Targeting the Microbiome in the MPTP-Lesioned Mouse Model of Parkinson’s Disease: Live Biotherapeutic Products (LBPs) Demonstrate Disease Modifying Effects

S. Chetali,1 P. Ravenscroft2, A. Ettorre1, J.B. Koprich2, M.P. Hill2, J.M. Brothie2 & I.E. Mulder1

14D Pharma Research Ltd., Aberdeen, United Kingdom; 2Atuka Inc., Toronto, ON, Canada

Aim

To assess the disease-modifying potential of microbiota-derived novel Live Biotherapeutic products (LBPs) in a mouse model of Parkinson’s disease (PD).

Introduction

Parkinson’s disease (PD) is a progressive neurodegenerative disorder predominately affecting dopamine-producing (dopaminergic) neurons in the substantia nigra. PD affects more than 10 million people worldwide, making it the most common movement disorder and the second most common neurodegenerative disorder.

The cause of PD is unknown, with both genetic and environmental factors speculated to play a role. Characteristics of PD is progressive loss of muscle control, leading to tremors, rigidity, dyskinesia, vocal symptoms, postural instability and walking/gait difficulties. In addition, 15% of people with PD have gastrointestinal (GI) abnormalities, primarily constipation.

Accumulating evidence suggests an interplay between the GI tract and brain in PD, supported by findings such as alteration in the gut microbiome composition and presence of α-synuclein deposits in the enteric nervous system (ENS). Research has suggested that the gut microbiome has a potential role in the pathogenesis and treatment of PD. Identification of bacterial strains with disease-modifying actions, be they neuroprotective, neuroregenerative or compensatory to slow, halt or reverse disease and/or symptoms would be of great value in the treatment of PD.

Experimental Design

<table>
<thead>
<tr>
<th>Group</th>
<th>LBPs Administered</th>
<th>Treatment</th>
<th>Dose &amp; Route</th>
<th>Dosing Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PBS</td>
<td>PBS</td>
<td>0.5 µL, q.d.</td>
<td>10 days</td>
</tr>
<tr>
<td>2</td>
<td>MPTP</td>
<td>MPTP</td>
<td>5 mg/kg, q.d.</td>
<td>10 days</td>
</tr>
<tr>
<td>3</td>
<td>MRx0005</td>
<td>MRx0005</td>
<td>10 mg/kg, q.d.</td>
<td>10 days</td>
</tr>
<tr>
<td>4</td>
<td>MRx0029</td>
<td>MRx0029</td>
<td>10 mg/kg, q.d.</td>
<td>10 days</td>
</tr>
<tr>
<td>5</td>
<td>PBS</td>
<td>PBS</td>
<td>0.5 µL, q.d.</td>
<td>10 days</td>
</tr>
<tr>
<td>6</td>
<td>PBS + MRx0005</td>
<td>MRx0005</td>
<td>10 mg/kg, q.d.</td>
<td>10 days</td>
</tr>
</tbody>
</table>

MRx0029 protected against MPTP-induced losses in TH+ cell numbers and MRx0005 protected against MPTP-induced losses in striatal DOPAC.

Results

- MRx0029 protected against MPTP-induced losses in TH+ cell numbers and MRx0005 protected against MPTP-induced losses in striatal DOPAC.
- Administration of MRx0005 protected against MPTP-induced striatal dopamine loss.
- Administration of MRx0029 reduced MPTP-induced TH+ cell loss.

Bacterial Strains

MRx0005 Parabacteroides distasonis
MRx0029 Megaplasma massiliensis

Single strain Live Biotherapeutic products (LBPs) isolated from the gut microbiome of healthy donors.

Conclusion

The study evaluated the ability of two LBPs, MRx0005 and MRx0029, to reduce dopaminergic deficits in the MPTP-lesioned mouse model of PD. Treatment with MRx0029 reduced MPTP-induced deficits in striatal dopamine, in the substantia nigra from 46% to 11%. Treatment with MRx0005 reduced MPTP-induced deficits in striatal DopAC from 44% to 20%.

This study was conducted in male mice only. It would be interesting to see the effects in female mice in order to investigate the potential influence of sex.

In conclusion, the LBPs, MRx0029 and MRx0005, had a potential disease-modifying effect in the MPTP model. Further investigation is needed to fully elucidate their potential in the treatment of PD.

References