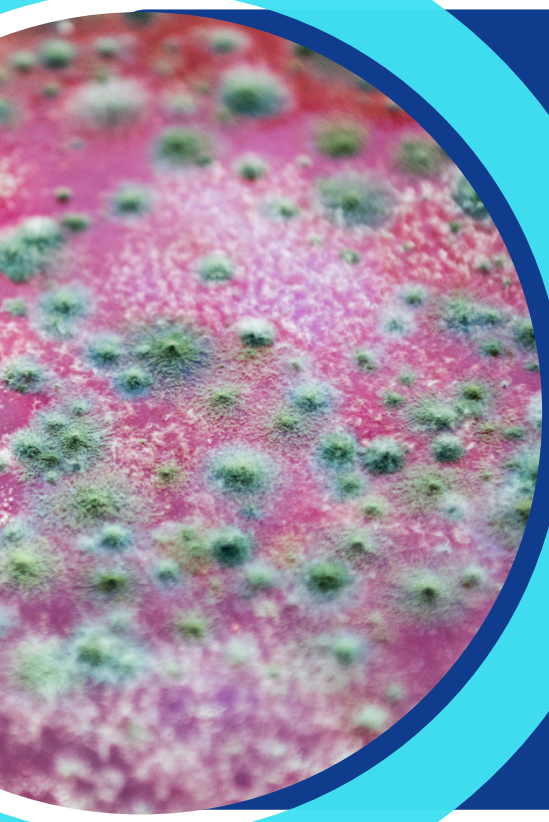

EMERGING FUNGAL INFECTIONS SYMPOSIUM

Understanding and Confronting Fungal Infections - An Underappreciated Public Health Threat

7 - 8 OCTOBER 2024

PROGRAMME BOOKLET

- Epidemiology and diagnosis of fungal pathogens
- Antifungal resistance and the development of new antifungal strategies/therapeutics
- Host-pathogen interaction
- Biology and virulence of fungal pathogens
- Mycobiome and human health

Jointly organised by A*STAR Infectious Diseases Labs (A*STAR IDL) and Institut Pasteur, the Emerging Fungal Infections Symposium marks the start of the International Network Programme for Infectious Diseases Partnerships and Preparedness (IGNITE) - a platform to promote connectivity and collaborations among regional and global experts to tackle global infectious diseases challenges. This symposium brings together experts from around the world, focusing on various crucial aspects of fungal diseases. It aims to foster collaborative efforts, advance our understanding of these infections, explore cutting-edge treatment strategies, and ultimately work towards effective solutions.

Organisers:

Infectious Diseases Labs
ID LABS

INSTITUT PASTEUR

In partnership with:

TEMASEK FOUNDATION

Co-Organisers:

A*STAR Skin Research Labs
A*SRL

National Centre for Infectious Diseases

SINGAPORE EYE RESEARCH INSTITUTE

KEYNOTE SPEAKERS

Professor Neil Gow

**University of Exeter,
United Kingdom**

Structure of fungal cell wall immune epitopes: the origins of immunity

We have used a variety of microscopic, forward and reverse genetic and immunological tools to generate a new spatially accurate model of the cell wall and to explore how dynamic changes in the wall influence drug efficacy and immune surveillance. Our molecular and cellular studies show that the cell has a mechanism to maintain wall robustness within physiological limits and has enabled the components of the wall to be defined with spatial precision. We have also demonstrated that immune relevant epitopes can be diffuse or clustered, superficial or buried in the cell wall and they changed during batch culture and between yeast, hypha and other cellular morphologies. Unbiased screening of a haploid mutant library has revealed gene sets for both predicted (e.g. cell wall glycosylation) and novel processes that are important for the assembly of the cell wall immune epitope. My presentation will focus on work that demonstrates recent advances that have generated a scaler and dynamic model of the cell wall that illuminates mechanisms of immune recognition and cell wall homeostasis

Professor Gow group studies the structure and function of the fungal cell wall in relation to growth, morphogenesis and as a target for immune recognition and the development of antifungal drugs. He is a founding member of MRC Centre for Medical Mycology which relocated to the University of Exeter, UK in 2019, which is the largest centre in this field in the UK. He has served as President of five international societies and is the current President of the European Confederation of Medical Mycology. He has been elected as a FRS, FRSE, FMedSci and FAAM.

