Project Details	
Project Code	MRC21IIREx Coelho
Title	How do fungal pathogen eat when inside us? Acquisition of energy in host niches by the pathogenic fungi Cryptococcus neoformans
Research Theme	Infection, Immunity & Repair
Summary	The fungus Cryptococcus neoformans kills approximately 200, 000 people yearly. Clinicians desperately need better therapies to treat fungal infections. To cause disease, a pathogen requires energy, scavenged from host nutrients. We will study how fungi scavenge food from the host, in a pathway that uses a new gene family that exists in all the major human fungal pathogens. The insights from this project have the potential to uncover a new antifungal target.
Description	Cryptococcus neoformans is a human fungal pathogen, responsible for over 180,000 deaths each year; this signifies C. neoformans causes 15% of HIV-related deaths worldwide. A fundamental issue in microbial infection is the acquisition of nutrients from the host, allowing the fungus to grow, thrive and cause disease. In C. neoformans these metabolic pathways are poorly understood. This knowledge may reveal ways to block fungal growth, and result in better antimicrobial drugs for this deadly disease. Recent exciting work by our team identified key enzymes of the nutrient acquisition machinery in C. neoformans. Deletion of these enzymes, using genetic tools, decreased capacity to cause disease in an invertebrate model of infection (wax moth), and decreased growth in conditions mimicking the mammalian host. This project will explore whether these newly-identified enzymes are needed for C. neoformans to grow in mammalian hosts. Ultimately this project will shed light on how the fungus feeds when infecting the human host. We seek a student to: 1: measure whether deletion of newly-identified nutrient-scavenging enzymes decreases fungal infection of mammalian hosts; 2: define the enzymatic functions of key components of the nutrient-scavenging metabolism; 3: identify the metabolic changes occurring in C. neoformans during host infection. This exciting project combines the expertises of an outstanding research team. The student will use interdisciplinary approaches, ranging from in vivo work to cutting-edge metabolic profiling to classical enzymology, taking advantage of the combined expertise of Coelho (Exeter), Curnow (Bristol) and Race (Bristol) laboratories. 1. Using fungal strains deleted for key components of nutrient acquisition machinery, the student will infect mice and measure the progression of disease, by quantifying fungal numbers in different organs, and by scoring signs of infection. To pinpoint specific defects in nutrient acquisition, the student will measure growth of gene-deletion strains in >90 different nutrients (commercially-available phenotypic arrays). All these tools are already established by PI Coelho (Exeter). 2. Of the already identified nutrient-scavenging genes, we will initially focus on the gene known systematically as CNAG_06760. There is virtually no information on the function of this gene, despite occurring in all major human fungal pathogens. Protein homology prediction9* suggests that this protein is an acyl-CoA hydratase, involved in carbon and fatty acid metabolism. The student will use classical enzymology to clarify the function of CNAG_06760. We will express CNAG_06760 recombinantly in E. coli and S. cerevisiae, using the

	expertise of co-I Curnow (Bristol) with both systems. Once sufficient protein is in hand, enzyme kinetics will be determined. We will simultaneously initiate trials to obtain protein crystals, aimed at high-resolution structure of CNAG_06760 via X-ray crystallography, which will provide first-of-its-kind data for this enzyme. We may characterize additional candidates (already identified by our pilot data). 3. We will determine how the metabolism of the fungus changes during infection, using a system biology approach. Taking advantage of the already defined in vitro host-mimicking conditions, we will measure fungal metabolism (via metabolomics), and accompanying gene expression changes (via RNA-Seq), during host infection. We will validate these insights by measuring gene expression by RT-qPCR from fungi extracted directly from mouse tissues. These combination of these data will provide a broad view of how the fungal metabolism acclimatizes to the host, and will likely reveal upstream gene regulators. This project is an outstanding opportunity to generate vital insights into an essential aspect of infection and will provide the student with key skills applicable to microbiology, biochemistry and antimicrobial research.
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