New approaches to the treatment of Parkinson’s

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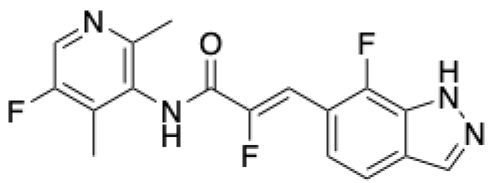
The New approaches to the treatment of Parkinson’s meeting was held at the Royal Society of Chemistry headquarters Burlington House on Wednesday, 12th November, 2025. The meeting had nearly 100 attendees, 81 in person. There were 9 oral presentations and 12 poster presentations.

The inspiration for the meeting came from a college reunion attended by Chris Swain, whilst it was lovely to meet all the year group the reunion was tinged with sadness in that several attendees had been diagnosed with Parkinson’s. This led to a discussion at the BMCS committee meeting and the suggestion for a meeting focussed on Parkinson’s, subsequently Parkinson's UK were invited to collaborate on the organisation of the meeting and provided invaluable input.

The opening talk for the meeting was entitled “Parkinson's: The journey to finding a cure” (David Dexter, Parkinson's UK) in which David Dexter gave a comprehensive overview of the area. Over 160,000 people have Parkinson's in the UK, and this is likely to be an underestimate as over 20,000 people are still waiting for diagnosis. Whilst Parkinson’s is usually thought of as a movement disorder in particular tremor and bradykinesia (slowness of movement), only 40% of patients display these symptoms. In the other patients gastrointestinal disturbances and REM sleep behavior disorders often appear years before motor symptoms develop. This has led to the “brain first” or “body first” origins of the disease. In the brain first, alpha-synuclein aggregates in the brain are key diagnostic features. In the body first it is thought the pathological agent originates in the periphery causing peripheral symptoms such as GI disturbances, and enters the brain via the vagal nerve. Since the vagal nerve also innervates the heart it is perhaps noteworthy that a blunted heart rate response during exercise has been observed in PD patients.

The mitochondrial permeability transition pore (mPTP) is a protein pore complex that forms in the inner mitochondrial membrane under stress conditions and has a role in neurodegeneration. It has been shown that α-synuclein oligomers interact with ATP synthase and open the permeability transition pore in Parkinson’s disease (Nature Communications volume 9, Article number: 2293 (2018)). In a talk entitled Giles “Orally available, brain penetrant mPTP inhibitors for the treatment of Parkinson’s.” (Gilles Ouvry, NRG Therapeutics) described work towards NRG1271 a potential treatment for PD and ALS.

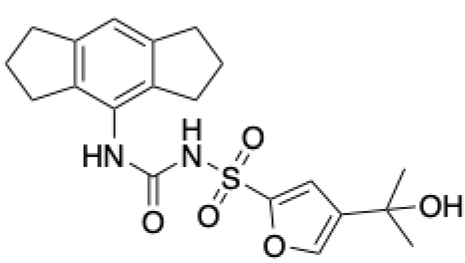


NRG1271

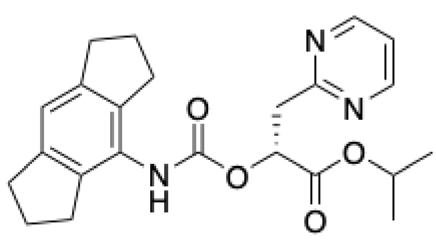
At scientific meetings it is sometimes forgotten that the patients perspective is very important and Anne Ferrett gave a moving account of her mother's struggles with PD, from the anxiety caused by multiple dosing regimes, pills in blister packs that someone with a motor disorder cannot open, unwillingness of medical staff to explain things to her. Anne has published a book of her mother's poems https://www.justgiving.com/fundraising/anne-ferrett2.

Sometimes breakthroughs in scientific research come from unexpected observations, as highlighted in "From serendipity to study in patients: The development of NLRP3 inflammasome inhibitor NT-0796 for the treatment of Parkinson's disease" (David Harrison, Nodthera). The innate immune system is the first line of defence in the recognition of pathogens. The nucleotide-binding oligomerisation domain (NOD)-like receptor, leucine-rich repeat and pyrin domain containing protein 3 (NLRP3) inflammasome is a key player in this response. Gain of function mutations and aberrant activation of the NRLP3 inflammasome in the CNS is thought to be involved in various neuroinflammatory disorders.

The known sulphonylureas like CRID3 were the starting point for this work, however physicochemical properties compromise cell and brain penetration. David Harrison described the observation that a series of esters that were inactive in a biochemical assay were actually potent in a cell-based assay. They hypothesised that the ester was acting as a prodrug to deliver the corresponding active carboxylic acid into the cell.



