Contents

Overview 4
Strategic Need 6
Vision 8
Research Portfolio 13
Structure and Management 34
Interactions 36
The Medical Research Council Centre for Medical Mycology (MRC CMM) was established in July 2016 at the University of Aberdeen. This Centre capitalises on the world-renowned expertise of the Aberdeen Fungal Group (AFG), and represents a joint investment of £6.5 million by the MRC and the University of Aberdeen. The creation of the MRC CMM represents one of the most ambitious strategic investments in UK medical mycology. This award empowers the AFG, enabling this group to utilise and expand its critical mass, promoting pioneering cross-disciplinary research that covers areas of scientific, translational and clinical importance. A major activity of the Centre is to increase future UK capacity in basic and clinical research through training programmes aimed at various levels, from medical students to early career researchers. This award also facilitates strategic interactions with other national and international groups and promotes public engagement and understanding of our science.

The AFG is one of the largest medical mycology groupings worldwide. The principal investigators (PIs) within the AFG represent a broad umbrella of expertise from fundamental research into the biology of fungal pathogens to patient care and translational science. This wide-ranging expertise enables the development of unique synergies within the AFG, facilitating the simultaneous analysis of both the host and pathogen to determine their individual contributions to the pathogenesis of disease. Originally located at different locations on the Foresterhill site, the formation of the Centre saw the relocation of all AFG members into contiguous laboratory and office space in the Institute of Medical Sciences building (IMS) to optimise interaction and collaboration.

The IMS which sits in the College of Life Sciences and Medicine (CLSM), is a cutting edge £50 million biomedical research institute that boasts a well-integrated interdisciplinary research infrastructure that includes state-of-the-art genomics, proteomics, microscopy, histology, cytometry and animal care facilities. Within the IMS, the Kosterlitz Centre for Therapeutics provides expertise in the development of novel drugs and clinical targets. Adjacent to the IMS, the Institute of Applied Health Sciences (IAHS), is a major research centre in health services research that provides complementary expertise in health technology assessments (including in diagnostics), evidence synthesis, clinical trials, health economics and medical statistics. The IMS is also located next to the Aberdeen Royal Infirmary (ARI), which serves one of the largest geographical areas of any hospital in the UK. The Rowett Institute (RI) is also immediately adjacent to the IMS providing
further sources of complementary expertise in human nutrition and health. The collocation of the IMS, the RI, the Suttie Centre for Teaching and Learning in Healthcare, the IAHS, and the ARI provides a tightly integrated biomedical centre for basic, clinical and translational medical research. There are also on-site incubator facilities for translational research and the development of biotechnology-based spin-out companies.
Of all microbial pathogens of humans, fungi are the least well studied and understood. Fungal infections of the nails, skin and mucosae affect approximately one quarter of the world’s population. In addition, around 3 million individuals suffer from life-threatening invasive infections that are difficult to diagnose and treat \([1, 2]\). Moreover, these infections often have mortality rates that exceed 50%, even when antifungal drugs are available. Fungi also contribute substantially to morbidity associated with asthma and other allergies, infection-related blindness and debilitating and disfiguring chronic subcutaneous infections. Collectively the cost of diagnosing, treating and providing prophylactic protection from fungal infections has major economic impact.

Three areas require our urgent attention:

1. We need to generate safer and more effective antifungal drugs.
2. We need to improve our ability to detect fungal infections, by developing robust, rapid, simple and cheaper diagnostics.
3. We need to better understand fungal virulence and host antifungal immunity, and to exploit these discoveries to help tackle these devastating infections.

References:


Our ability to tackle these urgent challenges is considerably constrained by a worldwide lack of capacity in basic and clinical mycology. The MRC CMM helps to meet this strategic need by facilitating pioneering cross disciplinary research addressing the priority areas of research, and by increasing UK capacity for basic and clinical research for the future.
The overarching vision of the MRC CMM is to facilitate innovative and world leading multidisciplinary research that will substantially advance our understanding of fungal pathogenesis and host immunity, enabling the generation and utilisation of knowledge that will improve the prevention, diagnosis and treatment of fungal diseases in the future.

Our vision will be achieved by delivering on the following objectives over the next five years:

- To add posts in bioinformatics and adaptive immunity that will catalyse new interdisciplinary activities.
- To enhance and integrate the broad and complementary expertise of the AFG to achieve new synergies across six themes of innovative interdisciplinary research.
- Deliver a strong cohort of basic and clinical researchers through our bespoke training programmes.
- To facilitate and promote collaborations with industry and the clinic.
- To promote medical mycology within the broader academic community and the general public.

The vision for the MRC CMM. Current areas of expertise in the MRC CMM (unfilled boxes), new areas of investment (blue filled boxes) and objectives and outputs (blue shaded boxes).
Delivering the Vision:

Research – Innovative and Interdisciplinary

Research in the MRC CMM refocuses existing synergies within the AFG into 6 key themes, generating integrated cross-disciplinary programmes of research that address the major challenges facing this field.

