Project Details	
Project Code	MRCNMH26Ex Migdalska-Richards
Title	Epigenetic profiling in Parkinson's disease: novel mechanisms and drug targets
Research Theme	NMH
Project Type	A particular strength of this project is that it combines both wet-lab work (microRNA profiling, cell culturing and transfection) and bioinformatics, allowing the student to acquire a valuable combination of skills that will be excellent preparation for their future career, be it in academia or elsewhere.
Summary	During this PhD, you will be one of the very first people to study the epigenetics of Parkinson's disease. You will determine and functionally evaluate the first-ever comprehensive microRNA profile in different brain regions of individuals with Parkinson's disease. This will involve combining the exciting areas of epigenetics, bioinformatics and molecular biology. This work will improve mechanistic understanding and suggest novel drug targets for this devastating condition.
Description	Parkinson's disease (PD) is the most common human motor disorder, affecting ten million people worldwide. With an increasingly ageing population, prevalence is predicted to double by 2040. Parkinson's significantly contributes to the global burden of disease, costing the NHS alone more than £1 billion/year. Currently, there are no treatments that can cure or modify the disease, so development of new therapies that can slow, prevent or reverse PD progression are urgently required. The few treatments that do exist only alleviate symptoms temporarily and become substantially less effective as the disease progresses. Although some genetic components of Parkinson's have been identified, much is still unknown about the aetiology. For example, the most common genetic risk factor (GBA1), which accounts for ~85% of all known genetic cases, shows incomplete penetrance, with only 30% of GBA1-mutation carriers developing the disease. Further, PD concordance rate between identical twins is only about 17%. This indicates that non-DNA-sequence variation (i.e. epigenetics) is likely to play a crucial role. Emerging work (including our own) shows that key epigenetic processes, including DNA methylation, histone modifications and microRNAs are significantly altered in the brains of people with Parkinson's disease. This important fact has only very recently been appreciated and there are currently no systematic epigenetic studies of Parkinson's. This project will fill this gap. This project will focus on a particular epigenetic mechanism, that of microRNAs. These are short non-coding RNA molecules, on average 22 nucleotides in length, that are directly involved in post-transcriptional downregulation of target gene expression either by translational silencing or by mRNA degradation. Importantly, recent advances in high-throughput technologies mean that it is now possible to accurately quantify microRNA differences with unprecedented detail and coverage, using an unbiased approach that does not pre-select candidate microRNAs. We can then start, for the first time, to determine the role of microRNAs in Parkinson's. One of the most exciting prospects from this is that the identified microRNA changes are potentially reversible, and so better understanding the microRNA variation would open

	up the tantalising prospect of new epi-drugs that could be used to treat this debilitating condition. During this project, the student will learn a broad range of experimental and theoretical skills, including microRNA profiling, cell culturing, microRNA mimic and antagonist transfection (to examine biological effects of specific microRNAs on cell function), and bioinformatics, including microRNA target prediction and functional enrichment analysis of microRNA targets. The student will be able to take ownership and steer project in both experimental and theoretical aspects of this project, with the biggest influence being anticipated in exploring relevant bioinformatics approaches for selecting relevant microRNAs for further validation and replication, and exploring the best methods to be employed for functional analysis of the most promising microRNAs. Although mainly based at the University of Exeter, six months will be spent investigating functional aspects of microRNA analyses at the University of Bristol in the group of Professor James Uney. Further, through collaboration with interdisciplinary scientists at the Living Systems Institute, the student will have the opportunity to develop basic computational modelling skills in order to analyse microRNA-mediated gene regulatory networks. In addition, via collaboration with Catapult Medicines Discovery (CMD), the student's training will be further enhanced by regular visits to CMD for industrial experience. Finally, public involvement and engagement will play an important part of this PhD. This will build on existing links that we have recently developed with local Parkinson's support groups, particularly those in Okehampton, Crediton and Exmouth. The student will participate in a number of public workshops, where they will be able to explain their work and interact directly with individuals affected by Parkinson's disease.
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