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Strategic Research Funding: A Success Story for Medical Mycology

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The Wellcome Trust Strategic Award in Medical Mycology and Fungal Immunology is a unique investment that aimed to bolster capacity, training and research activity throughout the UK. This article summarises the rationale for collective collaboration of multiple institutions to achieve synergies and address a common medical problem.

Background about Fungal Infections

Medical mycology is one of many areas in the biomedical sciences that is served by a small, dispersed community that is below critical mass. Whilst funders may be sympathetic to the challenges in stimulating growth and research activity in such areas, they may lack appropriate funding mechanisms to create synergies and draw research communities together. This article reports on the outputs and achievements of a Wellcome Trust Strategic Award in Medical Mycology and Fungal Immunology (WTSA-MMFI)[i] (Figure 1) that links 13 institutions to build capacity in the field, stimulate interdisciplinary research and train a new generation of researchers in the UK and in low- and middle-income countries (LMIC).

Fungi are critical to the function of the world's ecosystem, and many species provide vital chemicals, drugs and food products. As model systems, fungi have been the organisms of choice for a dozen Nobel laureates to illustrate fundamental principles in genetics and cell biology. Some fungi are known for their ability to cause skin infections (ringworm, athlete's foot, dandruff etc.), whereas others are a feared cause of fatal human infections [1]. Deaths per annum due to fungal infections are greater than the global mortality due to malaria, breast or prostate cancer, and are similar to that inflicted by tuberculosis (TB) or HIV [2][ii]. A systematic analysis of the fungal disease burden in 2017, covering 883 million people in 14 countries, revealed that an average of 2% of people have a serious fungal infection [3]. In many of these countries, the figures can only be estimates, due to inadequate or late diagnosis and a lack of effective reporting systems, suggesting a significantly higher actual burden. Current global estimates suggest that over a million people die of fungal infections, 10 million suffer severe fungal allergy, 100 million women are victims of recurrent vulvovaginal infections annually, and more than a billion people suffer skin infections [2][ii]. There are no vaccines or immunotherapies for mycoses and only a limited arsenal of antifungal drugs to treat infections, with invasive infections often diagnosed too late to save the patient.

Building Critical Mass

In the UK, between 1997 and 2010, total investment in all infectious disease research was £2.6 billion [4], but only 2% of this was spent on medical mycology research [5]. A strategic MRC review in London in 2014[iii] indicated that this reflected the small number of applications submitted, rather than a low funding success rate. This situation was reflected in other European countries and in the USA.

The UK mycology research community is small, comprising fewer than 60 principal investigators (basic scientists or clinical academics). There are three established clinical mycology reference centres (Bristol, Manchester and Leeds) and only around ten medical mycology specialist clinicians serving the whole UK population. Only eight small/medium enterprises (SMEs) are engaged in medical mycology, and there are two major specialist research centres: the MRC Centre for Medical Mycology at Aberdeen and the Manchester Fungal Infection Group and National Aspergillosis Centre at Manchester. National mycological training is mainly provided by the British Society for Medical Mycology (BSMM) Masters level course and Public Health England (PHE) at the Bristol Mycology Reference Laboratory. However, it has been recognised by both Wellcome and the MRC that capacity in the UK is suboptimal and that significant investment is required to bring critical mass to the sector. In addition, the true burden of serious fungal disease falls hardest on areas of high endemic disease in LMIC – many of which have little local expertise.

In 2011 the Aberdeen Fungal Group (AFG) was successful in securing a £5.1 million WTSA award to establish and direct the MMFI consortium to address these problems. The AFG, based at the University of Aberdeen, is now the home of the MRC Centre for Medical Mycology – a world-renowned multidisciplinary research group at the forefront of medical research into mycoses with expertise encompassing basic molecular biology and immunology through to clinical research. Between 1997 and 2010 the AFG had received £16.9 m (35%) of all medical mycology funding awarded in the UK [5]. By 2015, the MMFI consortium had grown to include the Universities of Birmingham, Exeter, Glasgow, Kent, Liverpool, Manchester, Newcastle, Sheffield, Imperial and King's Colleges and St George's University in London.

