10TH ANNUAL PEMRIG RESEARCH FORUM - OCTOBER 9TH 2021

A perspective by Martin Rumsby

This summary highlights some aspects of the Forum talks that the writer found interesting. Please listen to the full talks using the YouTube link provided..

The first talk '**Using technology to Accelerate Parkinson's Research**' by Professor David Dexter, Associate Research Director at Parkinson's UK (PUK), highlighted several technological advances which are helping to move Parkinson's research forward in collaboration with academic and pharmaceutical companies world-wide.

One controversial question addressed initially was whether PUK should offer genetic screening to identify any of the ten or so mutated genes known to be associated with the familial form of Parkinson's. Pre-pandemic there had been a consensus in favour of offering such screening and this issue is to be discussed again when the Covid situation improves since drugs against two of the mutant proteins already identified in familial Parkinson's are in clinical trials and it would therefore be valuable to identify those PwP who would benefit from such drugs if the trials are a success.

I had not thought much about the problems of running Parkinson's clinical trials so David's comments about how wearable devices and apps for smart phones are being developed by PUK with partners to improve patient selection for trials to reduce placebo effects, improve accuracy and save money were of great interest. All these new technological approaches need approval by Regulators so the Oxford PARKAI app on a smart phone, for example, is currently in trials needed to prove to the Regulatory Authorities that the data collected on the phone accurately mirrors what clinicians also measure about Parkinson's progression. Such technology including artificial intelligence (AI) can now identify sub-groups of patients for trials increasing the accuracy of results with the potential for personalised care plans.

I was especially interested to hear about the development of MRI-focussed ultrasound (FUS) as a potential non-invasive alternative to deep brain stimulation and that with FUS new areas of the brain, for example those controlling balance and gait can be targeted. Funding to make Dundee a centre of excellence for the development of FUS is being sought. Let's hope there's no FUS about getting the funding! Sorry, couldn't resist that.

'**Could the cells' energy status be the key to Parkinson's in all people with Parkinson's?** This was the question addressed by Dr Heather Mortiboys from the Institute of Translational Neuroscience, University of Sheffield. Heather explained that mitochondria are the energy producing organelle in cells and that her research over the last 20 or so years has shown that the mitochondria in nerve cells from many but not all PwP are not producing enough energy, have a different shape from normal and are not recycled efficiently by a process called mitophagy. Her work has revealed that these same defects also occur in mitochondria from skin, muscle and white blood cells from PwP. This set me wondering if mitochondria in all the different cells in the body

of PwP show the same defects, if the defects are the same in all PwP and whether they have been present from birth to contribute later in life to the onset of Parkinson's. I would have liked to hear a bit more detail about exactly what is wrong with mitochondria from PwP to explain their defect in energy production and shape and whether this energy problem in mitochondria is what contributes to the oxidative stress associated with PD.

Apparently dopaminergic neurones in the brain are very branched and need lots of energy to send nerve signals along the branches so they are supersensitive to any reduction in energy production by their mitochondria.

It was interesting to learn that skin cells from PwP and controls can be cultured in the laboratory to screen drugs. **A techniques video showed what day to day working on this research is like. A sonic wave machine is used to get the many different drugs being studied onto the cultured cells.**

The good news is that a drug which boosts ATP production by the defective mitochondria found in PwP is in clinical trial (see final talk) and many more compounds, especially repurposed drugs which do not have to go through rigorous safety testing again, are being screened.

It was also exciting to hear that the skin cells from PwP and controls can be reprogrammed into stem cells and then ultimately into dopaminergic neurones on which drugs to restore mitochondrial function can now be tested and mitochondrial DNA analysed against controls to identify what is going wrong with mitochondria in Parkinson's.

'**Getting under the surface of Parkinson's Disease: Metabolomics and Diagnostics from swabbing skin'** was the intriguing title of the talk given by Professor Perdita Barran, an expert in Mass Spectrometry (MS) from Manchester University. **MS is an ultrasensitive separation technique which can identify individual chemical molecules in a mixture and measure how much of a each substance is present**.

We heard how MS and related techniques are being used by the Manchester group to analyse sebum following observations first made by Joy Milne (who has hyperosmia) that certain chemicals in this skin secretion from PwP have a distinctive odour. The chemicals in the sebum from PwP are specific biomarkers which make it possible to detect PD before clinical signs develop and facilitate monitoring disease progression by using a biofilm detector as mentioned by David Dexter.

The MS work has identified several fatty type molecules which suggest that some aspects of fat metabolism in PwP are abnormal. It wasn't clear to me which of the abnormal fat molecules identified accounted for the odour of Parkinson's that super smellers like Joy Milne can detect. The careful analyses have ruled out the possibility that the observed chemical differences are due to medication effects. Apparently problems with sebum secretion in PD were first identified in 1927 but have not been followed up.