Research Themes:

1. Fungal cell surface dynamics and its impact on antimicrobial chemotherapy and host immunity.
2. Fungal components as antifungal drug targets, diagnostics, vaccine antigens and adjuvants.
3. Fungal growth, adaptation and morphogenesis in the context of infection.
4. Temporal host-fungal interactions and key mediators that influence disease establishment and progression at molecular, cellular and organismal levels.
5. Exploiting emerging technologies to generate global perspectives that broaden our mechanistic understanding of host-fungal interactions.
6. Unravelling patient susceptibility to enable directed diagnosis, treatment and prevention of fungal disease.
Training and Capacity Building

The creation of the MRC CMM enables us to address the shortage in medical mycology expertise in the UK, by training excellent basic and clinical scientists, and to consolidate our position as an international “Centre of Excellence” for training in this field. A central component of this programme will be the development and mentoring of our trainees, with the ultimate aim of helping them to establish themselves as independent researchers in this field in the UK in the future. We have a track record of over 30 postdoctoral fellows and students that were trained in the AFG, that now hold permanent research positions or fellowships in medical mycology across the UK and worldwide.

We offer the following bespoke training programmes:

- 13 MRes-PhD Studentships
- 5 Academic Clinical Training Fellowships
- 3 Early Careers Fellowships
- 10 Medical Student Summer Scholarships
Translation to Clinic and Industry

The strong foundational science base of the MRC CMM scientists have led to translatable opportunities, which are significantly enhanced by the formation of the MRC CMM. Support for these translational activities is provided by the University of Aberdeen which has active pipelines for facilitating commercial exploitation of promising research results and encourages the formation of spin-out companies, collaborations with industry and other knowledge exchange activities. Early stage translational activities are supported by a MRC Confidence in Concept (CiC) Award and a Wellcome Trust Institutional Strategic Support Fund (ISSF).

Our objectives include:

- Increasing and promoting opportunities for translation of Centre research.
- Increasing collaborations and other interactions with industry and the clinic.
- Increasing the numbers of patents and commercial contracts.
Communication – Public Engagement and Scientific Dissemination

Our objective is to raise general awareness of the importance of medical mycology and to communicate the research and training being carried out in the MRC CMM. This will be achieved utilizing several channels of communication, including print, web-based and social media as well as live events. Our activities include:

- **Local and national science exhibitions**
  - e.g. Killer Fungus exhibit at the 2016 Royal Society Summer Science Exhibition in London and Kingdom of Fungi at The Aberdeen Science Centre.

- **Public meetings and lectures**
  - e.g. Café Scientifique, Café Med, Doors Open Day at Institute of Medical Sciences, UK Fungus Day, May Festival (University of Aberdeen), MRC Festival of Medical Research and Explorathon16.

- **Social media**
  - e.g. MRC CMM website, Twitter @MRCcmm, Facebook and YouTube videos.

- **News and radio**
  - e.g. Press releases, radio and TV interviews, and podcasts to promote major scientific publications.

- **Outreach**
  - e.g. school science days (primary and secondary pupils), schools’ careers days and local Girl Guide events.

- **Academic audiences**
  - e.g. national and international conferences, universities’ seminar series, lectures and scientific publications.
The AFG represents roughly 25% of UK scientists working in medical mycology.

Each of the PIs within the AFG brings specific expertise to the group, creating a uniquely broad scope of activities. This expertise spans from fundamental to clinical mycology, facilitating the simultaneous analysis of both the host and pathogen. The creation of the MRC CMM enables us to establish an optimal configuration that will exploit our collective strength and maximise our potential for fundamental and translational science, as well as for providing world-leading training in medical mycology. To do this we are recruiting individuals with expertise in bioinformatics and in adaptive immunity, adding substantial value to the MRC CMM in terms of scope, depth and translatability of our existing strengths in medical mycology.

The recruitment of a Senior Lecturer in Bioinformatics to the MRC CMM will release the bottleneck that has been created by the explosive increase in the generation of our sequence-based datasets. The appointee will be physically embedded within the MRC CMM, to maximise interactions within the group, but will also be associated with the Centre for Genome Enabled Biological Medicine (CGEBM) at Aberdeen, which has infrastructure and expertise in \textit{de novo} sequencing, epigenomics, transcriptomics, metagenomics, SNP discovery, as well as whole genome and targeted re-sequencing of microbes and animals from tissues, single cells and ancient DNA samples. This post will dramatically accelerate our conversion of large genomics datasets into biologically informative outputs that will shape the future directions of our research programmes.

