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Conference Reports

Models in Parkinson's Research: Are we addressing the right questions?

Conference details: 18 May 2011; London, UK. ***Reviewed by:*** Dr Rosemary Fricker, Senior Lecturer, Keele University, UK.

The seventh Research Conference of the UK Special Parkinson's Research Interest Group (SPRING) brought together leading scientists and clinicians from across the globe to debate the value of current models of Parkinson's disease (PD). The aim of this one day meeting was to discuss the usefulness of current PD models in broadening our understanding of the disease process, and as a tool to test future therapies.

The first session set the scene by identifying the key features of PD that need to be reproduced in models. Jose Obeso (Navarra Medical School, Spain) and Tamas Revesz (UCL, London) described the complexity of neurodegeneration in PD, which affects many neuron subtypes and not solely the nigrostriatal dopamine neurons, causing a long phase of preclinical pathology, and evolving not only the cardinal motor symptoms but also cognitive impairments and dementia seen in PD. In addition, neuronal pathology appears as Lewy neurites in neuronal processes as well as Lewy bodies within cells, suggesting that problems with neurotransmission may be a key component of the disease process. There was some disagreement as to whether PD pathology is synchronized and multisystemic, or if it spreads in a caudo-rostral fashion from one region to another (the Braak hypothesis).

However, both speakers concluded that an ideal animal model should incorporate: age dependent and focal loss of dopamine neurons with associated motor dysfunction; Lewy body and Lewy neurite pathology; and progressive neurodegeneration that represents the non-motor components of the disease. The second session focussed more specifically on rodent models of PD.

Tim Greenamyre (Pittsburgh University, USA) gave an eloquent overview of the rotenone model developed in his laboratory, highlighting the strengths of this toxin-induced neuron degeneration. Rotenone targets complex 1 in the mitochondria, inhibiting mitochondrial respiration and thus energy metabolism.

Greenamyre's group have observed iron deposition in the Substantia nigra pars compacta (SNc) following rotenone administration, suggesting that iron may contribute to the pathology of the disease. Peter Magill (Oxford University) reported work to elucidate the nature of neuronal firing patterns in the basal ganglia circuitry, and how these are affected in PD to cause an increase in bradykinesia and rigidity. Injecting 6-hydroxydopamine to the basal ganglia (the 6-OHDA rat model) causes large changes in the β oscillation firing patterns of basal ganglia neurons, with increased synchrony of pairs of neurons particularly within the Globus Pallidus (GP).A single GP neuron can innervate neurons in the GP, Entopeduncular nucleus, Subthalamic nucleus and Substantia nigra pars reticulata. Thus, death of SNc dopaminergic neurons may cause whole networks of neurons to undergo

changes in rhythm, oscillation and synchrony and, by firing at the wrong time or in the wrong place within the basal ganglia, causing many of the symptoms of PD.
Dysfunction of the proteasome in clearing unwanted proteins from neurons is a candidate pathway that may be involved in the development of idiopathic PD. Dr Lynn Bedford Parkinson's UK Senior Fellow, Nottingham University) presented her work to develop a genetic mouse model, by conditional deletion of the 26S proteasome in tyrosine hydroxylase positive neurons. Mice with this deletion show progressive neurodegeneration and the formation of Lewy-like inclusions containing α-synuclein, ubiquitinated proteins and mitochondria. However, when these mice were crossed with α-synuclein null mice, lack of α-synuclein had no effect on Lewy body formation suggesting that it may not be a key player in the process.

The third session of the conference focussed on modelling PD in other animals and human cellular systems. Tilo Kunath (Parkinson's UK Senior Fellow, Edinburgh University) presented research to generate induced pluripotent stem cell lines (iPSCs) from a patient with familial PD caused by triplication of the SNCA gene encoding α-synuclein.

These iPSCs were differentiated into midbrain dopamine neurons and were shown to express double the levels of α-synuclein when compared to neurons derived from iPSCs generated from an unaffected family member.

Animals such as zebra fish, *Caenorhabditis elegans* and *Drosophila* have been used to model neurodegenerative disease and offer advantages such as short life cycles, relatively straightforward gene manipulation, simplicity or easier visualisation of neuronal circuitry, and the potential to screen large numbers of animals for pathology or potential therapies. Oliver Bandmann (Sheffield University) described techniques by his group for transient knock down of the PD-related genes DJ-1, parkin and PINK1 by injecting antisense oligonucleotides into zebrafish embryos at the single cell stage.This morpholino strategy can generate stable lines that display key features of PD such as mitochondrial dysfunction and loss of dopaminergic neurons.

Anton Gartner (Dundee University) presented research to generate PD models in C.elegans via α-synuclein gene mutation or using the 6-OHDA toxin to induce neurodegeneration. Using the 6-OHDA model to screen for neuroprotective genes, they have found that the membrane protein tetraspanin-17 may have a neuroprotective role for dopamine neurons depending on its specific expression level.

Alex Whitworth (Sheffield University), presented data on Drosophila models of PD derived by mutating the genes: PINK1 and Rhomboid-7. Their research suggests that aberrant fusion of mitochondria stops their degradation and this may play a role in neuronal death in PD.
The conference ended with an open discussion between the audience and a panel of experts: Paul Bolam, Oxford; Kieran Breen, Parkinson's UK; Jose Obeso, Navarra; Richard Wade-Martins, Oxford; and Rosemary Fricker, Keele. Many issues were raised including: Is PD a syndrome rather than a single disease, and should we therefore be developing more complex models, or indeed using humans as models? Which models might be most useful for the Pharmaceutical industry, enabling better therapeutics to be developed for early PD? One of the problems discussed was the lack of biomarkers for models,particularly for

in vivo imaging of rodents and primates to assess neuron degeneration and repair. The final conclusion? We should continue with both current and new avenues of research, as all models are good but none are yet sufficient.