The sebum analyses have identified problems with what is known as the carnitine pathway involved in fatty acid metabolism and I wondered if such findings relate to the problems of reduced energy production in mitochondria in PwP described earlier by Heather Mortiboys.

Mitochondria in cells utilise long chain fatty acids (e.g. palmitic/oleic acids) as an energy source. These fatty acids need the help of the carnitine transport pathway to get into mitochondria where they are then oxidised for energy. **So if there are defects in the movement of fatty acids into mitochondria because of problems with the carnitine cycle the oxidation of fatty acids as a fuel for energy production will be reduced.**

This sensitive work seems to indicate that altered fat metabolism is a key factor in Parkinson's as changes to other aspects of fat metabolism besides the carnitine pathway have been revealed.

The question to be resolved is exactly how these defects detected in fat metabolism lead to damage to dopaminergic neurones in the CNS and PD?

Bile, BlueRock, Beyer and Bial was the provocative title of the final talk given by Dr Simon Stott, Deputy Director of Research at Cure Parkinson's, a Charity solely focussed on disease modification in Parkinson's research and operating internationally.

I always look forward to Simon's upbeat account of what trials are in progress. He described their Linked Clinical Trials Initiative, where 21 of the leading experts on Parkinson's meet annually to evaluate drugs which have potential to be disease modifying in Parkinson's based on results in animal models. If a drug is prioritised then clinical trials are rapidly set up. The programme has been running for 10 years. Eight trials have been completed with 16 trials for 15 compounds on going.

When you think back to how few drugs were being considered not that long ago this is real progress. Of interest to what we heard from Helen Mortiboys and Perdita Barran is a trial with UDCA, a naturally-occurring bile acid used to treat gallstone problems. UDCA has been shown to improve mitochondrial health in animal models of Parkinson's and it has been studied in depth by Heather Mortiboys' and colleagues at Sheffield. A Phase 2 trial is in progress and will report shortly.

Another positive was the news about Exenatide (a drug used to treat blood sugar levels in Type 2 diabetes) which has shown beneficial effects on motor problems in Parkinson's. Exenatide is now in a Phase 3 trial and two new drugs with the same target as Exenatide are in Phase 2 trial.

Transplantation of cells into the brain is back in the news, Simon reported. BlueRock Therapeutics in the USA have started a Phase 1 trial with stem cell-derived precursor dopaminergic neurones grown in culture. The pharmaceutical company Beyer have acquired BlueRock so must think the approach has

potential. The 10 participants will be monitored for two years so there is some time to wait for results. Two other transplantation studies are in progress or are being planned.

One other trial also supported by a pharmaceutical company involves a collaboration between the Universities of Cambridge and Lund. The transplantation approach is being taken still further by Aspen Neuroscience to get round the problems of immune rejection. Aspen are using gene correction technology with neurones grown from a patients' own stem cells to treat Parkinson's, a really exciting approach using the latest technology available. So some very exciting treatments are in the pipeline.

In the meantime, I will continue supplementing my usual prescription with some antioxidant pills!

A very stimulating question and answer session followed ending a successful and informative Forum. It was especially interesting to hear what had led to each speaker getting involved in Parkinson's research.

Simon Stott's interest in Parkinson's started when he was working on the problem at a company called Neuronz in New Zealand and later at Cambridge University. He remembers thinking that because the problem is confined to parts of the brain rather than all over as in Alzheimers Parkinson's should be easier to understand and treat. He now realises this view was naïve but solving it has become something of an obsession. So his work at Cure Parkinson's organising and following the progress of trials allows him to continue the obsession.

Helen Mortiboys said that she got into Parkinson's largely as the result of one lecture during her university degree course where she was struck by comments that while much is known about Parkinson's nothing is known about controlling its progression. She thought well, if we know so much about Parkinson's why are we unable to limit progression. So she then studied for a PhD in Parkinson's and has followed a career in Parkinson's research ever since trying to reduce the gap between what is known and still not known and how progression can be stopped.

David Dexter said that his introduction to Parkinson's started on the dance floor going with his mother as a reluctant teenager while doing a degree. PwP came to the dance hall and while they walked in rather slowly when the music started their movements became more fluid as they danced around the hall. This set him off on a doctorate in Parkinson's research which he has been involved in ever since expanding our knowledge of the problem and designing drugs to slow progression or even stop and reverse progression. For him it all started on the dance floor!

Perdita Barran's earlier research work involved biophysical studies on the aggregation of proteins and stems from the time of 'mad cow disease' where misfolded prion proteins aggregate and kill nerve cells. This extended to work on amyloid protein aggregation. Her interest in Parkinson's came about when she met Joy Milne and began using her specialist mass spectrometry expertise to identify what the chemicals were in Parkinson's sebum that Joy could detect. Now this work has opened up a whole new area of research using mass spectrometry to define the changes in lipid metabolism that may be at the basis of Parkinson's.