

Project Details	
Project Code	MRCIAR25Ex Neutzmann
Title	Investigating the impact of epigenetic modifiers, a new treatment for cancer, on fungal pathogens
Research Theme	Infection, Immunity, Antimicrobial Resistance & Repair
Summary	Fungal pathogens threaten our health and kill over a million patients worldwide. In this project, we will deploy cutting-edge epigenetics research and medical microbiology to better understand how pathogenic fungi respond to anti-cancer drugs. Our goal is to rationalise the impact of cancer treatment on fungal pathogens.
Description	<p>Recently, a new class of anti-cancer drugs, so called epigenetic modifiers, that target the epigenome of human cells have been developed. These drugs have shown great promise in cancer treatment. However, it is unknown how they affect the growth and pathogenicity of pathogens thriving in immunocompromised cancer patients. Epigenetic modifications and the enzymes that set these modifications are largely conserved throughout eukaryotes. As such, the use of epigenetic modifiers will not only affect human cells but also fungi within the microbiome of the patient, including dangerous fungal pathogens. Fungal pathogens can cause allergic, acute and chronic diseases. <i>A. fumigatus</i> is one of the most important fungal pathogens for human health and can cause fatal invasive infections. A lack of effective treatment against this fungus has led to high mortality rates ranging from 30 – 95 % among infected patients. Due to their weakened immune system, cancer patients are particularly exposed to <i>A. fumigatus</i> infections.</p> <p>In this PhD project, we will test the hypothesis that clinically applied epigenetic modifiers manipulate the epigenome and behaviour of fungal pathogens. Our objectives will be: (i) to characterize the general fungal response to epigenetic modifiers (ii) to define the epigenomic signatures of pathogenic fungi, and (iii) to establish how anti-cancer pharmaceuticals affect the human immune cell – pathogen interaction. In detail, we will investigate how epigenetic modifiers affect growth, morphology and stress resistance of <i>A. fumigatus</i>. As such, we will coinubate the fungus with different epigenetic modifiers, which have been selected for target specificity and relevance in clinical settings. In our pilot analyses, we have observed that epigenetic modifiers induce macroscopic changes to fungal morphology and change the fungal response to antifungal drugs. We will further assess how treatment with epigenetic modifiers will affect fungal resistance to host stresses, antifungals, antimicrobial peptides and co-incubation with human immune cells. Then, we will analyse the changes to the fungal transcriptome and epigenome induced by the epigenetic modifiers by RNAseq, Western blot and Cut&Tag. These molecular experiments will enable us to identify the areas of the genome that are affected by the epigenetic modifiers and help us to understand the epigenetic response</p>

	<p>of the pathogen to anti-cancer pharmaceuticals. In addition, we will perform biochemical analyses to identify and characterise the target proteins of the epigenetic modifiers and their molecular interaction. Together, these analyses will advance our understanding of the effects of drugs applied to cancer patients on fungal pathogens and provide an exemplar case for the central role of epigenetics in fungal pathogenicity. The knowledge gained from this project will help to optimise the treatment regime of immunocompromised patients to prevent the proliferation of fungal pathogens.</p> <p>Overall, this PhD project will offer multidisciplinary training in molecular 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, the Biosciences Department in Exeter and the Milner Centre for Evolution, Bath, and will provide access to a world-leading network of scientists. Throughout the project, the prospective student will actively participate in the design of the project and is encouraged to bring in their own research ideas.</p>
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