Novel Small Molecule SIRT6 Activators/Inhibitors

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Technology description

The epigenetic modifier SIRT6 is of the sirtuin class of proteins. In transgenic mice, increased SIRT6 expression lowers LDL and triglyceride levels, improves glucose tolerance and increases mitochondrial respiration. Whole-body knockout of SIRT6 leads to profound metabolic defects and an accelerated aging phenotype. Liver-specific disruption of SIRT6 increased glycolysis and triglyceride synthesis, reduced beta oxidation, and increased fatty liver formation.

Reduced SIRT6 expression is observed in human patients diagnosed with fatty liver disease, as well as those with hepatocellular carcinoma and ovarian cancer. Discovery of SIRT6 loss-of-function point mutations in human cancer patients has provided additional evidence that diminished SIRT6 function is causative for cancer. Also, sirtuin activity is linked to the inhibiting of replication of diverse viruses, such as human cytomegalovirus, influenza A (H1N1) virus and an RNA virus.

Lastly, the targeted overexpression of SIRT6 in insulin-producing beta-cells causes increased secretion of insulin in response to glucose. Thus, compounds that promote activity of SIRT6 could be useful for treating liver disease, diabetes and cancer. UW–Madison researchers have developed three novel compounds (CL-5D, SW-055, SW-062) that activate SIRT6 in biochemical assays. Two other compounds (CL-5D-Me and SW-055-Me) are methyl esters that are not expected to be active in biochemical assays but are expected to be more cell permeable and act as prodrugs, becoming active upon ester hydrolysis in cells.

The Wisconsin Alumni Research Foundation (WARF) is seeking commercial partners interested in novel compounds that could be developed into treatments for nonalcoholic fatty liver disease or cancer.

Application area

Pharmaceutical development

Advantages

Potential drug leads

Institution

Wisconsin Alumni Research Foundation

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