KEYNOTE SPEAKERS

Professor Julian Naglik

**King's College London,
London, England**

Role of candidalysin in Candida pathogenicity

Candida albicans is a major fungal pathogen that causes superficial mucosal infections as well as life-threatening systemic infections. A key pathogenic feature of C. albicans is its ability to morphologically transition from spherical yeast to an invasive hypha, which is accompanied by the secretion of candidalysin. Candidalysin is a cytolytic peptide toxin that damages host surfaces and activates epithelial immunity via epidermal growth factor receptor (EGFR), mitogen-activated protein kinase (MAPK) signalling, which in turn drives innate immune protection. We have now identified orthologs of candidalysin in C. dubliniensis and C. tropicalis, identifying the candidalysins as a family of cytolysins. Recent investigations have revealed that candidalysin is critical for both mucosal and systemic infections, in addition to driving allergy and inflammatory bowel disease. An overview of candidalysin biology, structure and immunology will be provided.

Dr Julian Naglik obtained his Ph.D. in 2001, Lectureship in 2006 and became Professor in Fungal Pathogenesis & Immunology at King's in 2016. His research relates to the molecular analysis of host/Candida interactions at mucosal surfaces. His laboratory recently identified candidalysin, the first cytolytic peptide toxin identified in any human fungal pathogen. He has co-authored over 100 publications and his research has been supported by the Wellcome Trust, MRC, BBSRC, EU and NIH. He is an Honorary Member of the British Society of Medical Mycology and an Elected Fellow of the American Academy of Microbiology.

INVITED SPEAKERS

Professor Yue Wang

A*STAR Infectious Diseases Labs (A*STAR IDL), Agency for Science, technology and Research, Singapore

Genome-wide search for drug resistance mechanisms in Candida

The worldwide emergence of drug-resistant fungal pathogens poses a serious threat to public health. Particularly, multi-drug resistant Candida species or strains severely limit our treatment options, leading to high mortality rates. While several general drug-resistance mechanisms have been elucidated, such as the mutation of drug targets, increased expression of efflux pump, and enhanced stress response, whole-genome sequencing of many clinical isolates fail to find mutations affecting these mechanisms, indicating the presence of unknown mechanisms. To discover new drug-resistance mechanisms, we developed a piggyBac transposon-mediated mutagenesis system to conduct a genome-wide search for mutations that cause antifungal resistance in several *Candida* species, including C. albicans, C. auris, and C. glabrata. Applying this system has enabled us to discover new resistance mechanisms, including:

(1) The deletion of FEN1 and FEN12 genes causes significant fluconazole resistance by upregulating cellular levels of sphingolipids in C. albicans.

(2) The long non-coding RNA (lncRNA), DINOR, is a global stress regulator and influences antifungal resistance in C. auris.

(3) The transcription factor Rpn4 activates its own transcription and induces efflux pump expression to confer fluconazole resistance in C. auris

(4) The loss of the F1F0 ATPase complex causes fluconazole resistance in C. glabrata by upregulating efflux pumps.

Professor Yue Wang obtained his Ph.D. from the Department of Genetics, Cell and Developmental Biology, the University of Minnesota, in 1988. He joined the Institute of Molecular and Cell Biology in Singapore as a Postdoctoral Research Fellow in 1989 and was promoted to Principal Investigator in 1993 and Research Director in 2009. In 2022, he joined A*STAR Infectious Diseases Labs as a Senior Principal Investigator. He is an adjunct professor in the Department of Biochemistry at the National University of Singapore and a fellow of the American Academy of Microbiology.

