Project Details	
Project Code	MRC22IIAREx Coelho
Title	Deadly fungus in the brain: Impact of infection on immunometabolic responses in glia
Research Theme	Infection, Immunity, Antimicrobial Resistance & Repair
Summary	Fungi cause deadly brain infections in humans; to better combat these deadly invaders and prevent brain damage. we must understand brain-specific immune responses during infections. To achieve this, the student will use key models of infection, including mouse and zebrafish, coupled with state-of-the-art tools in live quantitative microscopy, metabolism and immunology to uncover the mchanisms which determine the outcome of this deadly disease.
Description	Fungal infection of the brain is deadly: The the top killer of all human pathogenic fungi is Cryptococcus neoformans, causing 15% of AIDS-related deaths each year. This fungus invades the mammalian brain to cause deadly inflammation of the brain and meninges. Fungi triggers immune responses in glia: To tackle this major Global Health issue we need to better understand how brain-specific immune cells attack the fungus, as early brain-specific immunity is key to the establishment of this lethal infection (Coelho, 2019). There are two main types of brain-resident "immune cells". Microglia are really the brain resident macrophages, while a second type of glial cell, the astrocytes, are critical for maintaining blood-brain barrier and nutrient levels (Ellacott, 2020). An important yet unresolved question is the role of these glial populations in anti-cryptococcal immunity. Immunometabolite itaconate worsens cryptococcal disease Itaconate is a vital checkpoint for integration of metabolism and of immunity: this mitochondrial metabolite downregulates critical inflammatory cascades. Shown to be strongly involved in peripheral immunity, little is known regarding the role of itaconate in immune responses in the brain. Critically, the Coelho lab has already shown that itaconate leads to premature mouse death during cryptoccocal disease, whilst itaconate-deleted mice survive longer, presumably due to downregulating inflammation in the brain. Thus, we will test the overarching hypothesis that changes in cellular metabolism, mediated by itaconate, control anti-cryptococcal responses in microglia and astrocytes. This knowledge may reveal ways to potentiate immune response in the brain, and mitigate this enormous Global Health issue. To test this hypothesis, the student will use state-of-the-art tools established in host laboratories, taking advantage of the outstanding and interdisciplinary PI team, to complete the following objectives: 1. Delineate glial immunometabolic responses to C. neoformans infection (MRC Centre for Medical Mycology, Exeter): Glial cells will be infected with fluorescent C. neoformans and inflammatory, metabolic and viability assessed over time. This will ascertain for the first time the immunometabolic response of glia upon fungal infection. For these studies the student will receive training in primary cell culture of mouse glia (microglia and astrocytes), flow cytometry, molecular biology (RT-qPCR, ELISA) and cellular metabolism (Seahorse bioanalyser, enzymatic activity) [PI Coelho and Ellacott]. 2. Delineate how itaconate impairs anti-cryptococcal immunometabolism in glia (Exeter): The student will uncover the glial functions under the control of itaconate,

	including: i) antimicrobial capacity ii) cytokine secretion and iii) glial activation status/polarization, as in objective 1. The student will manipulate itaconate levels in glial cells, by exogenous addition of itaconate, and by abolishing itaconate via gene-deleted mice and/or Crispr-Cas9. Key insights will be tested in vivo via intranasal infections of itaconate-deleted mice [PI Coelho]. 3. Define the itaconate-dependent immunometabolic changes in vivo (Bristol): Immune responses require complex tissue and cellular interactions; since zebrafish are translucent and allow real-time imaging they are are a remarkable model for these interactions. Using newly-developed zebrafish metabolite-reporter strains (a lactate reporter is already available in Martin laboratory, and others are available shortly from colleagues in Manchester and Edinburgh), the student will quantify in real-time how brain infection triggers immune and metabolic changes. Zebrafish have itaconate-dependent immune responses, which, if time allows, we will manipulate using genetically knockdown/knockout approaches [PI Coelho and Martin]. This project will generate vital insights into brain-specific immunity and immunometabolism.
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