Professors Gordon Brown, Neil Gow and Adilia Warris provide capacity in innate immunity, but the MRC CMM lacks expertise in experimental adaptive immunity - a critical area required to promote our translational ambitions. Although there have been significant advances in this area, our understanding of these key antifungal responses is still in its infancy and they offer great potential for future exploitation. We are therefore creating a new permanent Lecturer post in experimental immunology, who will drive their own independent research programme alongside collaborative projects with other MRC CMM members, exploring the influence of fungal and host components on the development of adaptive antifungal immunity and their diagnostic, preventive and therapeutic potential.
Biography
Gordon Brown completed a Ph.D. in microbiology at the University of Cape Town, South Africa. He was a Wellcome Trust travelling postdoctoral fellow at the University of Oxford, UK, then a Wellcome Trust Senior Fellow at the University of Cape Town, South Africa, and is now a Professor of Immunology, Wellcome Trust Senior Investigator and Director of the MRC Centre for Medical Mycology at the University of Aberdeen. In addition, he is a co-Director of the Wellcome Trust Strategic Award in Medical Mycology and Fungal Immunology, based out of Aberdeen, and maintains a research group at the University of Cape Town, where he holds an honorary Professorship. His primary research interests are C-type lectin receptors and their role in homeostasis and immunity, with a particular focus on antifungal immunity.
Lay abstract of research
To recognise infection, the immune system utilizes sensors on immune cells called “pattern recognition receptors” which detect invading pathogens. These sensors then trigger a number of responses which are aimed at providing protection against the infection. My group is focussed on understanding a particular family of these pathogen sensors, called the C-type lectins (CLRs), which stemmed from our discovery of the first receptor in this class, Dectin-1. We have shown that CLRs are able to induce essential immune responses, and have determined the mechanisms that they utilize to trigger these effects. Importantly, we have shown that CLRs play a central role in protective immune responses during fungal infections and identified genetic variants of Dectin-1 in humans, which can confer susceptibility to disease. We have also determined that defects in recognition by pathogen sensors can result in an untreatable fungal infection of the skin, called chromoblastomycosis; work which has led directly to the testing of a novel treatment in humans. Our current research is aimed at gaining a more detailed understanding the role of CLRs in immunity during fungal infection, and exploring the roles and functions of new CLRs that we have recently identified.

Scientific abstract of research
The induction of antimicrobial immunity is critically dependent on the sensing of pathogens by cells of the immune system. This is achieved by germ-line encoded “pattern recognition receptors” (PRRs) which sense highly conserved microbial structures. My group is focussed on determining the roles and functions of a particular class of PRR, the C-type lectins (CLRs), which stemmed from our discovery of the first receptor in this class, Dectin-1. We have subsequently shown that CLRs can induce intracellular signalling to trigger a variety of cellular responses, such as the production of cytokines and chemokines, and are capable of inducing and modulating innate and adaptive immunity. Importantly, we have shown that CLRs play an essential role in anti-fungal immunity and identified polymorphisms of Dectin-1 in humans, which can confer susceptibility to disease. We have also determined that defects in immune recognition can result in an untreatable fungal infection of the skin, called chromoblastomycosis; work which has directly led to the testing of novel treatment regimens in humans. Our current research is focussed on better understanding the role of CLRs in the development of adaptive immune responses during fungal infection, and exploring the roles and functions of new CLRs we have recently identified.

www.abdn.ac.uk/ims/profiles/gordon.brown
Biography

Neil Gow is a microbiologist with specialist research interests in medical mycology and in particular the biology of the fungal cell wall and host-fungus interactions. He trained at Edinburgh, Aberdeen and Denver USA before taking up a position at Aberdeen. He is a founding member of the Aberdeen Fungal Group (AFG). More than 25 of his past laboratory students and postdoctoral researchers now have their own laboratories in the field. He is the Director of a Wellcome Trust Strategic Award that coordinates research and training activity in the field of medical mycology and fungal immunology across the UK and in developing countries. He is also co-Director for research for this MRC Centre for Medical Mycology and is funded via a Wellcome Trust Senior Investigator award and Collaborative Award. He is current President of the Microbiology Society.
Lay abstract of research

Fungi are aesthetically beautiful organisms that are central to world ecology and provide vital food and drink products, drugs and materials. But there is a sinister side to them that is not properly appreciated. Fungal skin infections affect one in three people worldwide but, more seriously, fungi also kill over a million people through infection every year and more people die of fungal infections than malaria, tuberculosis or breast cancer.

My group is focused on life-threatening fungal diseases. These infections pose difficulties in diagnosis, there are no vaccines for fungal disease, and treatment options are limited. Fungi have a cell wall that is composed of signature molecules that are not represented at all in the human body. The cell wall is therefore the target which the immune system uses to recognise the presence of a fungal invader and it is also an excellent target to aim the design of antifungal drugs. For these reasons my group’s speciality is to understand how the fungal cell wall is made, how it is detected by our immune system and how we might kill fungi by blocking cell wall assembly. This research is therefore informing the design of new generations of antifungal drugs and diagnostic tests.

Scientific abstract of research

The cell wall of fungal pathogens determines their pathobiology and immunological signature. It is the ideal target for chemotherapies and immunotherapies because all the major cell wall components are essential and fungal-specific. My group aim to understand how the cell wall is assembled and recognised by the immune system. The group are world leaders in the analysis of the major human pathogen Candida albicans, and in cell wall biology. The major research questions they are addressing are:

(i) What are the key processes that articulate cell wall assembly? To answer this, we are exploiting recent advances in C. albicans genetics and novel screens, phenotyping methods and in vitro biology approaches to dissect the functions of key families of cell wall genes to pioneer the genetic analysis of multigene families involved in cell wall synthesis.

(ii) What is the fine chemical structure of cell wall molecules that stimulate, attenuate and imprint the innate and adaptive responses of the immune system? We use novel, bespoke reagents and combinations of host and pathogen functional analysis tools to study the key immunologically relevant cell wall glycoconjugates.

