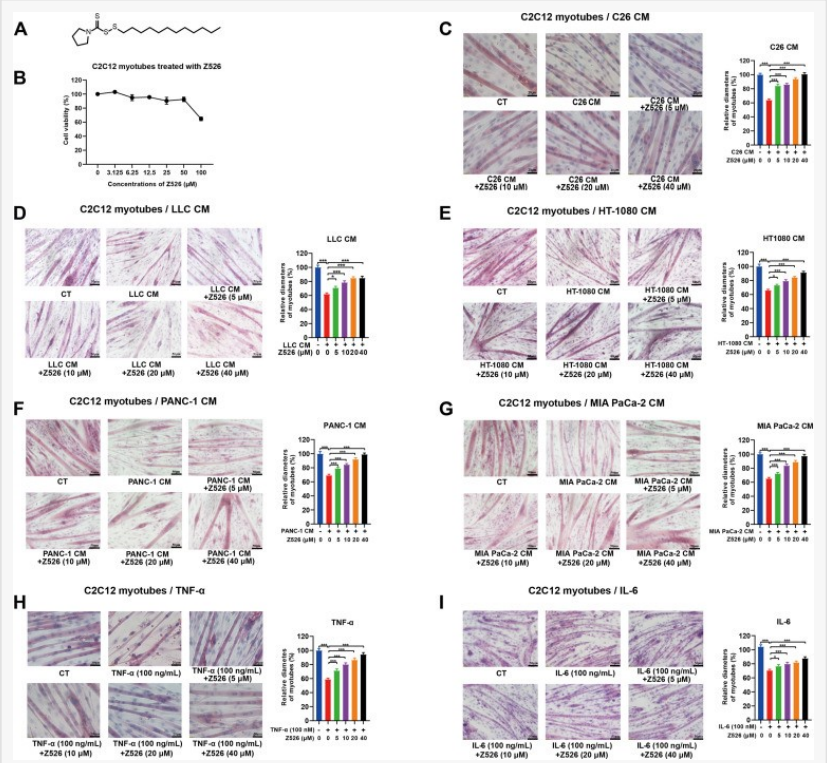
Z526- A NOVEL THERAPEUTIC CANDIDATE AGAINST CANCER ASSOCIATED CACHEXIA

Z526- a novel dithiocarbamate-like compound reverses cancer associated cachexia via mitigating NF-kB signaling and oxidative stress.



C2C12 myotubes were treated with CMs of cachectic tumor cells or pro-cachectic inflammatory cytokines in the presence or absence of Z526 at various concentrations for 48 h. (A) The structural formula of Z526. (B) Z526's effects on cell viability of C2C12

CHONGQING, CHONGQING, CHINA, January 29, 2025 /EINPresswire.com/ -- In a recent study, researchers demonstrated that Z526, a novel dithiocarbamate-like compound, mitigates cancer-associated cachexia (CAC) both in vitro and in vivo. Oral administration of Z526 slowed weight loss and improved muscle atrophy, fat loss, and grip force. Furthermore, the authors elucidated that Z526 potentiates anti-CAC effects by regulating NF-kB signaling and suppressing oxidative stress.

Cancer-associated cachexia is a metabolic disorder characterized by weight loss, anorexia, systematic inflammation, and redox imbalance. CAC is prevalent in 50–80% of cancer patients and causes 30-80% of cancer-related mortality. Since CAC is a multi-factorial and pathologically complex disorder, no single intervention is effective; with NF-kB signaling and oxidative stress playing critical roles in the onset and progression of CAC, targeting these might offer options for its treatment.