INVITED SPEAKERS

Professor Christophe D Enfert

**Fungal Biology and Pathogenicity Unit,
Institut Pasteur, France, Paris**

Functional genomics by overexpression in the fungal pathogen Candida albicans

Candida albicans is a diploid yeast species responsible for life-threatening infections in hospitalized patients and the most frequent fungal commensal of the human gastro-intestinal and genital tracts. To elucidate gene function and advance our understanding of C. albicans pathogenesis, gene deletions have been widely used. However, this approach has some limitations due to the diploid nature of C. albicans. An alternative strategy is to create overexpression strain collections and screen for gain of functions or suppression of mutant phenotypes. To this aim, we have established resources for systematic gene overexpression in C. albicans. I will illustrate how these resources and innovative screening strategies have been leveraged to identify new players in biofilm formation and the control of genome plasticity that are intimately linked to C. albicans resistance to antifungals.

INVITED SPEAKERS

Professor Ana Traven

Biomedicine Discovery Institute and the Centre to Impact AMR, Monash University, Melbourne, Australia

Metabolic drivers of host-pathogen interactions in fungal infections

Serious infections present a large metabolic challenge for the organism as pathogens disrupt normal metabolic homeostasis and compete for nutrients with host cells. Moreover, energy is required for mounting a robust immune response, and all the while vital organs need to keep functioning to that infection can be survived. This means that metabolic regulation of host-pathogen interactions presents opportunities for therapeutic interventions that could limit pathogen growth, promote productive immune response and reduce inflammatory damage to host tissues. In this talk, I will discuss how fungal pathogens, specifically Candida albicans and Candida auris, use metabolic strategies to grow in host niches, mount infections and evade the innate immune system. I will focus on the interface between immune cell metabolic health, antifungal inflammatory programs and their associated cell death pathways, and the metabolic strategies that could be used to improve the outcomes of life-threatening fungal infections.

Ana Traven is a Professor in the Biomedicine Discovery Institute at Monash University in Melbourne and co-Director of an international training program in antimicrobial drug resistance within the Monash-Warwick University Alliance. Her research focuses on how metabolic homeostasis is disrupted by fungal infections and therapeutic opportunities in restoring metabolic health. Her contributions to mycology have been recognised by Fellowship of the American Academy of Microbiology and Australian Society for Microbiology, the Georgina Sweet Award for Women in Quantitative Biomedical Science, and two recent prestigious research fellowships, the Australian Research Council Future Fellowship and the Investigator Grant from the NHMRC.

INVITED SPEAKERS

Dr Clement Tsui

**Infectious Disease Research Laboratory,
National Center for Infectious Disease, Singapore;
Faculty of Medicine,
University of British Columbia, Canada**

Genomic epidemiology reveals Candida pathogens outbreaks during COVID-19 pandemics

Invasive candidiasis poses a significant health concern, causing substantial morbidity among immunocompromised patients. There was increased incidence of Candida infections among patients with COVID-19 worldwide. This problem is complicated by the surge in antifungal resistance among many clinically relevant Candida spp., such as C. auris, C. tropicalis, and C. parapsilosis. We have integrated whole genome sequencing (WGS) approach, population genomics analysis with conventional microbiological techniques to investigate the epidemiology, and antifungal resistance mechanisms in these pathogens in the Middle East regions. WGS data confirmed the clonal outbreak and ongoing dissemination of C. auris among various healthcare facilities in Qatar, particularly among COVID-19 patients. Similarly, WGS data revealed high genetic diversity in C. glabrata within the Qatari populations and identified signatures of recombination, inbreeding and clonal expansion within and between hospitals, including evidence for nosocomial transmission among COVID19 patients. Genome wide association studies also identified both known and novel genomic variants associated with reduced susceptibilities to fluconazole, 5-flucytosine, and amphotericin B in several isolates. In addition, we detected a clonal spread of fluconazole-resistant C. parapsilosis in Qatar, despite its variability. Understanding the genetic diversity, and epidemiology of Candida infections and antifungal resistance mechanisms is important to inform therapy and infection control strategy.

