Project Details	
Project Code	MRC22IIAREx Warris
Title	Emerging Aspergillus infections: tackling fungal adaptation.
Research Theme	Infection, Immunity, Antimicrobial Resistance & Repair
Summary	Fungal infections caused by Aspergillus species are a serious threat to immunocompromised patients and those with chronic lung disorders and influenza or SARS-CoV-2 induced pneumonia. Moreover, resistance to antifungals and host defences are emerging and increasing the case-fatality rate. Deploying cutting-edge 3D chromatin genetics, we aim to unravel how changes in chromosome architecture underpins fungal adaptation and to find new ways to tackle fungal infections.
Description	More than 300,000 cases of invasive aspergillosis are reported per year, and over 3 million people with chronic lung conditions (asthma, cystic fibrosis) are suffering from Aspergillus infections. In addition, patients with severe COVID-19 and influenza are at risk to develop pulmonary aspergillosis with a high case-fatality rate reported. The threat posed by Aspergillus infections is amplified by an increasing number of immunocompromised patients, emerging antifungal resistance and its ability to adapt to the host and evade host immune responses. New ways to tackle the impact of Aspergillus infections must be found. Aspergillus species are common in nature, dormant airborne Aspergillus spores are inhaled into the lungs where they germinate in susceptible hosts, forming hyphae that cause invasive disease. Spore germination is accompanied by metabolic shifts and cellular reorganizations, which enable the fungal pathogen to evade and withstand host immunity. But how do pathogenic fungi achieve these drastic changes to their lifestyle? Here, we propose a studentship that investigates the hypothesis that changes to the three-dimensional (3D) chromosome architecture orchestrate how fungal pathogens respond to the host environment and promote adaptations associated with disease. Chromosomes form dynamic 3D structures within the nucleus which are critical for regulating transcriptional activity. We will use cutting-edge Hi-C and RNA-seq molecular techniques in conjunction with high-resolution microscopy. This will enable us to associate changes in 3D chromosomal architecture with transcriptional activity during conditions relevant to infection and treatment, such as exposure to host immune defense mechanisms and antifungal drugs. As part of the project, we will analyse 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 chromosomal and transcriptional changes underpinning the observed phenotypic in-host adaptations, as well as the development of antifungal resistance. 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. 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 Milner Centre for Evolution, Bath, and the MRC Centre for Medical Mycology, Exeter, and will provide access to a world-leading network of scientists.
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