Modulators for Human Sirtuin 6 in Obesity and Diabetes Treatment and Assays for Screening Sirtuin 6

Invention Summary

This invention relates to a method, assay and inhibitors / activators associated with sirtuin 6 (Sirt6) mechanisms for treatment and prevention for obesity and diabetes.

Technology Overview

Sirtuins are known as NAD+-dependent deacetylases. Human sirtuins one through seven have been shown to regulate a variety of biological processes, including aging, transcription, metabolism, and apoptosis. Whereas Sirts 1-3 are known to have high deacetylase activity, Sirts 4-7 had not been previously recognized to have significant activity, but may utilize alternative substrates.

Sirt6, a nuclear sirtuin, has been reported to be important for DNA repair, transcriptional regulation of genes important for metabolism and immune responses, and longevity. However, lack of information on the activity of Sirt6 has been a major hindrance for development of Sirt6 inhibitors and activators. The present invention represents a breakthrough that can help in developing treatments targeting Sirt6 for obesity and diabetes.

The Lin group at Cornell has discovered that Sirt6 has unique and robust novel enzymatic activity, 300-fold more efficient than its deacetylase activity, which preferably and efficiently hydrolyzes long chain fatty acyl groups such as myristoyl lysine and palmitoyl lysine. Based on this discovery, a novel fluorogenic assay has been developed to screen for Sirt6 modulators.

Lysine fatty acylation is an abundant and important protein modification. One of the fatty acylated proteins is TNFα, a pro-inflammatory mediator. The researchers have proven that Sirt6 regulates TNFα fatty acylation and its secretion in THP-1 cells, a human monocyte cell line, and in bone-marrow-derived mouse macrophage.

Stage of development:

1/ A fluorogenic assay was demonstrated to work in vitro and is ready to be used in a commercial setting in vitro.

2/ Inhibitors that selectively target Sirt6 were also identified, and some of them have shown the ability to control cancer cell proliferation. Amongst the selected inhibitors, the inventors have evaluated Thiomyristoyl (TM) peptides and demonstrated that TM peptides are potent inhibitors for Sirt6, are cell-permeable, and increase TNFα fatty acylation in mammalian cells.

This technology represents the first discovery of new epigenetic modifications that can be targeted to treat human diseases.

Potential Applications

- A fluorogenic high-throughput assay for screening Sirt6 inhibitors or activators
- Lead compounds for the development of more potent Sirt6 inhibitors, which could be used as treatments for obesity and diabetes
Advantages

- Reliable assays to screen for inhibitors/activators of Sirt6
- Designed inhibitors for Sirt6
- Mechanism-based inhibitors

Publications

- PCT Application Number WO2012088268