metabolic solutions development company

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Metabolic Solutions Development Company announces publication of data describing a new drug target for diabetes

Modulating mTOT may represent a new way forward to treat metabolic diseases associated with age-related mitochondrial dysfunction – especially insulin resistance and type 2 diabetes

KALAMAZOO, Mich., May 15, 2013 - Metabolic Solutions Development Company, LLC (MSDC) announced today the publication of data in the latest issue of the scientific journal PLOS ONE (http://dx.plos.org/10.1371/journal.pone.0061551) on a new drug target for type 2 diabetes located in the inner mitochondrial membrane, which includes recently identified proteins that control mitochondrial pyruvate import.[1] mTOT™ (**m**itochondrial **t**arget **o**f **t**hiazolidinediones) is a mitochondrial protein complex through which new anti-diabetic drugs exert their insulin sensitizing effects. Data suggest mTOT functions as a molecular sensor switch that coordinates carbohydrate, lipid, and amino acid metabolism with cell function. Recently published Phase 2b clinical data from a study[2] in 258 type 2 diabetic patients further demonstrate modulating mTOT could constitute a new approach for the discovery and development of potentially more useful and novel insulin sensitizers. This new drug target may also play a role in other diseases of aging such as Alzheimer's disease and Parkinson's disease.

Diabetes is an undertreated global epidemic affecting an estimated 340 million people world-wide, with a rapidly increasing incidence throughout the developed and developing world. In the United States alone, nearly 26 million adults and children live with the disease. An additional 79 million have pre-diabetes, placing them at increased risk for developing type 2 diabetes. Recently released research by the American Diabetes Association estimates the total costs of diagnosed diabetes have risen to $245 billion in 2012 from $174 billion in 2007, when the cost was last examined. This figure represents a 41 percent increase over a five-year period.

"The only drug that attacks both insulin resistance and beta cell dysfunction, the root causes of type 2 diabetes, is an insulin sensitizer," said Ralph A. DeFronzo, M.D., professor of Medicine and Chief of the Diabetes Division at the University of Texas Health Science Center and the Audie L. Murphy Memorial VA Hospital in San Antonio, Texas. "There is a growing interest in a new generation of insulin sensitizers that appear to bind to proteins in the mTOT complex, but not activate the PPARγ receptor at therapeutic doses. As such, these new therapeutic agents likely will not elicit the side effects associated with currently approved insulin sensitizers."

Previously, it was believed that both the activity and the side-effects of the only approved class of drugs used to treat insulin resistance, thiazolidinedione (TZD) insulin sensitizers, were mediated through PPARγ. It is now generally accepted that activating PPARγ drives the side effects of this class of therapeutic agents (e.g., increased adiposity, volume expansion, bone loss and congestive heart failure), which has limited the use of current drugs and prevented the development of new insulin sensitizing agents.[3] With the discovery of the mTOT complex, researchers now have a clear path forward to create new, more useful insulin sensitizers.

The mTOT discovery team is led by MSDC's co-founders, Jerry Colca, PhD and Rolf Kletzien, PhD, who were among the original researchers in the field of insulin sensitizers, and who selected and led the early development of Actos® (pioglitazone), a PPARγ agonist. MSDC scientists are utilizing their unique insight into the potential key role of the mTOT complex in the regulation of metabolic function to develop several classes of novel insulin sensitizers, which do not have the side effects that have prevented the development of new therapeutic treatments for type 2 diabetes.

Phase 2 Clinical Results Support New Target Hypothesis

Phase 2b clinical data published in the January 18, 2013 issue of *Clinical Pharmacology & Therapeutics* on the company's prototype compound, MSDC-0160, a novel once-a-day oral insulin sensitizer and the first in a new class of therapeutic agents called mTOT Modulators™, showed this new generation of insulin sensitizer met the study's primary endpoint of significantly reducing fasting plasma glucose (FPG) and significantly reduced hemoglobin A1c (HbA1c). The study was a 90-day, randomized, double-blind, comparator- and placebo-controlled, multi-dose study completed in 258 patients with type 2 diabetes. The study compared three doses of MSDC-0160 (50 mg, 100 mg and 150 mg) to maximum dose Actos

(pioglitazone 45 mg) or placebo taken orally once daily for 12 weeks. All treatments were well tolerated. There were no serious adverse events attributed by investigators to the MSDC drug.

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 type 2 diabetes.

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[1] Bricker, *et al*. (2012) A mitochondrial pyruvate carrier required for pyruvate uptake in yeast, *Drosophila*, and humans. *Science* **337**, 96-100; and Herzig, *et al*. (2012) Identification and functional expression of the mitochondrial pyruvate carrier. *Science* **337**, 93-96.

[2] Colca, *et al*. Clinical Proof-of-Concept Study With MSDC-0160, a Prototype mTOT-Modulating Insulin Sensitizer. *Clinical Pharmacology & Therapeutics* doi:10.1038/clpt.2013.10 .

[3] Colca, *et al*. (2006) What has prevented the expansion of insulin sensitisers? *Expert Opin. Investig. Drugs* **15**, 205-210.