Project Details	
Project Code	MRC22IIAREx Farrer
Title	Genome evolution and epidemiology of hospital-acquired Candida infections in the UK.
Research Theme	Infection, Immunity, Antimicrobial Resistance & Repair
Summary	Fungal diseases kill more than 1.5 million people every year, and cause disease in over a billion people. One of the most important fungal pathogens of humans worldwide is Candida albicans. We use genomic epidemiology to understand its evolution and the genes that drive its pathogenicity. The project will use both dry-lab and wet-lab approaches to make fundamental discoveries in medical mycology.
Description	Fungal pathogens pose an increasing threat to human health. They are responsible for >1.5 million deaths per year. Candida albicans is both a ubiquitous commensal yeast of the human gastrointestinal tract and a prevalent opportunistic pathogen. C. albicans remains the most common cause of invasive candidiasis across the world. C. albicans is therefore an important contemporary global medical issue. We have amassed and sequenced the genomes of 210 C. albicans clinical isolates from across the UK. The successful applicant will be trained in state-of-the-art genomic analysis in order to reveal the phylogenetic placement of the isolates. We will then identify selection pressures on pathogenicity genes for each clade and correlate it with our extensive metadata (patient outcome, drug treatment, age, co-infections etc.). Using our gene knockout collection (based on the genomic work), we will test for changes in virulence using the Galleria mellonella infection model and LDH assays. Finally, we will explore how gene disruption impacts gene expression using an RNAseq approach across wildtype and mutant strains. My group has extensive knowledge and experience in each of these approaches. Our novel approach will make fundamental discoveries about C. albicans genomic epidemiology and the molecular mechanisms driving pathogenicity. The most recent whole-genome based phylogenetic study (Ropars et al.) has identified at least 17 distinct genetic clusters/clades, with a predominantly clonal population structure. Each clade shows some biological variation, including clade-specific differential gene expression (e.g. genes involved in phosphatase activity), and some hypovirulent clonal clades (e.g. Cluster 13) that have undergone pseudogenization of genes required for virulence and morphogenesis. Despite C. albicans' significance, little is currently known about its global population structure, or indeed how extant strains reflect their evolutionary history – although it is thought to have emerged 3-16 million years ago – coinciding with early hominid evolution. We will compare our own panel to global genomes in publicly available databases. We will use and develop bioinformatic methods to perform micro-evolutionary analysis and Bayesian inferences of transmission using tip-dating. This work will determine the prominent genotypes present in the UK, and reveal how past and present transmission events are shaping the genetic and phenotypic landscape of pathogenic fungi. Understanding how genetic makeup has changed over time may permit useful predictions for future patient management, including hospitals that should invest in additional disease surveillance, or make other policy changes based on perceived risk. We will focus

	our virulence assays on known key virulence factors that have undergone rapid evolutionary change between clades, indicating potential functional divergence. Particular foci will include genes encoding proteins that mediate adhesion to and invasion into host cells such as HWP1 and ALS3, cytolysis (ECE1/Candidalysin), secreted hydrolases, genes involved in dimorphism, host contact sensing, biofilm formation on catheters and mucosal cell surfaces, mutations in antifungal drug targets, and a range of other fitness attributes. By identifying polymorphisms in those genes and directly testing their function using gene knockouts and virulence assays, we will characterise their function at the population level. This level of detail has not previously been achieved. Indeed, this project will be the largest and most comprehensive of its kind to date – and conclusively establish inter- and intra-clade variation at the genomic, phenotypic and host mortality levels. The knowledge gained from this project will be important for describing new molecular mechanisms of pathogenicity and identifying new potential drug targets.
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