These complementary research questions are informing the design of new generations of therapeutics and diagnostics.
Biography
Adilia Warris is a paediatric infectious diseases specialist with a specific interest in medical mycology and holds an Honorary Consultant position in Paediatric Infectious Diseases at the Royal Aberdeen Children’s Hospital. She is a principal investigator of the Aberdeen Fungal Group and co-director of the MRC Centre for Medical Mycology at the University of Aberdeen.

Prof Warris’ research profile has a strong translational focus and specific areas of interest include the host-fungus interaction in specific patient groups with an emphasis on Aspergillus species, the unique interaction of A. nidulans and the CGD host, Aspergillus infections in the cystic fibrosis (CF) host, the development of new management strategies for invasive fungal disease in children, the epidemiology of invasive fungal infections in children, and the pharmacology of antifungals in paediatrics. She chairs the European Paediatric Mycology Network (EPMYN) which aims to improve the management and understanding of paediatric fungal infections.
**Lay abstract of research**

My research is directly targeted to improve the outcome of infections caused by Aspergillus species in specific patient populations.

Patients with chronic granulomatous disease (CGD), suffering from an inborn error in the function of white blood cells, have an extremely high-risk to develop invasive aspergillosis and often these infections are fatal. Invasive aspergillosis in patients with a compromised immune system (as patients with cancer and those undergoing a bone marrow transplant) is mainly caused by Aspergillus fumigatus. In patients with CGD however, invasive aspergillosis caused by Aspergillus nidulans is unique to this patient group and not seen in other patient groups. Our studies have shown that the interaction between the two Aspergillus species and white blood cells of CGD patients is different and are causing different disease patterns. Currently we are investigating new treatment strategies in an experimental model of invasive aspergillosis in CGD mice based on our observations.

Comparable studies are done with immune cells from patients with cystic fibrosis (CF). Half of the patients with CF will be infected with A. fumigatus in their lungs leading to exacerbation of lung disease. One explanation may be that CF immune cells are impaired in the clearance and killing of A. fumigatus. Another is that A. fumigatus may induce hyperinflammation in the CF lungs resulting in progressive lung damage. By studying the interaction between CF immune cells and A. fumigatus we have already observed that CF immune cells are able to kill A. fumigatus but at the cost of an exaggerated inflammation.

**Scientific abstract of research**

My research is directly targeted to improve the outcome of infections caused by Aspergillus species in specific patient populations.

Invasive aspergillosis (IA) in chronic granulomatous disease (CGD) is the main cause (35%) of premature death and reflects the vulnerability of this patient group to this devastating infection. Our recent research has shown that the interaction between Aspergillus and the host is species specific and show marked differences with regards to antifungal killing mechanisms and IL-1ß release. A. nidulans infections behave more aggressively and are associated with a higher mortality which seem to be due to an increased inflammatory response characterized by an excessive release of interleukin-1 (IL-1). By using an experimental model of IA in CGD mice we are exploring in detail the pathogenesis and to test our hypothesis that IA in CGD is an IL-1 driven disease and necessitates a different therapeutic approach to improve the outcome of these devastating infections.

Cystic fibrosis is the most common genetically inherited disease in Western populations. Although survival of CF patients is improving, median age of death is < 30 years. Half of those patients will be infected with A. fumigatus leading to an increased risk of hospital admission due to exacerbation of lung disease. It remains unclear why A. fumigatus is able to reside in the CF lung and how it can cause progressive lung disease. We are aiming to gain an increased understanding of the effect of the CFTR-deficiency on the innate immune responses. Therefore we are investigating the innate antifungal immune response of CF immune cells by using a zebrafish model and ex-vivo blood phagocytes of CF patients.

www.abdn.ac.uk/staffnet/profiles/a.warris
Biography
Al Brown studied Biochemistry at the University of Aberdeen, and then worked in Surrey and at MIT before returning to the UK to take up his first faculty position in Genetics at Glasgow University in 1983. In 1989 he moved back to Aberdeen University where he is now a Professor of Molecular and Cell Biology in the Institute of Medical Sciences. Together with Neil Gow, he formed the Aberdeen Fungal Group (AFG) in the early 1990’s. Since then the Group has blossomed into a large tightly integrated and interdisciplinary team addressing a wide range of questions in medical mycology and fungal immunology. This has led to the development of the Wellcome Trust Strategic Award in Medical Mycology and Fungal Immunology [www.abdn.ac.uk/mmfi: directed by Neil Gow] and the UK Medical Research Council’s Centre for Medical Mycology [www.abdn.ac.uk/cmm: directed by Gordon Brown]. Al Brown’s research team combines genomics, molecular biology and modelling to study the adaption of Candida albicans, to dynamic and complex host niches during colonisation and infection.
Lay abstract of research
My group studies the pathogenic yeast, *Candida albicans*. *Candida* normally lives in our gut, doing us no harm. However, it is also the cause of common infections such as thrush, and the cause of life-threatening infections in intensive care patients. Our aim is to understand what makes this yeast so adept at switching from a harmless component of our microbiota into an aggressive cause of infection. In part this is because *Candida* is able to rapidly tune its own physiology to different niches within our bodies. We are investigating the molecular mechanisms that mediate these adaptive responses to the local nutrients and environmental stresses in these niches, and the interactions between these nutrient and stress responses. This is increasing our understanding of how *Candida* survives inside us. In the longer term, this will promote the development of better diagnostics and more effective antifungal therapies.

