

News Release

Metabolic Solutions Development Company to present at the Benzon Symposium No. 58 on *Adipose Tissue in Health and Disease*

KALAMAZOO, Mich., Aug 29, 2012 – Researchers at Metabolic Solutions Development Company, LLC (MSDC) have identified a mitochondrial protein complex through which insulin sensitizers achieve their anti-diabetic effects. Findings from this research are being presented August 30 at the Benzon Symposium No. 58 in Copenhagen, Denmark.

The newly identified mitochondrial target is being referred to as the mitochondrial Target of Thiazolidinediones, or mTOT™. Key proteins in this complex include Mpc2 (BRP44) and Mpc1 (BRP44-Like), which have recently been shown to function as the mitochondrial pyruvate carrier^{1,2}.

The mTOT complex functions as a molecular “sensor switch” connecting mitochondrial metabolism to important cellular activities, such as carbohydrate and lipid metabolism, that are out of balance in patients with type 2 diabetes. Activation of mTOT increases cell differentiation and favors fat oxidation, resulting in increased insulin sensitivity, generation of brown fat and preservation of pancreatic β -cells.

“Identification of this new mitochondrial target, and understanding its role in metabolic signaling, has enabled a new approach to developing the next generation insulin sensitizers for the treatment of type 2 diabetes,” said Rolf Kletzein, PhD, MSDC’s co-founder and senior vice president of research.

Using a novel drug analog photo-catalyzable affinity probe and mass spectrometry-based proteomics, MSDC scientists identified two phylogenetically-conserved proteins in the inner mitochondrial membrane, Mpc2 (BRP44) and Mpc1 (BRP44-Like). These proteins are present in, and play an important role in the development of organisms from yeast and fruit flies to humans. Proof of identity has been demonstrated by gene expression and knockdown of expression.

MSDC’s discovery suggests the lowering of plasma glucose can be achieved without having to activate the nuclear receptor PPAR γ . Previously, it was believed that both the activity and the side-effects of the only approved agents 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 this

¹ Bricker *et al.* Science. 2012 Jul 6;337(6090):96-100. Epub 2012 May 24.

² Herzig *et al.* Science. 2012 Jul 6;337(6090):93-6. Epub 2012 May 24.

transcription factor drives the unwanted and often unacceptable side effects associated with the currently approved anti-diabetic insulin sensitizers, which are PPAR γ agonists.

MSDC Compounds Demonstrate Clinical Proof of Concept

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 the company's prototype mTOT Modulator™, MSDC-0160, as well as Phase 2 clinical studies in diabetic patients of MSDC's lead mTOT Modulator, MSDC-0602, support the company's hypothesis that the insulin sensitizing pharmacology can occur independent of the activation of PPAR γ .

mTOT Modulators represent a new class of therapeutic agents for the treatment of type 2 diabetes that 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.

#