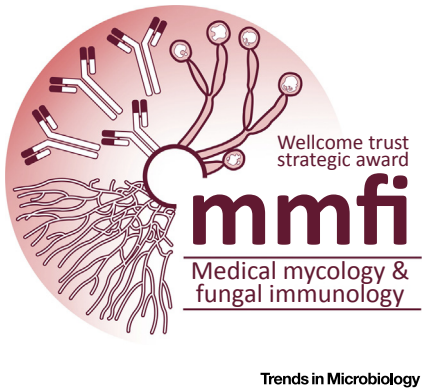

Figure 1. Logo of WTSA-MMFI.

The overarching rationale of the WTSA-MMFI was to harness the collective research capacity in the UK community to undertake cross-institutional interdisciplinary research and training that could help develop capacity in the UK whilst simultaneously addressing problems in countries with the greatest fungal disease burden. Therefore, the consortium funded a cohort of 12 international PhD studentships from LMIC: Cameroon, Colombia, India (2), Malawi (2), Mexico, Nigeria, South Africa, Uganda (2) and Uruguay, as well as 3 clinical PhDs and 6 postdoctoral fellowships (from the UK/EU). Most of the funded posts were supported by new cross-institutional partnerships. In addition, one clinical academic in medical mycology was recruited to the UK.

The specific aims of the consortium were: (i) to promote research excellence and new interdisciplinary scientific initiatives in medical mycology and fungal immunology; (ii) to integrate, expand and resource complementary skills in the field, thereby increasing understanding of fungal disease and translating basic research into the clinic and pharmaceutical industry; (iii) to establish a national consortium to coordinate a research and training programme that harnesses the excellent, but dispersed, expertise within the UK to understand and treat fungal infections and to train a new generation of scientists and (iv) to promote the public understanding and profile of this often misrepresented and underappreciated area of science.

International student recruitment was supported by LMIC academic leaders who maintained engagement in the students' UK-based training and, upon successful completion of the training programme, facilitated their redeployment into jobs in their home countries. The students all undertook an MRes degree at the University of Aberdeen to provide basic expertise in medical mycology, molecular biology and immunology, before selecting a university within the UK to complete their PhD training. All projects offered to the MRes/PhD students, postdoctoral researchers and clinical fellows were vetted by an International Advisory Board and local Management Board for excellence and alignment against strategic priorities. All trainees met annually at meetings of the BSMM to present their research, and attended courses in careers, scientific paper and grant writing, fellowship applications, research commercialisation, and other generic skills. All students also attended a workshop on fungal diagnostics and epidemiology hosted by Dr Elizabeth Johnson and colleagues at PHE in Bristol, and information sessions hosted by Wellcome on funding opportunities relevant to their future careers. The students therefore benefited from the collective expertise available throughout the MMFI consortium and from the building of a vibrant network of colleagues and expertise that extended across the whole UK sector. The MMFI consortium also worked alongside other Wellcome-funded infectious disease centres in Dundee, Glasgow and Edinburgh to present showcase events for eukaryotic medical microbiology that led to cross-disciplinary analyses, for example, drug resistance in eukaryotic pathogens [6].

Outputs and Impact

Since 2012 the consortium has generated more than 250 communications (talks, posters, workshops, videos, podcasts and press articles) and 120 research publications in high-impact journals, including *Nature*, *Science*, *Nature Immunology*, *Nature Microbiology*, *Journal of Experimental Medicine*, *PLoS Pathogens*, *mBio*, *PNAS* and *Molecular Microbiology*. In addition, the WTSA-MMFI has supported numerous public engagement activities across the UK. A major exhibition entitled '*Killer Fungus*' was held at the Royal Society Summer Science Exhibition in London in 2016. This exhibition, involving 80 consortium members, attracted over 14 000 visitors. A further exhibition '*Killer Fungus* Outbreak' took place at the Manchester Science Festival in 2017, and an extended exhibit 'The Kingdom of Fungi' was established at the Aberdeen Science Centre in 2016 and is still running. Many smaller scale public engagement events were also held by members of the consortium, leading to world-wide coverage by the BBC, CNN and major newspapers and magazines. The *Killer Fungus* public engagement brand created movie clips, apps and games (including the *Killer Fungus Evolution* and *Fungal Invaders* games) that are freely available to inform the public of medical mycology issues[iv].

