

Project Details	
Project Code	MRC21IIRBa Brown
Title	UNDERSTANDING THE COMPLEX THREAT OF ASPERGILLUS INFECTIONS WHEN TREATING VULNERABLE PEOPLE WITH CYSTIC FIBROSIS
Research Theme	Infection, Immunity & Repair
Summary	Cystic fibrosis (CF) is an inherited life-limiting disease. Respiratory fungal infections, especially aspergillosis, contribute significantly to disease progression. Here, we will use clinical mycology, genomics and big data science to study how the genetic determinants of Aspergillus pathogenicity and CF patient treatments interact and impact on disease progression. This will deliver the knowledge of this complex disease required to improve future CF patient care.
Description	<p>SIGNIFICANCE: Cystic fibrosis (CF) is an inherited life-limiting disease exacerbated by chronic lung infections. People with CF receive frequent and aggressive antimicrobial treatments, leading to antimicrobial resistance concerns. Aspergillus species are important fungal pathogens for people with CF. Aspergillus spores are present throughout nature and people inhale up to 1000 spores each day. CF patients have deficiencies in clearing Aspergillus from the lungs, resulting in repeated or chronic lung colonisation leading to invasive infections. These conditions are associated with declining lung function and high mortality rates. Common treatments received by CF patients, particularly steroids, can increase vulnerability to Aspergillus infection. The emergence of Aspergillus populations resistant to antifungal drugs is a major concern to the CF community, while Aspergillus CF lung colonisation has been linked with parasexual recombination and the evolution of antifungal drug tolerance. Therefore, greater awareness of the interactions between CF patient histories, drug treatments and the genetics of Aspergillus populations causing CF patient infections is essential to advance our management of this disease.</p> <p>RESEARCH WITH IMPACT: We hypothesize that subsets of the Aspergillus population with shared genetic traits infect specific patients depending on their clinical histories. Therefore, this study will establish a CF Aspergillus collection, including historic isolates obtained from the National Mycology Reference Laboratory (Public Health England PHE) and new isolates with their associated clinical data from cohorts of CF patients throughout the South West. We will use next-generation sequencing, molecular mycology and CRISPR-Cas9 genome editing to evaluate the Aspergillus population and reveal the shared genetic determinants for fungal pathogenicity and antifungal susceptibility in CF patients. Finally, we will deploy big data science and AI to identify interactions between clinical management, Aspergillus population adaptations within the CF lung, and the development of fungal complications. These studies will advance our understanding of i) which CF patients are particularly vulnerable to Aspergillus infections, ii) which Aspergillus populations pose the greatest threat, aiding in the development of molecular diagnostics, and iii) how different medical treatments impact on fungal infections. Collectively, this will help improve future CF patient management.</p> <p>INTERDISCIPLINARY TRAINING THROUGH COLLABORATION: This project will deliver excellent interdisciplinary training the student and ECRs, facilitated by knowledge/resource transfer across the partner</p>

	<p>institutions. This will be achieved by combining clinical expertise in CF treatment (Mitchelmore, Exeter) and medical diagnostics (Johnson; PHE Bristol) with molecular mycology and big data science (Brown and Sheppard; Bath). The student will benefit from spending time and receive expert training at all three partner institutions. The student will attend Medical Mycology conferences to promote the dissemination of research findings and interactions with leading international experts. Additional added value will be provided through networking opportunities and/or student involvement in collaborations within the GW4 alliance and with the Prof. Goldman, University of São Paulo-Brazil, applying function genomics to study <i>Aspergillus</i> pathogenicity. This collaborative transfer of knowledge/resources among the partner institutions and the cross-disciplinary mentorship provided by experienced academics and clinical scientists, Sheppard and Johnson, will benefit the professional development and future grant success of ECRs, Brown and Mitchelmore.</p>
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