Gut microbiome-derived bacterial strains have the ability to modulate neuroinflammation and neurodegeneration in Parkinson’s Disease

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4D Pharma PLC is a pharmaceutical company focussed on developing live biotherapeutic products (LBPs) from the human gut microbiome. LBPs represent a new class of drugs that contain live organisms for the prevention, treatment or cure of disease. 4D Pharma currently has clinical stage programmes in IBS, IBD and cancer, and a strong pipeline of pre-clinical programmes in autoimmunity, inflammation, oncology and CNS disease.

Parkinson’s disease (PD) is a neurodegenerative disorder affecting around 7-10 million people worldwide. PD is characterised by the degeneration of dopaminergic neurons in the substantia nigra of the brain. It is a multifactorial disease where genetic and environmental factors contribute to disease aetiology in a “multiple hit hypothesis” model. Recent studies have demonstrated an interplay between the brain and gut in PD (Westfall et al., 2017). Moreover, analysis of mucosal and faecal samples have highlighted microbiome dysbiosis in PD compared to healthy donors (Minato et al., 2017). Identification of bacterial strains that can ameliorate the neuroinflammatory and/or neurodegenerative processes associated with PD, may lead to the development of new therapeutic approaches for the clinical management of the disease.

As a microbiome company with a proprietary culture collection of commensal bacterial isolates from healthy donors, we have developed the multi-disciplinary MicroRx® functional screening platform enabling us to target specific biological functions. A panel of bacterial strains from our culture collection was screened during our PD Discovery Campaign on different in vitro neuro-immune cell models. We have identified two bacterial strains, Parabacteroides distasonis MRx0005 and Megasphaera massiliensis MRx0029, with different and complementary cell responses to the stimuli used to mimic different features of PD pathology, namely neurodegeneration, neuroinflammation and effects on the gut barrier function.

Results

Neuroprotection- In vitro

Chemical and environmental factors are well-known triggers of oxidative stress, which plays a key role in neurodegeneration. While MRx0005 showed protection from oxidative stress induced by different stimuli in both glioblastoma and neuroblastoma cells (A, B and C), MRx0029 specifically protected differentiated neurons from oxidative stress induced by tert-Butyl hydroperoxide (TBHP) and completely reverted the cytotoxicity induced by MPP+ (B and C), showing a tropism for neuronal-like cells.

Neuroinflammation

Alongside misfolded α-synuclein proteins, toxins produced by bacteria such as LPS play a role in neuroinflammation. Both MRx0029 and MRx0005 decreased secretion of IL-6 in glioblastoma cells (U87) alone and in co-culture with differentiated neuroblastoma (SH-SYSY) cells (A and B). MRx0005-fed mice showed a decrease of IL-6 gene expression in the amygdala of the brain (C).