Parkinson's disease over the last 20 years

– new concepts and developments

ACNR came into existence in 2000 following discussions between myself and Rachael Hansford in 2000 and so we thought we would use this 20th anniversary to review advances in certain fields over this same time frame, including one of my main research areas- Parkinson's disease (PD).

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In the time it has taken Cambridge University to realise that it has lost two priceless original notebooks belonging to Charles Darwin (https://www.bbc.co.uk/news/entertainment-arts-55044129) much has changed in our understanding and approach to Parkinson's Disease (PD). This in part is because of new scientific methods such as the discovery of how to make induced pluripotent stem cells (iPSCs);[1] the development of improved gene editing techniques such as CRISPR/Cas9[2] and the ability to undertake single cell RNA analyses.[3] However, much of our new understanding comes directly from observations made in the clinic and related biomaterials. In this short review I will highlight some of this.

The alpha synuclein prion hypothesis

In 2008 it was reported that patients in receipt of human fetal ventral mesencephalic allografts for their PD had, at post-mortem, evidence of alpha synuclein pathology within the transplant.[4,5] Given that these dopaminergic cells were at most only 10 or more years old this raised intriguing questions as to how these cells could have "got PD". One theory was that these grafted cells were placed into a stressful environment with low grade inflammation and that this upregulated alpha synuclein expression leading to Lewy body pathology. An alternative theory, and one that has generated much interest, was that pathological forms of alpha synuclein from the host PD brain had spread into the grafted tissue and seeded pathology there (reviewed in Volpicelli-Daley et al, 2018).[6] Subsequently many experiments have been done showing that certain forms of alpha synuclein (most notably pre-formed fibrils) can spread and seed pathology in the adult CNS. This coupled to the description of the pathological stages of PD by Braak and colleagues[7] has led to the concept that PD begins in the gut/olfactory system and then spreads along the connecting nerves into the brain seeding pathology as it does so. This means that over time problems ascend up through the brainstem (eventually reaching the dopaminergic cells of the nigra) and then across the cortex. This has two major implications; (i) that there is a prodromal stage with PD before the nigral dopaminergic cells acquire pathology and express this through the early motor features of tremor, bradykinesia and rigidity and (ii) targeting this abnormal species of alpha synuclein as it spreads using immunotherapy may slow down or even stop the disease process.

The concept of prodromal PD

It has long been thought that a premotor state for PD must exist given that it only starts to express itself motorically when 50% of the dopaminergic nigral neurons are lost and 80% of its fibres in the striatum. However, the problems were: What would that look like clinically and how could we detect it – and does it matter given we have no disease modifying therapies? However, this has now been revisited given the Braak hypothesis on the pathological evolution of PD and the intense interest in trialling new disease modifying therapies based in part on the possible prion like behaviour of alpha synuclein.

Given that the earliest pathology in the Braak staging in PD targets the lower brainstem (and especially its connections to the gut) and olfactory system, one would predict that prodromal PD would be characterised by alterations in olfaction, changes in gut function and other behaviours linked to the networks of cells affected in the lower brainstem-namely sleep and mood. This has now been shown to be true for many patients as they report such symptoms ahead of developing overt motor PD. In addition, retrospective studies have shown there is alpha synuclein pathology in the gut years ahead of developing overt PD[8] and prospective studies showing that patients with hyposmia and/or a REM sleep behavioural disorder (RBD) have a high rate of conversion to PD or similar alpha synucleinopathy.[9] This concept has now been formally recognised through the establishment of research criteria for prodromal PD[10] and the move towards thinking about disease modifying therapies targeting this stage of disease.

The stratification of PD and the basis of its heterogeneity

It has been known since PD was first described in 1817 by James Parkinson that not all patients look the same and follow the same clinical course and this has also been used to argue against the Braak hypothesis, in that not all patients show this temporal pattern of pathology. In this respect, a new alternative classification has been proposed around whether the disease starts in the PNS and spreads centrally or starts within the CNS itself and then out to more peripheral sites. This has gained some traction with recent imaging studies supporting this concept of PD falling into these two subtypes.[11]

Over the last twenty years, though, hetero-

geneity of disease has been studied in two major ways; (i) clinically using non motor features of PD as much as motor problems and (ii) mechanistically using genetic and biofluid analyses to explain differences between patient groups – all of which has implications for more targeted therapies in subgroups of PD in clinical trials.

