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New Research Suggests Novel Insulin Sensitizer Works Through a New Mechanism to Treat Root Cause of Type 2 Diabetes

Washington University School of Medicine researchers show MSDC compound has anti-diabetic efficacy without side effects profile of current drugs to treat insulin resistance[1]

KALAMAZOO, Mich., May 29, 2012- A study published online in the *Journal of Biological Chemistry* (http://www.jbc.org/content/early/2012/05/23/jbc.M112.363960) showed a new drug to treat diabetes being developed by Metabolic Solutions Development Company, LLC (MSDC), MSDC-0602, improved insulin resistance and inflammation in obese mice. These findings by researchers at Washington University School of Medicine, in collaboration with colleagues at the University of Michigan and MSDC, suggest that MSDC-0602, a novel anti-diabetic drug which is in Phase 2 clinical trials, may constitute the first in a class of next generation insulin sensitizers that appear to work through a new biochemical mechanism to treat insulin resistance and type 2 diabetes.

"Currently-approved insulin sensitizing drugs are effective but their use is limited by side effects believed to be caused by the over-activation of the peroxisome proliferator-activated receptor gamma (PPARγ)," said Brian N. Finck, PhD, Research Assistant Professor in Medicine, Division of Geriatrics & Nutritional Science, Washington University School of Medicine. "Our findings provide the framework for the discovery and development of a new class of insulin sensitizers that can operate independent of the activation of PPARγ."

Previously, it was believed that both the anti-diabetic activity and the side-effects of these agents were mediated through activation of a nuclear receptor called PPARγ. However, it is now generally accepted that over-activation of PPARγ drives the unwanted and often unacceptable side effects associated with the currently-approved insulin sensitizers, which are PPARγ agonists, and emerging evidence suggests that the potent anti-diabetic efficacy can be separated from the ability to activate PPARγ. Some, including MSDC researchers, have suggested that key aspects of the insulin sensitizing actions remained to be identified.

"Having been among the original workers in this field, we have long been skeptical of the PPARγ hypothesis as an explanation for all of the actions of the insulin sensitizers and have been concerned the singular pursuit of compounds that activate PPARγ has hampered the development of safe, effective, and durable treatments for insulin resistance," said Jerry Colca, PhD, president, chief scientific officer and co-founder of MSDC. "The work of Dr. Finck and his colleagues affirms our goal to understand this important pharmacology in a way that will allow

the development of new therapeutic agents to improve treatment outcomes for patients with type 2 diabetes."

This study, titled "Insulin Resistance and Metabolic Derangements in Obese Mice are Ameliorated by a Novel Peroxisome Proliferator-Activated Receptor γ-sparing Thiazolidinedione," evaluated MSDC-0602 for its effects on insulin resistance in obese mice. These researchers found that MSDC-0602 markedly improved several measures of multi-organ insulin sensitivity, fat tissue inflammation, and metabolic disturbances in the liver including suppressing fat and glucose production, which are increased in diabetic liver cells. These beneficial effects were mediated, at least in part, via direct actions on liver cells and were preserved in liver cells lacking PPARγ, indicating that PPARγ was not required to suppress the formation of fat and glucose.

The study was conducted by the Department of Medicine at Washington University School of Medicine and the Department of Internal Medicine at the University of Michigan, in collaboration with scientists at MSDC.

MSDC is developing two novel compounds to treat type 2 diabetes that are intended to improve the body's sensitivity to insulin (which moves blood sugar (glucose) into cells, where it is stored and later used for energy), lower the percent of calorie-storing "white" fat, increase the production of calorie-burning "brown" fat, preserve the function of pancreatic beta cells (which produce insulin), and possibly protect neurons in the brain (which could be important in treating diseases such as Alzheimer's and Parkinson's disease).

Phase 2b results for MSDC-0160, a novel once-a-day oral insulin sensitizer, will be presented June 9, 2012 at the 72nd Scientific Sessions of the American Diabetes Association (Abstract #996-P). MSDC previously reported results from a Phase 2a study of MSDC-0602, a second novel once-a-day oral insulin sensitizer, which showed the potential of that agent to achieve significant glucose control, reduce HbA1c, and increase insulin sensitivity in type 2 diabetes patients.

About Metabolic Solutions Development Company

Metabolic Solutions Development Company (www.msdrx.com) is a drug discovery and development company investigating novel molecular targets and developing new therapeutics to treat metabolic diseases associated with age-related mitochondrial dysfunction, especially insulin resistance and type 2 diabetes. The company was founded in 2006 by former researchers of The Upjohn Company and has raised more than $55 million to support development of its lead compounds MSDC-0160 and MSDC-0602.

[1] News Release from Washington University School of Medicine, *"Investigational diabetes drug may have fewer side effects,"* and podcast can be found at: https://news.wustl.edu/news/Pages/23933.aspx.

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