"Exploration of the therapeutic potential of astrocytic connectivity in *in vitro* models of Parkinson's Disease". Update March 2021

Parkinson's disease (PD) is the second most common neurodegenerative disorder of older age for which no cure or disease-modifying therapy exists. Up to 10 million patients worldwide, and around 145 000 in the UK alone, are affected. This disorder is typically associated with the death of cells called dopaminergic neurones; however, recent research, including ours, suggests that multiple additional cell types in the brain and gut are also affected.

In our current study, we are focusing on a particular type of brain cells called astrocytes. These cells are known to play important roles in brain functioning, but their involvement in PD is not yet well understood, and no current clinical therapies address alterations in these cells. We have found that astrocytes lose the ability to send signals under conditions similar to those of PD in Petri dishes, and also that they suffer from inflammatory changes.

Interestingly, regional differences between astrocytes from different parts of the brain exist, and we hypothesised that the response of these cells to PD-like challenges would also differ, as pathological changes in this disorder are known to spread to some parts of the brain at earlier stages.

The main outcomes of the study that we conducted with support from Ferblanc are twofold:

> Firstly, we confirmed a number of important regional differences between astrocytes from different brain areas. Some brain regions show aggregation of a misfolded protein called alpha-synuclein at earlier stages of PD, and we found that astrocytes from those areas were also more prone to sustaining alpha-synuclein aggregation in Petri dishes. This is a novel finding since previous literature mostly focused on regional differences between cells called neurones.
> Secondly, we have tested the ability of a new therapeutic compound to counteract PD-associated changes in astrocytes in our models, and we found that indeed this treatment reversed a number of adverse changes; the effect was brain region-specific.

Most current PD treatments focus on replacement of dopamine, as its levels become low due to dopaminergic neurone degeneration. There are a number of limitations associated with this approach. For instance, many patients develop serious side effects such as drug-induced dyskinesias (involuntary movements) and hallucinations; moreover, current treatments only address motor symptoms of the PD, while many patients report that the non-motor symptoms, which include cognitive and gastrointestinal problems, also have a great impact on their quality of life. If our new treatment approach is successful in further trials, it could become a promising candidate for addressing motor and non-motor treatments of PD.

Dr Nataly Hastings, University of Cambridge.