MEDIA ADVISORY

Metabolic Solutions Development Company previews latest findings on newly identified potential mechanism of action for insulin sensitization at Keystone Symposium on *Pathogenesis of Diabetes: Emerging Insights into Molecular Mechanisms*

Overview

Metabolic Solutions Development Company, LLC (MSDC) is developing novel insulin sensitizers that focus on a yet to be disclosed mitochondrial target. This novel mechanism of action will be previewed during the Keystone Symposia meeting *Pathogenesis of Diabetes: Emerging Insights into Molecular* Mechanisms in Santa Fe January 30 – February 2, 2012.

MSDC compounds MSDC-0160 and MSDC-0602 are insulin sensitizers that are selective for a mitochondrial molecular target (mTOT) identified by MSDC researchers. mTOT is at the crossroads of metabolism linking the cytoplasmic pathways with those in the mitochondrial matrix. It functions as a "switch" connecting mitochondrial metabolism to important cell functions disrupted in age-related disease processes including insulin sensitization and lipid oxidation.

Defining a new mechanism of action like mTOT may provide an answer to the significant unmet need for safe and effective insulin sensitizers. According to the American Diabetes Association and the U.S. Centers for Disease Control, 25.8 million children and adults in the United States—8.3% of the population—have diabetes and of these, seven million are undiagnosed. There are an additional 79 million people in the U.S. with prediabetes.[1] In adults, type 2 diabetes accounts for about 90% to 95% of all diagnosed cases of diabetes.[2]

MSDC-0160 is one of two novel compounds the company is developing to treat type 2 diabetes. In a Phase 2a clinical trial in 76 type 2 diabetic patients, MSDC-0160 improved insulin sensitivity and lowered blood glucose levels in humans without the side effects of current therapies. MSDC recently completed a 90-day Phase 2b study of this compound. Results from this study are expected to be reported in the coming months. Results from a recently completed Phase 2a study of the company's second oral insulin sensitizer, MSDC-0602, showed its potential to achieve significant glucose control, reduce HbA1c, and increase insulin sensitivity in type 2 diabetes patients. The company plans to initiate a 90-day Phase 2b study of MSDC-0602 in 2012.

Oral Presentation

Wednesday, February 1, 1:00 – 4:30 p.m.
Workshop 2: New Therapeutic Targets and Challenges
Santa Fe Convention Center

[1] http://www.diabetes.org/diabetes-basics/diabetes-statistics/ and http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf
[2] http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf

The mechanism of action underlying the insulin sensitizing pharmacology of MSDC compounds will be previewed in the presentation **"Insulin Sensitization through a Mitochondrial Metabolic Switch that Modulates Wnt Signaling"** by Kletzien, R et al.

Key points:

- MSDC compounds exert insulin-sensitizing pharmacology and regenerate brown adipose tissue (BAT) via modulation of a previously recognized mitochondrial target called mTOT.
- The targeted knock out of mTOT in mice is embryonic lethal. However, mouse embryonic fibroblasts ($M^{E}Fs$) from mTOT knock-out embryos fail to respond to drug. A separate mutation making a shortened version of $mTOT^{peg}$ cells exhibits an enhanced response to experimental drugs.
- Modulation of the mitochondrial target by the active compounds results in a metabolic brake on a pathway that otherwise limits the function of brown adipose cells. This signaling pathway also has positive effects on the pancreatic beta cells, which make insulin.

Poster Presentations
Tuesday, January 31 – February 2, 7:30 – 10:00 p.m.
Santa Fe Convention Center, Sweeney F, Main Level, Breakout Rooms

"Downregulating mTOR with a PPARγ-sparing TZD decreases human β-cell insulin resistance and restores insulin content " by Rohatgi, N et al.

"New PPARγ–independent Insulin Sensitizers Produce Differentiation of Brown-like Adipose Cells from a Subcutaneous Fat Depot and Increase Secretion of Adiponectin *in vitro"* by McDonald, WG et al.

For more information about the meeting, please visit the Keystone Symposia website at www.keystonesymposia.org

About Metabolic Solutions Development Company
Metabolic Solutions Development Company (www.msdrx.com) is a drug discovery and development company investigating novel molecular targets and 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, Jerry Colca, PhD and Rolf Kletzien, PhD, and it has raised more than $55 million to support development of its lead compounds MSDC-0160 and MSDC-0602.

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