Project Details	
Project Code	MRC21NMHEx Migdalska-Richards
Title	Huntington's disease and microRNAs: searching for novel mechanisms and drug targets
Research Theme	Neuroscience & Mental Health
Summary	During this PhD, you will be one of the very first people to study the epigenetics of Huntington's disease. You will determine the first-ever comprehensive brain microRNA profile and then evaluate the most promising microRNAs in cell models. This project will combine the exciting areas of epigenetics, bioinformatics and molecular biology. It will lead to improved mechanistic understanding and suggest novel drug targets to treat this devastating condition.
Description	Huntington's disease is a progressive, long-term neurodegenerative disorder, affecting over a million people worldwide. The cardinal features include uncontrolled movements, behavioural problems and cognitive impairment. Huntington's significantly contributes to the global burden of disease, costing the NHS alone more than £200 million/year. Currently, there are no treatments that can cure or modify the disease, so development of new therapies that can slow, prevent or reverse Huntington's progression are urgently required. The few treatments that do exist only alleviate symptoms temporarily and become substantially less effective as the disease progresses. Huntington's disease is caused by a CAG trinucleotide repeat expansion in the huntingtin gene. However, despite this genetic origin being known for nearly thirty years, the underlying cellular and molecular mechanisms are still poorly understood. Excitingly, however, recent emerging evidence suggests that non-DNA-sequence variation (i.e. epigenetics) is likely to play a crucial role. Epigenetic changes predominantly act to regulate gene expression without changes in the underlying DNA sequence, and recent pilot work shows that key epigenetic processes (including DNA methylation, histone modifications and microRNAs) are significantly changed in individuals with Huntington's. This suggests that epigenetic deregulation is likely to play an important role in Huntington's aetiology, and could even be a key ingredient and signature of the disease. This important fact has only very recently been appreciated and there are currently no systematic epigenetic studies of Huntington's. This project will fill this gap. This project will focus on one 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. With these technologies, we are now able, for the first time, to determine the role of microRNAs in Huntington's. One of the most exciting prospects from this is that identified microRNA changes are potentially reversible, and so better understanding the microRNA variation would open up the tantalizing prospect of new epi-drugs that could be used to treat this debilitating condition. During this project, you will learn a broad range

	of experimental and theoretical skills, including microRNA profiling, cell culture, transcriptomics, microRNA mimic and antagonist transfection, and bioinformatics. Although mainly based at the University of Exeter, you will also spend six months investigating functional aspects of microRNA analyses at the University of Bristol in the group of Professor James Uney. Further, through collaboration with Dr Ryan Ames in the Living Systems Institute, you will have the opportunity to develop bioinformatics and computational modelling skills in order to analyse microRNA-mediated gene regulatory networks. In addition, using the group's links with Catapult Medicines Discovery, your training will be further enhanced by regular visits to gain industrial experience. Finally, public involvement will play an important part of this PhD. This will involve working with local Huntington's support groups, particularly the South West Huntington's Disease Association Group. You will participate in a number of public workshops and so be able to interact directly with individuals affected by Huntington's disease.
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Lead Supervisor	
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