Project Details	
Project Code	MRCIIAR24Ex Nuetzmann
Title	Epigenetic signatures in fungal host adaptation
Research Theme	Infection, Immunity, Antimicrobial Resistance & Repair
Summary	Fungal pathogens threaten our health and kill over a million worldwide. In this project, we will deploy cutting-edge chromatin genetics and medical mycology to better understand how pathogenic fungi sense and adapt to the human host. Our goal is to open novel paths to interfere with fungal disease.
Description	Organisms of the genus Aspergillus are ubiquitously distributed filamentous fungi that play major roles in environmental nutrient cycles. A range of species within this genus are of clinical importance and cause allergic, acute and chronic diseases. A. fumigatus is the most dangerous Aspergillus species for humans and can cause fatal invasive infections. More than 300,000 cases of invasive aspergillosis are reported per year, and over 3 million people with chronic lung conditions are affected by Aspergillus infections. Immunocompromised individuals are particularly exposed and their rise in numbers coincides with increasing rates of A. fumigatus infections. A lack of reliable diagnostics and effective treatment against aspergillosis has led to high mortality rates ranging from 30 – 95 % among infected patients. Colonisation of the human host is associated with dramatic changes to the survival niche of the pathogen and is accompanied with important transitions in the fungal life cycle. To adapt to the human host environment, Aspergilli alter their intra- and extracellular organization and metabolism. To enable these drastic changes to their life-style, it is essential for the fungal pathogen to precisely reconfigure the activity of multiple genes and entire genomic regions. But how are filamentous fungi reconfiguring genome activity during host adaptation? Here, we propose that the extensive transcriptional re-programming of the fungal genome is mediated by changes to the epigenetic modifications of chromatin and the three-dimensional folding of chromosomes. Epigenetic modifications of chromatin have been shown to be critical for regulating transcriptional activity in eukaryotes and enable long-term memory effects in their genomes. In this project, will use cutting-edge Cut&Tag, Hi-C and RNA-seq molecular techniques to analyse the epigenetic signatures of the fungal adaptation to the human host and connect changes in chromatin architecture with transcriptional activity. We will access selected strains of our unique series of isogenic Aspergillus fumigatus isolates obtained from a single patient (Ballard et al, Fungal Gen Biol 2018 and 2019) to assess epigenetic, chromosomal and transcriptional changes underpinning the observed phenotypic in-host adaptations. Furthermore, we will perform comparative assessments of clinical isolates of A. fumigatus and Aspergillus nidulans to better understand the molecular mechanisms resulting in their different behaviour in the human host. Our objectives will be: (i) to characterize how fungal host adaption is modulated on transcriptional and epigenetic level (ii) to define a reference map of the three-dimensional architecture of the A. fumigatus genome; and (iii) to establish the epigenetic signatures of fungal host adaptation. Understanding how pathogens reconfigure their genomes to respond to the host will offer

	opportunities for the development of new pharmaceutical interventions to combat fungal infection. This studentship is designed to provide an unprecedented view of the dynamic nuclear chromosomal environment of life-threatening airborne fungal pathogens. The knowledge gained from this project will enhance future research in our in-depth understanding of fungal behaviour associated with changes in chromosome architecture. It will offer multidisciplinary training in molecular and fungal biology as well as medical mycology - vital skills for establishing a successful career in medical biology. It will be embedded in a collaboration between the MRC Centre for Medical Mycology and the Biosciences Department in Exeter and the Milner Centre for Evolution, Bath, and will provide access to a world-leading network of scientists. In this project, the prospective student will actively participate in the design of the project and is encouraged to bring in their own research ideas.
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