A number of different methodologies have been taken in attempts to define the subgroups of PD of which the most powerful are those using community based epidemiological studies following patients over time to death.[12] These studies are not without challenges but do capture PD as it exists in the real world and avoids some of the biases that exist when such studies are done using selective patient groups such as those signing up on web based platforms or attending hospital clinics. Nevertheless, all these studies have essentially shown that younger patients tend to do better than older patients and that those with more PD related symptoms and signs at diagnosis do less well. The reason for this clearly relates in part to: ageing processes (whatever they are!); genetic variants (such as possession of a glucocerebrosidase (GBA) mutation for example);[13] other general medical problems (such as risk factors for cardiovascular disease)[14] and possibly the patient's immune system and its response to the disease process.[15]

The importance of all this is that disease modifying or restorative therapies can now better be targeted not only to certain patient groups (e.g. younger less advanced patients for cell based dopamine therapies[16]) but specific pathogenic pathways – e.g. ambroxol for patients with PD and GBA mutations.[17] Although interestingly low GBA activity may be a feature of PD even in patients without a GBA mutation.[18]

Inflammation and the microbiome

The brain pathology of PD has long been known to show a level of inflammation but this has for many years been assumed to be secondary to the loss of cells and thus of minor relevance to the disease process. However, a number of observations have changed this perception. Firstly, the discovery that genes relating to the immune system were associated with the risk of getting PD in several GWAS. Secondly, epidemiological studies showing that patients taking certain anti-inflammatories or immune suppressants had a reduced risk of getting PD. Finally, evidence that immune activation happened early on in the disease course and may even be driving the disease process as evidenced by the fact that patients with more immune activation at diagnosis tended to do less well (all reviewed in Greenland et al, 2020).[19]

At the same time as this data was emerging, there was a realisation that the gut microbiome was a major determinant of disease states more generally. Given that PD has a major GI pathology attention naturally moved to whether the gut microbiome was different in PD and could contribute to the disease state and clinical course for which there is now some convincing evidence.[20] As such the idea of treating PD using agents that target this system are now being trialled as well as anti-inflammatory/immune suppressing agents.

The rise of drug repurposing and advanced experimental therapeutics

All of these new concepts have clearly impacted on how we can now consider treating PD using agents that may actually slow down the disease process. This has involved two strategies – one involving developing new small molecules or experimental therapies (such as AntiSense Oligonucleotides (ASOs) and immune therapies targeting alpha synuclein) and the other drug repurposing – including agents thought to act on critical pathogenic nodes in the development of PD. These latter approaches have now evolved and include recently completed phase 2 and some phase 3 trials with drugs such as ambroxol,[17] exenatide,[21] isradipine,[22] nilotinib[23] and simvastatin (Carroll et al 2019 and https://www.cureparkinsons.org.uk/news/the-pd-statsimvastatin-study-results).[24] Both of these approaches are set to increase in the coming years especially given the initiative now being championed by the Cure Parkinson's Trust and their Linked Clinical Trials.[25] Ultimately, though, it may be that these agents can best be employed as combination therapies targeting different parts of the pathogenic cascade, in much the same way as agents have been successfully used to treat other medical and infective conditions (e.g. HIV, TB and ischaemic heart disease).

Finally, advances in gene and cell therapy are now also impacting on PD with trials being undertaken or about to start using a range of different dopaminergic therapeutic approaches. This includes stem cell based dopamine cell transplants that have now just entered early clinical trials in Japan[26] and which will soon be trialled in Europe and the USA[27] and have also been the subject of a recent case report using autologous cells.[28] In addition, different gene therapies have also been trialled that transfect cells in the striatum with either some[29] or the majority of synthetic enzymes for making dopamine.[30] As to whether these therapies will prove effective or competitive is still to be decided.

In conclusion, the last 20 years has seen major changes in the way we think about PD and with this how we might now consider better treating it with an aim to cure it. Hopefully in the next 20 years we will see some of these approaches being converted into proven disease modifying therapies for PD.

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