Scientific abstract of research
Metabolic and stress adaptation are central to the virulence of the major fungal pathogen of humans, *Candida albicans*. *C. albicans* tunes its metabolism and activates robust stress responses to optimize its survival, growth and colonization of diverse niches in the host. My group is dissecting these phenomena using a combination of genomics, proteomics, molecular genetics, mathematical modelling and infection biology. We are studying how combinations of host-imposed stresses affect *C. albicans*, how local nutrients affect the ability of the fungus to survive these stresses, and how this affects immune recognition and virulence. We have shown that *C. albicans* is particularly vulnerable to certain combinations of stress that are used by immune cells to control infection. However, we have also shown that adaptation to certain host nutrients can increase the ability of *C. albicans* to resist stresses. Indeed, metabolic adaptation affects virulence in several ways. As well as influencing stress susceptibility, it moderates resistance to antifungal therapies and the expression of key virulence factors. Furthermore, metabolic adaptation affects cell wall architecture, which turns the *C. albicans* cell into a moving target for our immune defences. These effects are controlled by an array of regulatory networks that integrate metabolism, morphogenesis, stress adaptation and cell wall remodelling. Together, these processes influence commensalism and infection.
**Biography**

Liz Ballou is a fungal geneticist and molecular biologist who studied at the London School of Hygiene and Tropical Medicine (Molecular Biology of Infectious Diseases) and Duke University (Genetics and Genomics). She earned her PhD at Duke in 2012 and joined the University of Aberdeen shortly thereafter as a research fellow. In 2015, Liz was awarded a BBSRC Anniversary Future Leaders Fellowship, and her lab is now part of the MRC Centre for Medical Mycology. Her research focuses on the basic biology of the human fungal pathogen Cryptococcus neoformans.

---

**Dr Elizabeth Ballou**  
*PhD*

Tel: +44 (0) 1224 437325  
Email: e.ballou@abdn.ac.uk
Lay abstract of research

Fungal pathogens kill an estimated 2 million people each year. The single biggest killer is a fungus called Cryptococcus neoformans, which causes 1 million infections and 600,000 deaths worldwide annually. Cryptococcus is associated with birds and trees on every continent, and most of us have been exposed to it without ever becoming ill. However, among immunocompromised individuals, Cryptococcus infections are fatal. In these patients, Cryptococcus in the lung enters the bloodstream and quickly moves to the brain and central nervous system. Unlike other fungi, which cause invasive tissue damage via penetrating hyphal growth, Cryptococcal meningitis is caused by simple growth of the budding yeast in the brain.

My lab is working to understand how Cryptococcus yeast grow in the human body by investigating the basic biology of this fungus. We are most interested in the unusual ability of Cryptococcus cells to transform from small yeast into very large Titan cells. These Titans are too large to be killed by our immune cells and also produce small buds that quickly spread to the brain. By investigating host signals that trigger Titanisation, and fungal signals that direct Titanisation, we hope to find new ways to treat and prevent Cryptococcal meningitis among vulnerable patients.

Scientific abstract of research

Cryptococcus neoformans Titan cells are a novel morphotype found in the host lung that are associated with poor outcome for the patient. Titans are significantly larger than haploid yeast cells, and are also polyploid, likely the result of endoreduplication. Polyploid Titans have the capacity to bud off aneuploid daughter cells, and this aneuploidy leads to altered drug and stress resistance and virulence profiles compared to the parent. In this way, C. neoformans clonal populations are able to generate genetic diversity within the host lung environment. Titan cells therefore represent both an important reservoir for infection in immunocompromised patients and a mechanism for the fungus to adapt to new environmental challenges. However, the signals that trigger Titanisation, and the mechanisms by which they form, are unknown.

My group aims to understand the basic biological mechanisms underlying Titan cell increases in size and ploidy in order to better develop therapeutic interventions. We have recently demonstrated that proteins involved in Cryptococcus morphogenesis and cell size are also involved in the localised generation of Reactive Oxygen Species (ROS) and the regulation of cell ploidy. Using molecular biology, genetic, proteomic, and cytometric approaches, we are investigating the role of ROS as signalling molecules within the cell to direct these key morphological transitions.
Biography
Alex Brand is a fungal cell biologist working on how the penetrative filaments of pathogenic fungi are tailored to promote invasive infections. Alex came to science as a second career after taking an Access course at the University of Aberdeen. She graduated in Biochemistry in 2000 and completed a PhD in Microbiology in 2004. She established her research group in 2009 with a Royal Society University Research Fellowship and an MRC New Investigator grant to investigate how fungi regulate invasive traits in response to the physical properties of the environment. Alex became Co-Lead of the University of Aberdeen Microbiology Programme in 2012 and was appointed Reader in 2015.
Lay abstract of research
Systemic fungal infections kill more than 1 million people a year. Almost half of these deaths are caused by two fungi that produce invasive hyphal filaments. These filaments penetrate deep within human tissue causing cell damage, inflammation and fatal levels of sepsis. A key virulence trait of these filaments is their ability to steer as they grow and respond to physical features they encounter in the environment. Although fungi are relatively simple organisms, we do not yet understand how this information is sensed or how the direction of growth is altered. We have developed an imaging system that enables us to monitor hyphal growth and track the movement of intracellular fluorescent proteins at the same time. By deleting candidate genes, we can compare the mutant strains with normal cells to find out which proteins are important for hyphal steering. Mutants that cannot steer normally are not able to penetrate human tissue so drugs that uncouple the steering mechanism in fungal cells might be effective at halting deep-seated tissue invasion by these fungal pathogens.