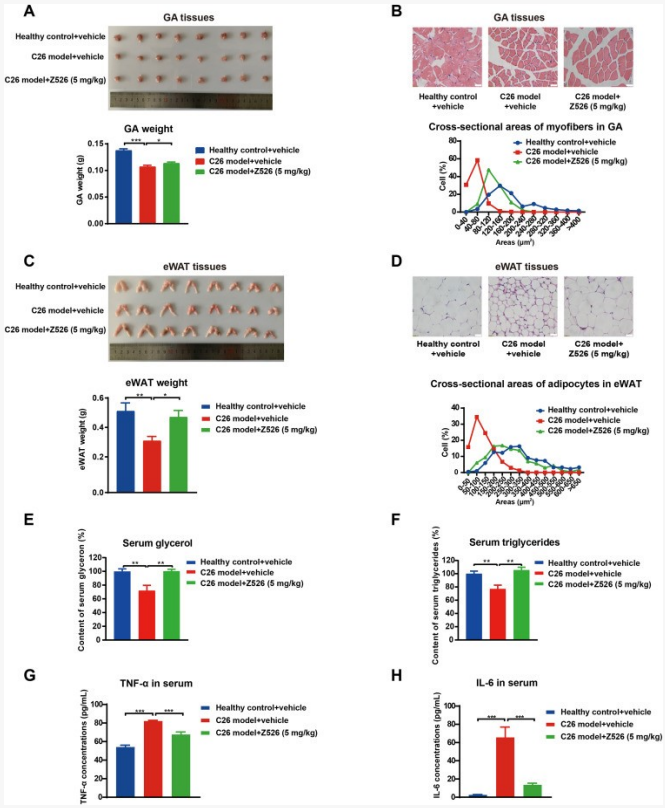
In this study, published in the Genes & Diseases journal, researchers from East China Normal University, Fudan University, and Shanghai University of Traditional Chinese Medicine investigate the anti-CAC effects of Z526, a novel dithiocarbamate identified during drug screening on the C2C12 myotube atrophy model of CAC. For the in vitro study, the authors used conditioned mediums derived from different tumor cell lines to induce C2C12 myotube atrophy and 3T3-L1

adipocyte lipolysis; C26 and LLC tumor-bearing mouse models were used for the in vivo study. Z526 administration improved C2C12 myotube diameter, suppressed lipolysis in 3T3-L1 adipocytes, and enhanced tumor-free body weight, muscle and fat loss, and grip force in tumor-bearing mice models. Mechanistically, Z526 exerts its anti-cachectic effects by i) regulating NF-kB signaling via inhibition of phosphorylation and subsequent nuclear translocation of P65, ii) reducing ROS levels in cachectic muscle and fat, and iii) regulating the metabolic signaling pathways mediated by NF-kB or ROS, such as protein synthesis (MHC, MyoD, AKT), protein degradation (MAFbx, p38), and lipolysis (AMPKα, HSL, p38).

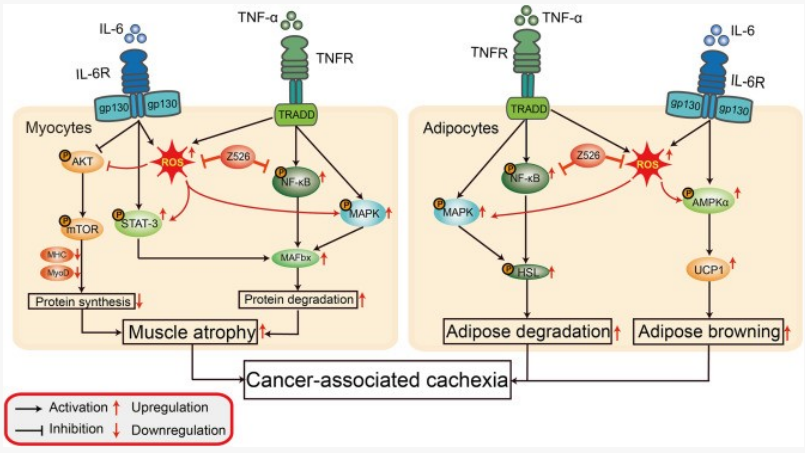
Z526 regulates metabolic signaling in muscle and fat to combat CAC by intervening in multiple pathogenic mechanisms (NF-kB signaling and oxidative stress) and its favorable preclinical safety profile presents it as a promising candidate for CAC treatment.

Reference
Title of the original paper Novel oral compound Z526 mitigates cancer-associated cachexia via intervening NF-kB signaling and oxidative stress

Journal Genes & Diseases
Genes & Diseases is a journal for molecular and translational medicine. The journal primarily focuses on publishing investigations on the molecular bases and experimental therapeutics of human diseases.



At the endpoint of the experiment, C26 tumor-bearing mice were executed, and tissues of interest were dissected for further analysis. (A) Representative images of GA and weight analysis and (B) CSA of myofibers in GA tissues and quantitative statistics. (



In cancer-associated cachexia, elevated TNF-α and IL-6 exacerbate muscle and fat loss by regulating multiple metabolic signaling pathways, which could be ameliorated by Z526's suppression of NF-κB signaling and oxidative stress. In cachectic muscle, Z526

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