

News Release

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Researchers present findings on new drug target for treatment of type 2 diabetes

**Data presented at 48th Annual Meeting of the
European Association for the Study of Diabetes**

BERLIN, Oct. 2, 2012 – Researchers at Metabolic Solutions Development Company, LLC (MSDC) have identified a mitochondrial target through which insulin sensitizers achieve their anti-diabetic effects. New insights into this protein complex and its role in metabolic signaling are expected to enable the pursuit of alternative approaches to the discovery of novel, insulin sensitizing agents. Data supporting this finding are being presented today at the 48th Annual Meeting of the European Association for the Study of Diabetes.

The newly identified mitochondrial protein complex is being referred to as the mitochondrial Target of Thiazolidinediones (TZDs), or mTOT™. Key proteins in the mTOT complex have recently been identified as playing an important role in the metabolism of pyruvate, an important chemical compound at the crossroads of metabolic regulation (EASD Abstract #593).

The mTOT complex appears to function as part of a molecular “sensor switch” connecting mitochondrial metabolism to important cellular activities, such as carbohydrate, lipid, and amino acid metabolism, all of which are out of balance in patients with type 2 diabetes.

Modulation of mTOT in some cells favors increases in cell differentiation and fat oxidation. The overall effects of compounds acting by this mechanism include increased insulin sensitivity, generation of brown fat, and preservation of pancreatic β -cells (beta cells).

“For the first time, we are beginning to understand that the mechanism by which insulin sensitizers reduce insulin resistance is through a direct mitochondrial action,” said Jerry Colca, PhD, MSDC’s co-founder, president and chief scientific officer. “Moreover, this new insight, coupled with our recent Phase 2 clinical results, suggests that we have taken a significant step forward to designing a new class of therapeutic agents for use in effectively treating patients with type 2 diabetes.”

Using a novel photo-catalyzable affinity probe modeled after one of their drug candidates together with mass spectrometry-based proteomics, MSDC scientists

identified two phylogenetically-conserved proteins in the inner mitochondrial membrane. The conservation of these proteins in different species from yeast and fruit flies to humans suggests that they play a fundamental role in cell regulations. Proof of identity has been demonstrated by gene expression and knockdown of expression.

Importance to the Future Discovery and Development of Anti-Diabetic Drugs

The discovery by MSDC researchers shows the lowering of plasma glucose can be achieved without having to activate a nuclear transcription factor called PPAR γ . Previously, it was believed that both the activity and the side-effects of the only approved class of drugs used to treat insulin resistance -- the core problem for persons diagnosed with type 2 diabetes -- were mediated through PPAR γ . However, it is now generally accepted that over-activation of PPAR γ drives the unwanted and often unacceptable side effects associated with the currently approved anti-diabetic insulin sensitizers, which are PPAR γ agonists.

MSDC Compounds in Development

MSDC is developing two novel insulin sensitizing agents that selectively modulate mTOT, a protein complex located in the inner mitochondrial membrane. Data from recently completed Phase 2 clinical studies of a prototype mTOT Modulator™, MSDC-0160, as well as Phase 2 clinical studies in diabetic patients of a second mTOT Modulator, MSDC-0602, support the company's hypothesis that the insulin sensitizing pharmacology can occur without the side effects associated with currently marketed insulin sensitizers.

mTOT Modulators appear to play a central role in the regulation of biochemical pathways essential to maintaining the appropriate level of blood sugar (glucose). These new drugs 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).

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.

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