Scientific abstract of research
Almost half a million deaths a year are caused by the filamentous fungi, Candida albicans and Aspergillus fumigatus, where hyphal invasion of internal organs leads to tissue damage and fatal levels of inflammation. Hyphae grow by continued polarised extension but are unable to penetrate host tissue without control of their growth direction. During growth on surfaces, the hyphal apex adopts an asymmetric morphology, which is required for normal directional behaviour in response to topographical features and include contour-following, gap penetration and maintenance of the growth trajectory. Tip asymmetry depends on the Ras-like GTPase, Rsr1, which localises the Cdc42 polarity complex, but how contact is sensed and outside-in signalling is mediated by Rsr1 is not known. We have identified additional protein complexes that are required to maintain a normal hyphal growth trajectory and may function in concert with the polarity complex during construction of the growing tip. Our findings confirm the importance of external cues in hyphal steering and develop our understanding of fundamental growth processes in filamentous fungal pathogens.

www.abdn.ac.uk/ims/profiles/a.brand
Biography
Deborah Lockhart is a Wellcome Trust Clinical Postdoctoral Research Fellow at the University of Dundee & Aberdeen and an Honorary Consultant Microbiologist in NHS Grampian. Deborah qualified in Dentistry with Honours at the University of Glasgow (2004) after intercalating a BSc (Microbiology, First Class). Following Royal College membership exams (2006), her career took an unusual twist by specialising, clinically, in microbiology based at Glasgow Royal Infirmary and becoming a Fellow of the Royal College of Pathologists in Medical Microbiology (2011). Inspired by the difficulties in diagnosing and managing patients with life-threatening fungal infections, Deborah completed a PhD at the University of Dundee with Daan van Aalten investigating novel cell wall antifungal targets in Aspergillus fumigatus supported by a MRC Clinical Research Training Fellowship. Her current Fellowship allows Deborah to consolidate her skills, explore new areas and lay the foundations for establishing her own group in the MRC CMM.
Lay abstract of research
Modern medical treatments including advances in cancer therapy and organ transplants weaken the immune system and make patients highly susceptible to infections that would not normally pose a threat. Invasive fungal infections are often fatal in these groups. Aspergillus fumigatus is a fungus that produces spores found widely in the environment. In healthy people inhaled spores are harmless and eliminated by the immune system but in certain groups, including those with existing lung problems, they cause disease. The most serious forms lead to life threatening infections that are notoriously difficult to identify and treat. A sugary coat or 'cell wall' protects the fungus. Many coat making machines 'enzymes' contribute to this process but there are many gaps in our knowledge. I have discovered a sticky pocket on an enzyme essential for A. fumigatus growth under laboratory conditions. I am investigating: (1) whether loss of this enzyme stops the fungus causing disease, and (2) developing the chemical anchor binding to the sticky pocket into a longer molecule to block the enzyme and I hope, ultimately, kill the fungus. This work may help uncover starting points for the development of a new class of antifungal drugs.

Scientific abstract of research
A limited number of antifungal drug classes against increasingly recognised clinical disease due to opportunistic fungi require validation of novel antifungal targets. The fungal cell wall is a potential source of new targets. In Aspergillus fumigatus, this dynamic multi-layered structure is almost entirely polysaccharide and contains chitin and glucan that are absent from the host. A sugar nucleotide precursor, UDP-N-acetyl-D-glucosamine (UDP-GlcNAc) is converted to a thin layer of chitin (essential for survival) by an orchestra of chitin synthases. An upstream 'proxy' target for chitin synthesis, glucosamine-6-phosphate N-acetyltransferase (Gna1), plays a key role in de novo UDP-GlcNAc biosynthesis.

