# THE PEMRIG INTERVIEWS

## OCCASIONAL CONVERSATIONS WITH PARKINSON'S RESEARCH SCIENTISTS

PEMRIG, your Parkinson's East Midlands Research Interest Group, is arranging occasional interviews with scientists involved in research into Parkinson's Disease (PD). In holding these interviews we hope to bring the latest Parkinson's research to your attention. Some of these interviews will be with scientists working in labs in the East Midlands but others will be with researchers from further afield so that the latest PD research is covered. In many cases the scientists being interviewed will have received funding from Parkinson's UK. The interviewer is PEMRIG member Martin Rumsby. The first PEMRIG interview is with

**Professor Flaviano Giorgini,**

**Department of Genetics and Genome Biology, University of Leicester.**

*Professor Flaviano Giorgini has a 3 year research grant from Parkinson's UK for a project entitled 'Unravelling the role of RAB39B in Parkinson's disease pathogenesis'. The grant employs a postdoctoral research associate and expires in January 2022. Here Martin provides a summary of the conversation with Flaviano.*

Professor Giorgini undertook doctoral training in Genetics at the University of Washington (Seattle, USA), and in subsequent postdoctoral studies became interested in the genetics of Huntington's disease, a neurodegenerative condition which has many similarities to Parkinson's – including gradual deterioration of parts of the brain. As there are also molecular overlaps between Huntington's disease and PD, he decided to study both problems when he started working at the University of Leicester. In PD changes occur in dopamine-producing neurones in an area of the brain called the substantia nigra, a characteristic being the presence of protein-rich aggregates in the cytoplasm of nerve cells. These aggregates are called Lewy bodies and they consist mainly of a protein called alpha-synuclein. In PD there is a problem in dopaminergic nerve cells in the normal pathways by which alpha-synuclein is degraded so that instead of being metabolised correctly alpha-synuclein accumulates as aggregates causing nerve cell death.

A problem Professor Giorgini's group is trying to understand is why the pathways involved in alpha-synuclein turnover and breakdown are faulty in dopamine-producing nerve cells causing the alpha-synuclein to aggregate. This is where RAB39B comes into the picture. RAB39B is a small protein which in normal cells

helps target other proteins to reach their correct location in a cell. In particular RAB39B helps target unwanted alpha-synuclein to lysosomal organelles where it is normally degraded without a problem. However, in some cases of PD it appears RAB39B can't do its normal job because it has mutated (i.e. some amino acids have been changed), so it doesn't work properly resulting in an accumulation of unwanted alpha-synuclein as aggregates.

Interestingly, RAB39B seems to be present widely in nerve cells throughout the brain and is not limited to only the dopamine-producing nerve cells. It could thus be one of the other factors that contributes to Parkinson's which causes the specific loss of dopaminergic nerve cells. Any one of these other proteins might be damaged specifically in the dopamine-producing nerve cells because we now know that the high levels of dopamine in these particular nerve cells can have damaging oxidation effects especially on altered forms of alpha-synuclein which occur in PD (1). Alpha-synuclein itself is involved in moving vesicles at synapses (the junctions between nerve cells where communication occurs). The movement of proteins and vesicles full of neurotransmitters around nerve cells, and the role of RAB39B in this process, is a very complicated story which Prof Giorgini and his colleagues have just summarised in a review (2).

A good deal of this project utilises fruit flies. While fruit flies seem a long way from humans, they are a fantastically useful experimental tool because of their fast reproduction cycle of ~10 to 14 days and because the levels of specific proteins can be raised, lowered or even knocked out completely by crossing one type of fruit fly with another. So the function of a particular protein can be studied more quickly and easily than using cultures of cells or even animals. The brain cells of fruit flies contain dRAB39, a version of mammalian RAB39B. When the levels of dRAB39 are lowered or knocked out altogether in fruit flies their life span, movement and mitochondrial function are all affected. These flies also show a loss of dopaminergic nerve cells as well as changes in circadian rhythms affecting sleep patterns. Such studies strongly suggest that there is a link between dRAB39 in flies and hence RAB39B in mammalian cells to many of the effects seen in PD. In the short-term this work is unlikely to lead to a new therapy, but it will help the research community understand how RAB39B plays a role in the development of PD. In the longer term controlling RAB39B function so it becomes more active – perhaps by targeting the proteins which control its activity - may have therapeutic relevance.

Professor Giorgini's group is also interested in the DJ-1 protein, which is linked to early onset Parkinson's. The DJ-1 studies (3) are performed in collaboration with Dr Mariaelena Repici at Aston University, Birmingham. DJ-1 is a small protein of 189 amino acids, which is found in many cells. It was first linked to early onset, familial forms of PD in 2003 and oxidized DJ-1 is found in the brains of many idiopathic PD individuals. Mutated forms of DJ-1 are associated with PD-like symptoms. DJ-1 is involved in protecting cells from oxidative stress which is important in most nerve cells and it has therapeutic potential as discussed by Repici and Giorgini in a recent review (3). DJ-1 has also been suggested as a possible biomarker to detect PD earlier than is currently possible.

It is hoped that the funding for this RAB39B-related work can be extended beyond the current end date to make up for the several months lost when the lab was completely closed during the first lockdown stage of the Covid pandemic. Professor Giorgini hopes to better understand by the end of grant where RAB39B fits in to the development of alpha-synuclein aggregates in PD and if more questions need to be answered further funding will be sought to continue this work.

**Further reading:**

1. Mor D F et al (2019) The usual suspects-dopamine and alpha-synuclein conspire to cause neurodegeneration. Mov Disord. Vol34(2): 167–179.

2. Koss et al (2021) Dysfunction of RAB39B-Mediated Vesicular Trafficking in Lewy Body Diseases. Mov Disord, in press.

3. Repici M, Giorgini F (2019) DJ-1 in Parkinson's Disease: Clinical Insights and Therapeutic Perspectives. J Clin Med Vol 8(9), 1377.