Report on a virtual visit to Professor Lisa Chakrabarti's Mitochondria laboratory, University of Nottingham at Sutton Bonnington, on August 9th 2022.

Professor Lisa Chakrabarti qualified from Oxford University as a biochemist. She developed an interest in the molecular basis of neurodegeneration when she worked at the University of Seattle, USA and then at the Institute of Neurology, Queen Square, London where she became began to study the role that mitochondria play in neurodegenerative diseases.

Lisa explained that most of the work in her lab is on mitochondria isolated from the cerebellum rather than the substantia nigra, the area of the brain most affected in Parkinson's. Her interest in the cerebellum is because this part of the brain controls balance and falls, emotion and anxiety, dyskinesia, sleep, dexterity and bladder function, all of which are problems in Parkinson's. Surprisingly, the cerebellum is not well studied in Parkinson's. Lisa stressed that there is an enigma here since there is no apparent loss of neurones in the cerebellum in Parkinson's as occurs in the substantia nigra and that the cerebellum may even have protective features in Parkinson's which if upregulated could form the basis of a new therapeutic approach. Lisa stressed the importance of the Parkinson's brain bank in enabling her to get cerebellar tissue from normal and Parkinson's brains for her studies.

We learned that mitochondria are the power houses of a cell producing the energy needed to drive all other reactions in a cell. Mitochondria are composed of many lipids (fats) and proteins and have a double membrane surrounding their matrix as Lisa showed in a high magnification image of mitochondria taken with an electron microscope. In Parkinson's mitochondria in the cerebellum undergo the same changes as occur in mitochondria in nerve cells from the substantia nigra but the changes do not lead to cerebellar nerve cell death. Lisa explained how her lab has analysed many matched mitochondrial samples from normal and Parkinson's cerebellar tissue to discover that there are big differences in the quantities of a class of lipid molecules called eicosanoids that regulate inflammatory reactions. The levels of some eicosanoids is increased in cerebellar mitochondria in Parkinson's affecting inflammation while the content of other eicosanoids is decreased. Eicosanoid levels in mitochondria from female cerebellar tissue are higher when compared with levels in mitochondria from males. Further work to define the importance of these male/female differences in eicosanoid levels in cerebellar mitochondria in Parkinson's is in progress.

Lisa is also investigating the influence of exercise on how mitochondria age. Her lab is using fruit flies with a PINK1 mutation as found in early onset Parkinson's to examine how exercise modifies mitochondrial function. So far the study has revealed that changes in the mitochondrial proteome caused by the PINK-1 mutation can be partially brought back to normal by exercise.

Lisa explained that her lab has discovered that the oxygen-transporting iron-containing molecule haemoglobin (Hb) normally found in red blood cells can also be detected in mitochondria where it is localised to the space between the outer and inner membranes. This is being studied in an ataxia model of neurodegeneration and the question being asked is does this mitochondrial Hb contribute to the observed neurodegeneration and if so how? I found this of particular interest since the metabolism of iron in nerve cells is disturbed in Parkinson's possibly contributing to the death of nerve cells in the substantia nigra. Lisa's group have shown that Hb levels in cerebellar mitochondria from Parkinson's are lower compared with cerebellar mitochondria from Alzheimer's disease and control tissue and that there are again male/female differences. The Michael J Fox Foundation has funded Lisa's lab to investigate this distribution of iron in mitochondria from Parkinson's brain tissue. The results so far reveal that Hb is present in mitochondria in frontal lobe, cerebellar and substantia nigra

tissue jn Parkinson's but questions about what the Hb is there for and why are there male/female differences remain to be answered.

Lisa concluded her talk by describing a comparative approach her lab is taking to understanding the role of Hb in mitochondria. This involves analysing mitochondria from different species with varying life spans to determine how their mitochondrial Hb levels vary. Mitochondria from Antarctic icefish have no Hb at all so are used as a 'knockout' animal to study the function of Hb in mitochondria. Lisa recounted how she spent two months on a ship in Antarctica catching icefish and analysing their mitochondria to discover how their energy producing ability compares with mitochondria which do contain Hb. Perhaps PEMRIG will be invited back to Lisa's lab to hear the results of this study.

The virtual talk raised many questions which Lisa answered before she handed us over to her PhD students Nial, Eve and Hannah for a virtual lab tour. Niall walked us round the spacious lab showing us -20oC and -80oC freezers and the crucial ice machine. He demonstrated western blotting and explained how an antibody is used to identify a specific protein separated on a gel. He described how mitochondria are isolated by centrifugation and how their oxygen consumption is measured. Thanks to all for a clear explanation of the techniques being used.

PEMRIG members and guests thanked Lisa for giving us insight into the exciting research being undertaken in her MitoLab to understand the role of mitochondria in Parkinson's and other neurodegenerative conditions.

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