia is lymphopenia. Lymphopenia reflects immune dysregulation and correlates with the severity of cachexia and poorer outcomes.

Therapeutic innovation has been a cornerstone of my work. In 2024, alongside Dr. Martina Schweiger, I demonstrated R-ketorolac (RK), a newly identified immunomodulator as a game-changer in two mouse models including classic C26 and newly established CHX207 [3]. RK slashed IL-6 levels, reversed T-lymphopenia, and boosted survival to 100% in treated C26 mice over 10 days, compared to 10% in controls. Unlike single-cytokine blockers, RK's broad action reflects my conviction that cachexia demands multi-target strategies. This led to the proof-of-concept trial we sponsored at Cedars-Sinai, using ketorolac in pancreatic ductal adenocarcinoma (PDAC)

Affiliation:

Akexis Inc., Austin TX 78748

***Corresponding author:**
Lingbing Zhang, Akexis Inc., Austin TX 78748.

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patients with cachexia. Ketorolac, a 50/50 mix of R-ketorolac and S-ketorolac, was given over five days to advanced PDAC patients with cachexia. The data shows weight loss reversal and increased daily steps (via FitBit) in majority patients [4]. Since S-ketorolac drives ketorolac's anti-inflammatory effects and its lethal side effects, and anti-inflammatory drugs consistently fail in cachexia trials, I'm convinced the efficacy hinges on R-ketorolac, mirroring its preclinical impact. R-ketorolac targets the immune disorder, halting the immune dysfunction that triggers wasting, reversing cachexia, and restoring patient health. This not only directly improves survival but also enables patients to withstand and benefit from anti-tumor treatments like chemotherapy and immunotherapy.

Current cachexia treatments, i.e., appetite stimulants like megestrol acetate, miss the immunological root I've uncovered. Our Cedars-Sinai trial with ketorolac, building toward R-ketorolac validation, sets a new path: R-ketorolac reverses cachexia and restores health by correcting the immune disorder, paving the way for anti-tumor therapies to pursue long-term remission and the ultimate cure of advanced cancer. We are advancing R-ketorolac-focused immunotherapies to realize this vision.

In my view, cancer cachexia, in essence, is an immunological syndrome manifested as a metabolic one. My 15 years of study from cytokine pathways to MDSC roles to RK's potential, paint it as a battlefield where immunity turns against the host. By centering these mechanisms, we can move beyond palliation to meaningful intervention, offering patients not just survival, but resilience and dignity in their fight against the most dangerous stage of cancer.

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