



# Developing human-related approaches to understand and cure Parkinson's Disease

*The Dr Hadwen Trust believes that effective treatments for neurodegenerative disorders are one of the most important healthcare requirements of the 21st century and that only humane approaches are valid approaches to human disease.*

Parkinson Disease (PD) is a widespread progressive neurological condition. Although 1% of the population over the age of 55 is affected by this disease, 1 in 20 sufferers is under the age of 40.

First reported by James Parkinson in 1817, the etiology of PD is still unknown. Primary symptoms of PD, characterised by muscle rigidity, tremor and slowing of physical movement, are thought to be the result of a deficiency in dopamine, one of the brain neurotransmitters. Secondary symptoms, which can be as debilitating and include non-motor functions such as cognitive dysfunction, memory, learning and subtle language problems, may also result from toxicity of drugs, head trauma, or other medical disorders. Although dopamine-related medications sometimes improve cognitive function, they can induce other cognitive impairments that are distinct from those associated with PD itself. Therefore, understanding the neural basis of motor dysfunction, as well as the under-appreciated non-motor dysfunction, in PD are equally important.

## A human disease

Although animal models of PD involving non-human primates, rodents, dogs, cats and goldfish are still the main approaches used in medical research, there is currently no available animal model that successfully reproduces the human disease. Whereas a range of symptoms might be understood, the causes of human illnesses and their progression are often impossible to identify in animals.

Chemicals such as MPTP can be injected into the brains of mammals to cause certain human-related symptoms but often with diverse effects. Since PD does not exist in rodents, and a different response to MPTP is found between species, the validity of the rodent model to comprehend the origin, development and possible therapies of motor impairments related to PD can be challenged.

In non-human primate models, the condition can improve over time, whilst in humans the onset of PD is gradual with no spontaneous recovery. Another inadequacy of the model is the lack of the clumps of abnormal protein called Lewy bodies, which are the pathological hallmark of PD in patient brains. Experts have stated that the MPTP-treated primate model must be put into perspective and should not be taken as the complete representation of PD.

Consequently, poor models of the human condition and the adverse cost/benefit of such experiments may actually be delaying medical progress.

## Human-related approaches

Advanced technologies are now being implemented and researched to further our understanding of the disease and develop new treatments.

## Advanced cell culture

Understanding what happens inside the nerve cells that die in PD is fundamental to understanding the disease. Cell culture experiments have suggested that cell death mechanisms distinct from classical apoptosis play a central role in the pathogenesis of PD. Researchers are looking for genetic changes in cells that may increase the risk of developing PD. At Oxford University, a team of researchers is using a molecular approach known as RNA interference (RNAi) as a potential therapeutic agent to silence target genes in neurodegenerative disorders. They are also developing a supply of nerve cells producing dopamine, a promising tool for the development of new drugs and cell based therapies.

## Human tissue

Studies are now being conducted on human brain tissues from patients to understand the progression of the disease and how it spreads slowly from one part of the brain to the next. Such studies can only be done using human tissues since the condition does not spread in the same way in the animal brain.

## Gene therapy

Gene delivery is a potential alternative to drugs that become less effective in long-term use. Following the identification of PD-related genes, gene therapy has been proposed as a means to deliver these genes into nerve cells in order to improve their ability to make dopamine. In the past five years, several clinical trials have been conducted with promising results.

## Computer simulation

In a recent study, researchers at Rutgers University have developed a computational model that shows how PD affects attentional performance during learning. This computational approach, which addresses how PD and dopamine medications affect learning processes, demonstrates how the interaction of dopamine with the prefrontal cortex is key for attentional learning, whereas the interaction dopamine with the basal ganglia is key for motor learning.

## Brain imaging

Non-invasive methods such as magnetoencephalography (MEG) have been useful in studying neurological disorders such as PD, for example, in underlying physiological mechanisms involved in the relief of Parkinsonian motor symptoms through deep brain stimulation. The Dr Hadwen Trust is one of the major funding bodies of the MEG system located at the recently launched Aston Brain Centre, a Centre of Excellence. Aston University has a 40-year track record of leadership in clinical neurophysiology. MEG is an extremely powerful tool for improving understanding of drug/brain interactions with a particular interest in PD and diseases such as epilepsy, stroke and pain across the life span.

## System biology

System biology uses the wealth of data already available to build an *in-silico* approach to PD, combining mathematical modelling, systems analysis and associated measurement techniques. Computational models of the disease will allow multiple *in-silico* investigations of the origin and progression of PD that will provide a platform to researchers to design new experiments and trials.

## Volunteer studies

Volunteer studies are extremely useful to investigate subtle differences between patients. A collaborative project at Oxford Parkinson's Disease Centre is studying DNA from patients, in combination with brain imaging, to identify potential biomarkers to detect PD earlier. This might permit the protection of healthy nerve cells and as such may delay the onset of the disease.

## Conclusion

Currently, neither genetic models nor those using neurotoxins, fully recapitulate all key features, which characterise PD. Technological advances have led to the development of more human-relevant approaches, which have already permitted the implementation of successful studies.

By replacing animal models, these techniques lead to more human-relevant results through humane approaches to human disease. Although the development of such new methods often brings new challenges for researchers, it will result in improving the quality of scientific data and human health, while preserving the life of animals.

## The Dr Hadwen Trust for Humane Research

The Dr Hadwen Trust for Humane Research (DHT) funds and promotes innovative human-relevant research, which replaces the use of animals in research in order to accelerate the progress of medicine.

In doing so, the Trust supports Replacement methods as defined in 1959 by Russell and Burch, "any scientific method employing non-sentient material which may, in the history of experimentation, replace methods which use conscious living vertebrates".

For 40 years, relying solely on donations and legacies, the Trust has funded advanced non-animal research across the UK, into all areas of medicine including neurological disorders, cancer, autoimmune diseases, genetic disorders, and infectious diseases amongst others. To apply for funding or to support the aims of the DHT, visit: [www.drhadwentrust.org](http://www.drhadwentrust.org).

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