Project Details	
Project Code	MRC22IIAREx Richards
Title	The filamentous growth of fungal killers: a combined mathematics and lab approach
Research Theme	Infection, Immunity, Antimicrobial Resistance & Repair
Summary	In this PhD, you will use mathematics, computer programming and lab-based experiments to investigate the invasive growth of the two major filamentous human pathogens - Candida albicans and Aspergillus fumigatus. The findings will have important implications for understanding tissue invasion during life-threatening fungal infections. Unlike most PhDs, this is an excellent opportunity to be trained in both the experimental and mathematical aspects of modern research.
Description	Background: Globally, filamentous fungi cause over 600,000 life-threatening infections in humans per year, hall-marked by hyphal invasion of host tissues that induces hyper-inflammation and organ failure, and with mortality rates up to 95%. The vast majority of deaths is caused by the commensal fungus Candida albicans and the environmental fungus Aspergillus fumigatus. C. albicans causes life-threatening systemic candidiasis as well as the debilitating mucosal infection commonly referred to as 'thrush', whilst A. fumigatus infects the lungs of patients with pre-disposing conditions such as cystic fibrosis. These fungi have contrasting biology and lifestyles, yet rely on their ability to invade host tissue by forming penetrative elongated filaments called hyphae. At present, there are very few treatment options, with only three classes of approved compound. Thus, understanding of hyphal growth in these fungi is urgently required in order to guide new treatment strategies. The approach: Often the quickest way to make progress with this type of problem is to intimately combine wet-lab experiments with image analysis and mathematical modelling. We have already captured a large quantity of time-lapse images of C. albicans growing in various environments and these will form the basis of this PhD. The student will undertake a truly multidisciplinary PhD, including creating image analysis algorithms, designing mathematical models, generating fluorescent fungal cells and conducting time-lapse imaging experiments. This approach will allow the student to learn a highly-desirable combination of quantitative and experimental skills, leading to excellent future career prospects. Project plan: This cross-disciplinary studentship will be based within the Living Systems Institute at the University of Exeter with lab work undertaken within the world-renowned MRC Centre for Medical Mycology. The student will learn further skills at the University of Bristol and so will spend time at multiple GW4 institutes. The student will also join the new Quantitative Health Network in order to obtain a broad understanding of the role of mathematical modelling throughout human health (see http://www.exeter.ac.uk/quantitative-health-network/). The project itself will include: 1. Software-driven image analysis. Building on existing custom-built software within the Richards group, image analysis software will be developed that automatically interprets the time-lapse images of filamentous fungal growth, focusing on developing quantitative measures that describe the shape and dynamics of hyphae. 2. Mathematical modelling. A mathematical model/computer simulation

	will be designed that describes fungal growth from a single cell/spore to the full hyphal network. This will be based on a model that we are currently developing as part of a Wellcome Trust-support seed-corn project. For the first time, this model will include nuclear migration, the dynamics of the microtubule network and the behaviour of cell polarity protein complexes. 3. Wet-lab experiments. The student will generate new fungal strains with gene deletions or expressing GFP-tagged proteins. These will be imaged in novel micro-fabricated environments designed by the student to validate and test the mathematical models. Outreach: Public involvement will also play an important part of this studentship. The student will work directly with the MAGPIEs (a group of lay people involved in medical research) in order to disseminate results and guide research. In particular, this part of the PhD will directly build on the 3D-printed model of fungal hyphae that we have recently created as part of a public outreach display.
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