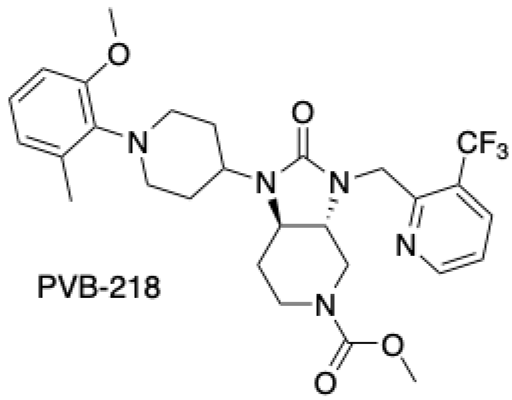
CRID3



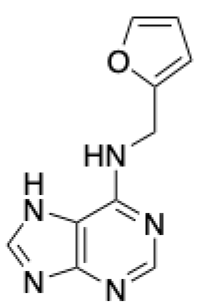
NT-0796

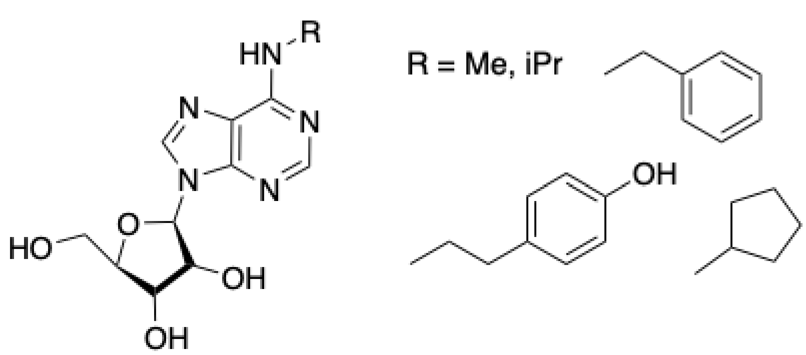
Whilst described as "serendipity" this probably undersells their efforts, since they had to make and test the esters, and understand the implications of the cell-based activity observed. NT-0796 has shown anti-inflammatory effects in patients with Parkinson's (https://doi.org/10.1002/mds.30307). Nodthera have several other NRLP3 inhibitors in development.

C5a, an inflammatory peptide binds to the Complement component 5a receptor 1 (C5aR1) a GPCR that is found on the surface of immune cells and is involved in the inflammatory response. In his talk entitled "Development of C5aR1 negative allosteric modulators with potential benefits for neuroinflammation" (Jonathan Powell, Domainex) described their work looking at allosteric modulators of C5aR1, leading to PVB-218.


PVB-218

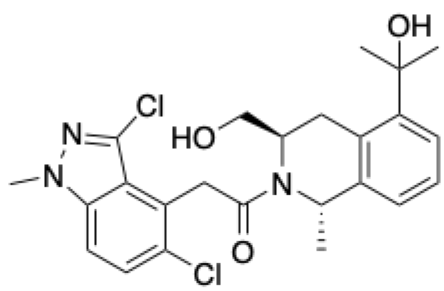
PTEN-induced kinase 1 (PINK1) plays an important role in mitochondrial health and mutations in the PINK1 gene are strongly linked to an increased risk of early-onset Parkinson's disease. When the mitochondria are damaged, PINK1 gets stabilized on the outer mitochondrial membrane, subsequent autophosphorylation leads to activation. Active PINK1 then phosphorylates the E3 ubiquitin ligase parkin leading to resulting in ubiquination of membrane proteins and mitochondria degradation. An approach to PINK1 activators was presented in "Discovery of PINK1 Activators as Potential Treatments for Parkinson's Disease" Youcef Mehellou" (Cardiff University). The starting point was the known activator Kinetin, this is thought to activate PINK1 after its metabolism to the corresponding kinetin riboside triphosphate The nucleosides below all activated PINK1, however the corresponding nucleobases were inactive.


Kinetin



The movement disorders seen in Parkinson's patients is due to degeneration of the substantia nigra subsequent disruption of the nigrostriatal pathway and decrease in dopamine levels.

Whilst dopamine does not efficiently cross the blood brain barrier, Levodopa a precursor to dopamine does. Clinicians use levodopa as a dopamine replacement agent for the treatment of Parkinson disease, dopamine can act on multiple dopamine receptor subtypes and can cause a number of side-effects. In addition the use of a direct agonist results in a loss of normal tone in the system. An alternative strategy was described in the presentation “Discovery of glovadalen (UCB0022), an oral, brain penetrant positive allosteric modulator of the dopamine D1 receptor (D1 PAM) currently in Phase 2 clinical trials” (Anne Valade, UCB). A PAM acts to amplify the signal whilst maintaining the normal tone of the system. Glovadalen is an orally active brain penetrant small molecule D1 PAM.



Glovadalen

Glovadalen has completed Phase I studies successfully and is currently in phase II studies (https://clinicaltrials.gov/study/NCT06055985).

Glucocerebrosidase (GCase) is a lysosomal enzyme found to be deficient in Parkinson’s patients and activators are being explored as possible treatments. One approach was described in “The discovery of CNS penetrant GCase activators for the potential treatment of Parkinson’s disease” (Ryan Hudson, Neumora).

Whilst considerable efforts have been made to identify genetic markers for PD, in the talk “Reconceptualising Parkinson’s Disease to Define Stage-Specific Therapeutic Opportunities”. (Mina Ryten, UK DRI) it was emphasised that the factors that cause the disease are not necessarily those that drive its progression, or are as a result of the disease.

The poster prize was won by Anabela Moreira with a poster entitled “Modelling Parkinson’s disease features in human 3D dopaminergic neuron cultures for therapeutic research”.

The feedback on the day and after the meeting was extremely positive, 100% of respondents were satisfied or very satisfied with the meeting. In addition all the speakers and presentations were rated good or excellent. There was significant enthusiasm for other disease specific meetings and Alzheimer's UK have contacted us to organise a potential future meeting. Several other participants emphasised the need for similar meetings focussed on neurodegeneration.

2. Overall, how satisfied are you with this conference?

Answer Choices			Response Percent	Response Total
1	1. Not satisfied		0.00%	0
2	2. Slightly satisfied		0.00%	0
3	3. Moderately satisfied		0.00%	0
4	4. Satisfied		42.86%	12
5	5. Very satisfied		57.14%	16
			answered	28
			skipped	0

3. How would you rate the range and interest of speakers and presentations?

Answer Choices			Response Percent	Response Total
1	1. Poor		0.00%	0
2	2. Weak		0.00%	0
3	3. Average		0.00%	0
4	4. Good		28.57%	8
5	5. Excellent		71.43%	20