INVITED SPEAKERS

Professor Daniel Kornitzer

Faculty of Medicine, Technion – I.I.T, Haifa, Israel

Novel fluorescent probes illuminate the pathway of host heme capture and transport

The interactions between the animal host and the microbial pathogen include a struggle for resources: the pathogens must extract nutrients from the host, and the host tries to deny them. Iron is an essential resource that is among the best studied in the context of this host-pathogen struggle. Fungal pathobionts of the Candida clade are able to acquire and utilize host heme as both an iron source and directly as a heme source. The intricate pathway that the fungi have evolved for heme utilization circumvents and even takes advantage of the host mechanism for iron withholding and scavenging. It relies on a dedicated family of fungal-specific extracellular hemophores that can capture heme from host proteins and convey it to the cell membrane, where it is endocytosed via specialized ferric reductase-like proteins. To study this pathway, we are applying forward genetic methods that are newly available in C. albicans. Furthermore, we have recently developed fluorescent derivatives of cytoplasmic heme binding proteins and of the secreted hemophores. Thanks to the light-absorbing property of heme, these reagents uniquely enable to follow in real time the transport of a host nutrient across the cell envelope into the fungal cytoplasm, as well as to analyze the kinetics of heme transfer between host and fungal proteins. Better understanding of a pathogen's mechanisms to cope with nutrient limitation by the host may lead to the development of new therapeutic modalities based on disruption or utilization of these mechanisms.

Daniel Kornitzer obtained his PhD in bacterial genetics at the Hebrew University of Jerusalem, Israel, and specialized in S. cerevisiae genetics during a post-doc with Gerry Fink at MIT, Cambridge, MA. Research in his laboratory has focused on mechanisms of posttranslational regulation, both in yeast and in the fungal pathogen Candida albicans. Currently, the main research topic is the mechanism of acquisition and utilization of host heme as iron source by fungal pathogens.

INVITED SPEAKERS

Dr Darren Ting

Academic Unit of Ophthalmology, University of Birmingham, UK
Birmingham and Midland Eye Centre, Birmingham, UK
Singapore Eye Research Institute, Singapore

Fungal keratitis: current clinical management and unmet needs

Fungal keratitis (FK) is a serious ocular infection that often poses significant diagnostic and therapeutic dilemma. The global incidence of FK has been estimated to be more than a million cases per year, particularly in Asia and African populations, placing significant burden on global health. FK is often associated with poor visual prognosis, primarily caused by variably low and slow microbiological culture yield, the propensity to deeper infection affecting the posterior cornea, limited antifungal treatment options, and resistance to treatment. Additional surgical interventions are frequently necessitated to eradicate the infection and salvage the eyes. This talk aims to provide a succinct overview of the current clinical diagnostic and therapeutic approach for FK and to highlight the clinical and research unmet needs.

Dr Ting is a UK accredited, dual trained, clinical academic Consultant Ophthalmologist with a subspecialty interest in Cornea and Ocular Surface. He completed his 7-year ophthalmology specialist training in 2018 (with double gold medals) and his MRC / Fight for Sight-funded PhD in 2021. To date, he has secured ~$1.4 million grant/fellowship as Principal Investigator, >25 academic awards, and ~140 peer-reviewed publications. His research interests span basic / translational research, clinical research, and systematic reviews, with a primary focus on cornea and ocular surface-related infectious diseases, antimicrobial drug discovery and development, artificial intelligence, and digital health innovations.