The WTSA-MMFI was conceived as a unique approach to tackling the major global impact of invasive fungal infection by harnessing collective medical mycology expertise in the UK to create synergies in research and training activities. As a result, the UK medical mycology research community has become more firmly integrated. Capacity in this critical sector has grown, and public awareness of medical mycology issues has increased. Invasive fungal infections continue to rise, and organisations such as GAFFI[v] and LIFE[vi] help to lever funds and enhance global surveillance efforts and promote the availability of key antifungals in LMIC. However, new problems are arising. Antifungal resistance due to the

agricultural use of azoles may be exacerbating the spread of drug-resistant *Aspergillus* species, and emerging multidrug-resistant species, such as *Candida auris*, are fast becoming major health threats [6–8]. These factors emphasise the need for high-quality medical mycology research, with strategic and targeted modes of funding, to enable capacity development and research interactions to counter these global threats.

Resources

[i]www.abdn.ac.uk/mmfi/
[ii]https://microbiologysociety.org/uploads/assets/uploaded/fe85786a-df67-48de-a60982800c1a0829.pdf
[iii]https://mrc.ukri.org/documents/pdf/fungal-disease-research-workshop-report/
[iv]www.killerfungus.org/
[v]www.gaffi.org/
[vi]www.life-worldwide.org/

Supplemental Information

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Spotlight

Mycobacterium tuberculosis: prePPARing and Maintaining the Replicative Niche

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***Mycobacterium tuberculosis* interferes with the ability of its host cell to undergo apoptosis. Arnett *et al.* report that the pathogen promotes macrophage survival by engaging the nuclear receptor PPARγ to induce the antiapoptotic protein MCL-1, yielding insights into the pathogenesis of tuberculosis and potentially unlocking new avenues for therapeutic intervention.**

Many of the most significant pathogens of humans and animals adopt at least a partially intracellular lifestyle in order to persist and cause disease. Apoptosis is a programmed cell death pathway thought to have evolved primarily as a defense against such intracellular pathogens [1]. Eliminating infected cells via apoptosis not only strips the pathogen of its intracellular replicative niche but can also directly kill the pathogen as well as stimulate adaptive immune responses [2]. For some pathogens, such as *M. tuberculosis*, the ability to subvert this altruistic host cell death is essential for their persistence. Indeed, the extent of macrophage apoptosis upon infection with different strains of *M. tuberculosis* has been inversely correlated with virulence, although there remains little consensus in terms of exactly how *M. tuberculosis* curbs apoptosis of its primary host cell. Nonetheless, several reports have reproducibly implicated the rapid and sustained upregulation of MCL-1 in infected macrophages as a key restriction factor for apoptosis, and therefore, for mycobacterial control [3,4]. MCL-1 is an antiapoptotic member of the BCL-2 protein family, which regulates the intrinsic pathway of apoptosis through interactions between its pro- and antiapoptotic constituents [5]. Until recently, mechanistic insights into *Mcl-1* regulation during *M. tuberculosis* infection have been lacking.

Arnett *et al.* [6] set out to identify effectors downstream of peroxisome proliferator-activated receptor (PPAR)γ – a nuclear receptor and transcription factor which is highly induced in alveolar macrophages infected with *M. tuberculosis*. Activation of PPARγ is known to promote intracellular growth of the pathogen, although the transcriptional changes leading to this enhanced growth had previously remained unclear. The authors performed gene expression analysis of human macrophages infected with *M. tuberculosis*, revealing a number of genes that are differentially regulated upon PPARγ knockdown, including *Mcl-1*, which is significantly downregulated [6]. This demonstrates that PPARγ promotes *Mcl-1* expression, thus establishing a potently antiapoptotic cellular milieu. Mechanistically, PPARγ expression is induced upon recognition of mannosylated lipoarabinomannan present in the cell wall of *M. tuberculosis* and is activated by lipid agonists generated by the host enzyme 15-lipoxygenase [6]. Activated PPARγ then binds to genetic elements within the *Mcl-1* promoter to enhance transcription. Knockdown of either PPARγ or MCL-1 was shown to promote a modest increase in the death of infected macrophages, highlighting the