**Attenuation of the toxic side effects of chemotherapy and statin treatment**

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Summary:

Modern drug therapies, such as chemotherapy cancer treatment or statins for cholesterol and cardiovascular-associated diseases, often suffer from high incidence of side effects due to damage to healthy cells. Since some side effects severely compromise patients health, they require dose reduction thereby limiting the treatment efficacy.

One of the common causes of these drugs toxicity is the induction of endoplasmic reticulum (ER) stress through these compounds, triggering related apoptotic and necrotic cell death pathways.

This technology is based on the discovery of a previously unrecognized signaling pathway (MGST2-LTC4) leading to apoptosis and/or necrosis following ER stress triggered by various drugs. Inhibition of this pathway by various antagonists is an effective means of attenuating the toxic side effects of chemotherapy and statin treatments when applied in combination, whilst still preserving their effectiveness.

Applications:

* Co-treatment with chemotherapy
* Co-treatment with statin treatment

Advantages:

* Lower collateral toxicities allow for greater flexibility in treatment dosage.
* Enhanced patient survival rate.
* More favorably considered as a line of therapy due to decreased side effects.
* Utilization of well-characterized compounds alleviates safety and toxicity considerations.

Technology's essence:

ER stress, elicited by chemotherapeutic agents such as doxorubicin, 5FU, vincristine and bortezomib, or statins such simvastatin, triggers cell death at least in part through generation of leukotriene C4 (LTC4), which induces ROS accumulation, DNA damage and subsequent cell death. LTC4 can be produced by two parallel pathways. Cells of hematopoietic origin express C4 synthase (LTC4S) and secrete their LTC4 load, thereby affecting nearby tissues. In contrast, as discloses by the present invention, non-hematopoietic cells generate LTC4 by the enzyme MGST2 (an isoenzyme of LTC4S), and retain it to act internally leading to their demise. This difference is the basis for the present invention. Thus, LTC4 receptor antagonists (montelukast, pranlukast, etc.) will alleviate the toxicity of chemotherapy towards non-hematopoietic tissues and cells, but retaining the therapeutic effectiveness of chemotherapy on lymphocytic leukemia, lymphoma and myeloma patients. In conjuction, it was found that pranlukast attenuated cell death triggered by a broad range (0.5-4 µg/ml) of simvastatin (a statin) concentrations.