Two equally important questions any potential drug target must overcome during validation relate to (1) in vivo phenotype and (2) ligandability i.e. are chemical-protein interactions possible? Fragment screening assesses the latter and together with X-ray crystallography I have discovered a fungal specific binding pocket on the target protein Gna1 next to the active site. In vitro growth of my gna1 knockout is tightly regulated by glucose in the presence of exogenous GlcNAc. I am currently investigating the contribution of Gna1 to pathogenicity using in vivo models of infection and together with the Dundee Drug Discovery Unit, developing early chemical scaffolds into inhibitors.
Biography
Donna MacCallum graduated from the University of Aberdeen in 1994 with a first class Honours degree in Genetics, then completed a PhD in Microbiology (1998) investigating yeast-hypha dimorphism in Candida albicans. From 1999-2009, Donna was a postdoctoral research fellow building expertise in animal models of immune diseases and fungal infections. She became an independent research fellow in 2009 and was promoted to Senior Lecturer at the University of Aberdeen in 2012. Donna is currently the Programme Coordinator of the MSc Microbiology, MSc Genetics and MRes Medical Mycology programmes. She is also on the management board of the MRC Centre for Medical Mycology at the University of Aberdeen and is the current treasurer of the International Society for Human and Animal Mycology (ISHAM). The focus of her research is fungal pathogenesis and developing the 3Rs in medical mycology. Donna is also very active in public engagement.

Dr Donna MacCallum
FHEA FRSB PGCE (Higher Education Teaching)

Tel: + 44 (0) 1224 437425
Email: d.m.maccallum@abdn.ac.uk
**Lay abstract of research**

Fungal infection models play a vital role in understanding how pathogenic fungi are able to cause disease, how the host responds to fungal cells and for evaluation of antifungal drugs. Fungi can cause infections of the skin, nails, mouth, genital tract, lungs, brain and even life-threatening systemic infections. My research develops and characterises models which mimic these different infections, using animal models, insect models or cells in the laboratory. My research is particularly directed at reducing, replacing and refining the use of animals in medical mycology research (3Rs). I have previously developed a shorter term fungal infection model, which significantly reduces the length of time required to determine whether a fungus is able to cause an infection or not. Current work has focussed on developing a laboratory assay which mimics interactions of fungal cells with kidney cells at the beginning of an infection to replace the use of animals, and we are developing fungal cells which can be imaged in living animals to reduce the numbers of animals required to evaluate new antifungal drugs.

**Scientific abstract of research**

Fungal infection models allow us to investigate the fungal virulence attributes required to initiate infection, the immune and physiological responses of the host to infection and, importantly for our translational work, how an infected host responds to novel antifungal therapies. My group develops and characterises infection models to address these specific scientific needs, with the 3Rs (reduction, replacement and refinement) firmly embedded in our research. We have previously determined that short term fungal infection models can predict the outcomes of longer term virulence assays and have developed an in vitro model which mimics the initial interactions occurring between Candida albicans and epithelial cells in the murine kidney, where infection progresses, allowing an estimation of virulence potential of C. albicans strains. Our current research is focussed on developing fungal strains which express fluorescent proteins for all of the major fungal pathogens, allowing fungi and infection progression to be imaged in living animals without the need to administer exogenous substances to the infected animals. These models will allow response to antifungal therapy to be followed in individual animals, greatly reducing the number of animals required to evaluate novel drugs.
Biography
Carol Munro has over 20 years’ experience studying human fungal pathogens. Her research investigates how surface components contribute to virulence, host interactions and drug tolerance. She has strong ties with industrial partner NovaBiotics Ltd developing peptide-based antimicrobial therapies. Her interests span genomics and proteomics-based approaches to gain a better understanding of fungal pathogenicity and in collaboration with Christophe d’Enfert at Institut Pasteur has generated a Candida albicans ORFeome library.

Professor Munro is a Fellow of the Royal Society of Biology, deputy Editor in Chief of the journal FEMS Yeast Research and will Chair the 2017 Advanced Lecture Course on Human Fungal pathogens. She has published over 80 scientific publications and obtained funding from the European Union, University of Aberdeen, Medical Research Council, Scottish Universities Life Sciences Alliance and the Wellcome Trust to fund her research. These funds have helped her mentor over 30 PhD and Masters students.
Lay abstract of research
My group is investigating the protein components of the outer coat of the fungal pathogen Candida albicans and the mechanisms that control their appearance at the cell surface. This outer coat plays an important role in the ability of the fungus to invade and infect the host, to escape recognition by the host, and contributes to the ability of the fungus to resist antifungal drugs. We are testing the potential of outer coat proteins as novel diagnostic and therapeutic targets to detect and block the invading pathogen. We are also contributing to the development of novel peptide-based anti-infectives to treat invasive fungal infections with industrial partner NovaBiotics Ltd. Another main focus is building important molecular tools and resources for the fungal research community to improve the characterisation of the Candida albicans genetic blueprint in order to gain a better understanding of the factors that make this fungus such a successful pathogen.

Scientific abstract of research
My research is focussed on characterising the function and regulation of C. albicans cell surface proteins that have roles in pathogenesis and antifungal drug tolerance mechanisms. We are developing antibodies, with the Scottish Biologics Facility, against cell surface proteins to assess their utility as biomarkers of invasive fungal infections and/or therapeutics. I am interested in the signalling pathways that regulate cell wall synthesis and re-modelling, and their downstream target genes. My group investigate how fungi respond to compounds that target cell wall biosynthesis and the potential of combination therapies that inhibit multiple cell wall components and cell wall regulatory pathways.

My research also spans antifungal drug development and I have partnership projects with NovaBiotics Ltd developing antimicrobial peptides as therapies for systemic fungal and polymicrobial infections.

