BACKGROUND
Currently, there are no disease-modifying treatments available for the 10 million people with Parkinson's worldwide. Changing the course of Parkinson's by slowing or stopping disease processes or repairing damage is the focus of considerable research, particularly now as there is greater biochemical understanding of the disease. New therapeutic targets have been discovered, and matching potential treatments are now being developed with ever greater urgency.

MITOCHONDRIAL DYSFUNCTION AS A FEATURE OF PARKINSON'S
Mitochondria have a prominent role in energy metabolism, but also are involved in various key cellular processes, such as the regulation of calcium homeostasis, stress response and cell death pathways. Mitochondrial impairment is suggested to play a role in Parkinson's; therefore, therapies that improve mitochondrial function might slow Parkinson's progression.

MITOCHONDRIAL PYRUVATE CARRIER AS A NOVEL TARGET FOR PARKINSON'S DISEASE MODIFICATION
The mitochondrial pyruvate carrier (MPC) (composed of proteins mpc1 and mpc2) is located in the internal mitochondrial membrane. Modulating MPC improves mitochondrial oxidative metabolism, which in turn mitigates over-activation of the mammalian target of rapamycin (mTOR), an important nutrient sensor that is inappropriately over-activated in Parkinson's.

WHY MSDC-0160?
A soon to be published paper in *Science Translational Medicine* reveals that modulation of MPC with MSDC-0160 is neuroprotective and anti-inflammatory in multiple models of Parkinson's. These results were associated with a reduced activation of mTOR.

MSDC-0160 is an experimental compound that has been in clinical development for the treatment of type 2 diabetes. It works by modulating the newly defined mitochondrial target (MPC), which coordinates mitochondrial metabolism with important cellular functions that are disturbed in metabolic diseases associated with age-related mitochondrial dysfunction. (1-7)

Given that MSDC-0160 has shown to be both neuroprotective and anti-inflammatory, it is a strong candidate as a therapeutic for neurodegenerative diseases such Alzheimer's and Parkinson's. (3,7-9)

EVALUATING MSDC-0160
In 2013, MSDC-0160 was evaluated by The Cure Parkinson's Trust's Linked Clinical Trials Committee, a world-renowned group of Parkinson's experts who assess dossiers developed on viable and novel drug targets that have the potential to mitigate the course of Parkinson's. In 2013, MSDC-0160 was discussed in detail, and the committee recommended further specific preclinical work (now completed and soon to be published in *Science Translational Medicine*). The Committee meets annually, and it has been following the preclinical developments with this important candidate each year. In 2016, MSDC-0160 was highly prioritized to move forward to the clinical trial stage.

ADDITIONAL EVIDENCE
Insulin resistance in Parkinson's
Systemic insulin resistance is one feature of type 2 diabetes that is thought to be associated with the onset of Parkinson's. People with Parkinson's commonly display impaired glucose tolerance, which can induce brain insulin resistance. This impaired insulin signaling has not only been associated with alpha-synuclein build-up and mitochondrial dysfunction but also behavioral abnormalities seen in Parkinson's such as impaired cognition, anxiety and depression.
Clinical trials are ongoing in Parkinson’s to understand the role of insulin resistance, and how GLP1s (peptide type 2 diabetes treatments) may be valuable to slow the progression of the disease. These studies suggest a potential disease-modifying utility of GLP1. While a first-generation thiazolidinedione (TZD) insulin sensitizer, pioglitazone, did not demonstrate a significant protective effect in subjects with early Alzheimer’s when dosed at the highest dose approved for treatment of diabetes (10), the new class of insulin sensitizer anti-diabetic agents that impact the mitochondrial target directly and can be dosed to higher peripheral, and presumably central, exposures (2,3). Such an agent may prove to be very useful in the treatment of Parkinson’s.

**Insulin resistance/sensitivity—why might an mTOT modulator be relevant?**

Unlike first-generation TZD insulin sensitizers, which are also direct activators of the nuclear transcription factor PPARγ, MSDC-0160 is selective for the modulation of the mitochondrial target of the TZDs (mTOT) (1-3). For this reason, MSDC-0160 can be dosed to achieve insulin-sensitizing pharmacology not only in peripheral tissues, but also in the brain. This pharmacology results in improved insulin sensitivity by modulating mitochondrial metabolism in a way that protects mitochondria and the control of inflammation and clearance of misfolded proteins (7) such as alpha-synuclein.

It is important to note that while compounds that improve metabolism in this way may be useful on their own, they may also prove to be powerful in combination with agents that work in other ways.

**REFERENCES**


