**Attenuation of the Toxic Side Effects of Chemotherapy and Statin Treatment**

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| **Project Number:** | #1686 |
| **Principal Investigator:** | Prof. Menachem Rubinstein |
| **Patent Status:** | Pending |

**Overview**

Statins are a remarkably effective class of drugs. Results have shown that statins can lower plasma LDL levels by 25–35% and reduces the frequency of heart attacks by 25–30%. With cardiovascular diseases on the rise globally it is no surprise that Lipitor, a statin manufactured by Pfizer, is the best selling drug of all times. However, statins are also plagued with numerous serious side effects ranging from myositis to rhabdomyolysis, to other more common side-effect such as headaches, difficulty sleeping, muscle aches, tenderness or weakness, drowsiness, dizziness, nausea or vomiting , and abdominal cramping or pain.

The new technology presented here, is based on the discovery that inhibition of key components of the recently discovered MGST2-LTC4 signalling pathway is an effective means of attenuating the toxic side effects of statin treatment, whilst still preserving the effectiveness of the treatment.

**Toxic Side Effects of Statin Treatment - The Unmet Medical Need**

Statins are another class of compounds which serves as the primary therapy for hypercholesterolemia and for preventing cardiovascular diseases. In general, statins are well-tolerated, but they are known to trigger skeletal muscle toxicity. In fact, an estimated 5–10% of patients discontinue statin use due to myopathic symptoms ranging from mild to moderate myalgia characterized by muscle weakness, fatigue, and pain, to life-threatening rhabdomyolysis, which is defined as a massive and acute destruction of muscle fibers resulting in the release of muscle fiber contents.

**The Technology**

The technology is based on the discovery of a previously unrecognized pathway (MGST2-LTC4) leading to apoptosis and/or necrosis following ER stress triggered by various drugs. ER stress, elicited by specific reagents such as Simvastatin, a common lipid-lowering medication, triggers cell death at least in part through generation of leukotriene C4 (LTC4). This LTC4 is generated by the enzyme MGST2, which is an isoenzyme of leukotriene C4 synthase (LTC4S) ER stress and can induce reactive oxygen species (ROS) accumulation mediated by the ER stress-activated pathway, which leads to DNA damage and subsequent cell death.

The expression of MGST2 and LTC4S is mutually exclusive. LTC4S is expressed only in cells of hematopoietic origin, whereas MGST2 is ubiquitously expressed in all cells of non-hematopoietic origin. Once produced by these two enzymes, the mode of action of LTC4 is also strikingly different. Whereas LTC4S-expressing mast cells secrete their LTC4 load, thereby affecting nearby smooth muscle cells, the present invention discloses that MGST2-expressing non-hematopoietic cells retain the LTC4, which acts internally, leading to their demise. This difference is the basis for the present invention. Hence, LTC4 receptor antagonists (montelukast, pranlukast, etc.) will alleviate the toxicity of statins towards non-hematopoietic tissues and cells,while preserving their therapeutic effect. For example, it was found that pranlukast attenuated cell death triggered by a wide range (0.5-4 μg/ml) of Simvastatin concentrations. This research has been published in the prestigious scientific journal of [*Nature*](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4682057/) [[1]](#footnote-0).

***Advantages***

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

***Applications***

* Co-treatment with statin treatment

**Development Status**

1. **Pranlukast Attenuates Simvastatin Triggered Cell Death**

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|  | **Figure 1**. Survival of human WISH cells treated with the indicated concentrations of Simvastatin in the presence (dashed line) or absence (continuous line) of pranlukast (10 μM, 48 hours). |

1. **BAY-cysLT2 and BAY-u9773 attenuate simvastatin-triggered cell death of differentiated C2C12 mouse myocytes.**

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|  | **Figure 2**. (A) Survival of mouse C2C12 cells following differentiation into myocytes, treated with 10 uM Simvastatin for 5 days in the presence of vehicle, pranlukast (10 μM), BAY-cysLT2 (10 μM), BAY-u9773 (1 μM) or Mevalonate (71.4 μM). The plates were then stained with Crystal violet and the relative cell viability was determined. (B) Quantification of the staining intensity is shown. |
| 1. **Zileuton attenuates simvastatin-triggered death of differentiated C2C12 mouse myocytes.** | |
|  | **Figure 3**. (A) C2C12 immortalized mouse myoblasts (15,000 cells/100 ul DMEM) were seeded for 24 and then differentiated for 3 days (initiated by serum free medium supplemented with 1×ITS medium) and then treated with 20 μg/ml Simvastatin with or without montelukast (2 μM), zileuton (10 μM) or mevalonate (71.4 μM). After 4 days the cells were stained with crystal violet and photographed under light microscope. (B) Quantification of the staining intensity is shown. |

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1. Dvash, Efrat, et al. "Leukotriene C 4 is the major trigger of stress-induced oxidative DNA damage." *Nature communications* 6 (2015): 10112. [↑](#footnote-ref-0)