A further area of research is functional genomics, and with Christophe D’Enfert Institut Pasteur, my group has been constructing C. albicans ORFeome and over-expression libraries that will be distributed to the community. My aim is to use the over-expression collection to perform high throughput phenotypic analysis to gain a better understanding of fungal virulence and fitness, and to improve the existing genome annotation by elucidating the roles of uncharacterised genes.
Biography
Duncan Wilson studied Microbiology at the University of Glasgow and went on to start his research career in medical mycology with a PhD at the University of Manchester and Pfizer (PhD: 2007) studying cyclic AMP signalling in Candida albicans. From there he moved to the Hans Knoell Institute in Jena, Germany, where he worked on the molecular basis of C. albicans pathogenicity with Prof Bernhard Hube. In 2014 he established his own research group in the Aberdeen Fungal Group with the support of a Wellcome Trust Sir Henry Dale Fellowship. The focus of Duncan’s current research is understanding how pathogenic fungi manage zinc homeostasis during infection.

Dr
Duncan Wilson
PhD

Tel: + 44 (0) 1224 437162
Email: duncan.wilson@abdn.ac.uk
Lay abstract of research
Our immune systems effectively prevent the vast majority of microbes from causing disease. One of the fundamental mechanisms underpinning this defence is called "nutritional immunity". This is a system in which the human body withholds access to certain essential trace minerals that microbes require for growth. Pathogenic microbes therefore must have evolved strategies to circumvent nutritional immunity in order to grow within their host and cause disease.

Zinc is absolutely essential for the growth of all microbes and my group is trying to understand how the major human fungal pathogen, Candida albicans, adapts to zinc restriction during infection. This is important because fungal pathogens are a huge threat to human health, and are responsible for more deaths per year than malaria, and understanding how pathogens feed during infection may pave the way to novel therapeutics.

Scientific abstract of research
Mammalian immunity restricts microbial access to key trace elements, including zinc, in a process called nutritional immunity. Because pathogens are able to thrive in the human body, they must have developed mechanisms to adapt to extreme micronutrient depletion. My group focuses on understanding how human fungal pathogens adapt to zinc restriction within the context of nutritional immunity, primarily using Candida albicans as a model pathogen. Our research seeks to answer three related questions: How do human fungal pathogens acquire zinc from their [host] environment? How do they regulate and manage zinc within their cells? And, what physiological adaptations do these fungi undergo in response to nutritional immunity? By answering these questions, we hope to develop better therapeutic strategies to combat fungal infections.

www.abdn.ac.uk/sms/people/profiles/duncan.wilson
The Director, Professor Gordon Brown has responsibility for the strategic direction and development of the MRC CMM, in consultation with the International Scientific Advisory Board, Management Board and other centre principal investigators. The Director is supported by three Deputy Directors (Professor Neil Gow [research], Professor Alistair Brown [training and technology development] and Professor Adilia Warris [clinical]), plus a Centre Manager (Dr Karen McArdle).
Management Board (MB)
The MB meets three times per annum to advise on scientific direction, strategy and training and monitor progress. The MB oversees the research and training programmes, allocation of funding, allocation of students and fellows to cross-disciplinary projects as well as the commercialisation, translation and outreach activities.

International Scientific Advisory Board (ISAB)
The ISAB is comprised of national and international experts in medical mycology, including an MRC representative. The ISAB provides the MB with objective, independent advice on our development, scientific strategy and research, training and translational activities. The ISAB receives minutes of all MB meetings, evaluates annual reports and undertakes formal Centre reviews (Years 2 and 4).

ISAB members

Professor Geraldine Butler (Chair)
University College Dublin

Professor Judy Berman
Tel Aviv University

Professor Axel Brakhage
Hans Knoell Institute

Professor Arturo Casadevall
Johns Hopkins

Professor Tom Harrison (MRC representative)
St George's University London

Professor Joseph Heitman
Duke University

Professor David Laloo
Liverpool School of Tropical Medicine

Dr John Rex (ad-hoc)
F2G Ltd and CARB-X
Scope of MRC
CMM Interactions

UK universities and institutes
Aberdeen, Birmingham, Bristol, Bath, Cardiff, Dundee, Exeter, Glasgow, Kent, Liverpool, Manchester, Newcastle, Oxford and Sheffield, Imperial College London, King's College London, St George's University of London, University College London and the Crick Institute.
Supporting the Centre

Dr Karen McArdle
MRC CMM Manager
Tel: +44 (0) 1224 437598
Email: e.karen.mcardle@abdn.ac.uk

Dr Barbara Gorgoni
Public Engagement & Training Officer
(Biomedical Sciences, Public Engagement)
Tel: +44 (0) 1224 272480, (0) 1224 437075,
Email: barbara.gorgoni@abdn.ac.uk

Ian Clarke
Digital Communications Officer for Life Sciences and Medicine
Tel: +44 (0) 1224 437073
Email: ian.clarke@abdn.ac.uk

Mrs Helen Strachan
Grants Administrator, Research Financial Services,
Tel: +44 (0) 1224 272120
Email: h.strachan@abdn.ac.uk