metabolic solutions development company

News Release

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Metabolic Solutions Development Company Identifies New Drug Target for Treatment of Type 2 Diabetes

Phase 2 Clinical Results Support a New Way Forward in the Development of the Next Generation of Anti-Diabetic Insulin Sensitizers

PHILADELPHIA, June 9, 2012 – Researchers at Metabolic Solutions Development Company, LLC (MSDC) have identified a mitochondrial protein complex through which anti-diabetic drugs exert their insulin sensitizing effects when used to treat patients diagnosed with type 2 diabetes. Findings from this research are being presented today at the 72nd Scientific Sessions of the American Diabetes Association.

The newly identified mitochondrial protein complex is being referred to as the mitochondrial Target of Thiazolidinediones (TZDs), or mTOT™ (ADA Abstract #1096-P).

The mTOT complex functions as a molecular "sensor switch" connecting mitochondrial metabolism to important cellular activities, such as carbohydrate, lipid, and amino acid metabolism, that are out of balance in patients with type 2 diabetes. Such imbalances may also play a role in other diseases of aging such as Alzheimer's disease and Parkinson's disease, as well certain genetic diseases such as polycystic kidney disease.

"There's a critical need to find safe insulin sensitizers that could effectively be used to treat and stop diabetes," said Jerry Colca, PhD, MSDC's co-founder, president and chief scientific officer. "This significant step forward in our understanding of the mechanism by which drugs reduce insulin resistance, combined with our recent Phase 2 clinical results, suggest that we are on the right track to realizing this goal."

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, meaning 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.

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

The discovery by MSDC researchers suggests the lowering of plasma glucose can be achieved without having to activate a nuclear receptor called PPARγ. 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 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 anti-diabetic insulin sensitizers, which are PPARγ agonists.

Data from recently completed Phase 2 clinical studies of MSDC-0160, as well as studies in obese mice[1] and Phase 2 clinical studies in diabetic patients of a second compound, MSDC-0602, support the company's hypothesis that the insulin sensitizing pharmacology of these first in class mTOT Modulators™ can occur independent of the activation of PPARγ.

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. These 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).

Phase 2 Clinical Results Support New Target Hypothesis

Phase 2b results for MSDC-0160, also which were presented at this ADA meeting (Abstract #966-P), showed that this novel once-a-day oral insulin sensitizer, the first in a new class of therapeutic agents being referred to as mTOT Modulators, met the study's primary endpoint of significantly reducing fasting plasma glucose (FPG), as well as hemoglobin A1c (HbA1c), in a 12-week study in patients diagnosed with type 2 diabetes. Of particular importance, the data showed that changes in body weight, total hemoglobin, and an important biomarker linked to production of white fat were significantly less in type 2 diabetic patients treated with MSDC-0160 than in patients treated with a comparator drug, pioglitazone 45 mg, even though glucose was lowered

[1] **Insulin resistance and metabolic derangements in obese mice are ameliorated by a novel peroxisome proliferator-activated receptor g-sparing thiazolidinedione**. *Journal of Biological Chemistry*, published online May, 2012; http://www.jbc.org/content/early/2012/05/23/jbc.M112.363960.

to the same degree as this highest approved dose of pioglitazone.

Previously, results were reported from a Phase 2a study of MSDC-0602, a second novel once-a-day oral insulin sensitizer the company is developing, which also 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.

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