INVITED SPEAKERS

Professor Guanghua Huang

Fudan University,
Shanghai, China

Genetic mutations underpin host-induced morphological transitions in *Candida auris*

Candida auris has emerged globally and become a serious threat to public health. The mechanisms of how C. auris adapts to the mammalian host are poorly understood. Morphological plasticity, which is often regulated by environmental cues through non-genetic or epigenetic factors, is a common survival strategy used by bacterial and fungal pathogens to invade and survive in the host. We found that C. auris is able to undergo rapid genetic mutation and form a multicellular aggregative morphology in the murine host during systemic infection. C. auris aggregative cells accumulate in the brain and exhibit obvious advantages over the single-celled yeast-form cells during systemic infection. Whole genome sequencing showed that genetic mutations, specifically de novo point mutations in genes associated with cell division or budding processes, underlie the rapid evolution of this aggregative phenotype. Gene-category enrichment analysis revealed that most mutated C. auris genes are associated with the regulation of cell wall integrity, cytokinesis, cytoskeletal properties, and cellular polarization. Genetic perturbations of these processes led to cell division, budding, or separation defects and thus the formation of multicellular aggregates in C. auris. Overall, to survive in the host, C. auris can rapidly evolve a multicellular aggregative morphology through genetic mutations.

Professor Huang earned his PhD at the Chinese Academy of Science and then had a postdoc with Dr. David R. Soll at the University of Iowa. In 2010, he joined the Institute of Microbiology, CAS. In 2019, he moved to Fudan University in Shanghai, China. His laboratory focuses on studying the molecular mechanisms of morphogenesis, pathogenesis, and sexual reproduction in Candida species. In the past several years, the Huang laboratory published over 40 scientific papers on environment-regulated morphological changes and sexual reproduction in Candida albicans and other non-albicans species. These studies shed lights on the development of pathogenesis and antifungal resistance in pathogenic fungi.

INVITED SPEAKERS

Dr Jessica Quintin

Immunology of Fungal Infections
Mycology Department,
Institut Pasteur, France, Paris

Harnessing innate immune memory against fungal infections

Advances in the field of immunological memory show that innate immune cells can recall previous microbial encounters and exhibit modified responses, a phenomenon called innate memory. Our previous work demonstrated that β-glucan from yeast (Candida albicans) induces this memory in human monocytes, enhancing immunity against unrelated pathogens. In vitro, β-glucan imprints monocytes transcriptionally, epigenetically, and metabolically within hours.

While circulating monocytes act as intermediates, they differentiate into macrophages in peripheral tissues. In contrast to current models, our observations demonstrate that β-glucan does not always enhance macrophage function and may even suppress it, depending on the environment.

We focused on IL-1β, a cytokine linked to inflammasome activation and autoinflammatory disorders, finding that β-glucan represses IL-1β-driven inflammation by modulating early activation upstream of the NLRP3 inflammasome. This suggests potential clinical applications for NLRP3-related diseases.

Lastly, our in vivo studies emphasize the significance of β-glucan structure in providing innate-mediated protection against fungal infections.
Altogether, we uncovered significant new features essential for fully understanding the biological impacts of β-glucan-induced innate memory and harnessing it for clinical use.

INVITED SPEAKERS

Dr Lakshminarayanan Rajamani

Singapore Eye Research Institute
Singapore

Cell selective antifungal polymers for the management of fungal keratitis

Fungal keratitis (FK) remains a silent epidemic and the major cause of blindness and vision loss in tropical and subtropical countries. The prognosis of fungal keratitis is poor as there is only one US FDA approved drug which is sparsely available as well as due to delayed diagnosis. Therefore, there is an urgent unmet need for the management of FK. In this study, we compared the antifungal activity of epsilon polylysine (ePL) and natamycin in vitro and in vivo. Unlike natamycin, the polymer elicited rapid fungicidal activity by targeting the cytoplasmic membrane of the fungi yet remained non-toxic to ocular surface cells. Next, we established that a high concentration of polymer (1.0% and 2.0% w/v) did not alter the wound healing rate of injured rabbit cornea. In a rabbit model of Fusarium keratitis, topical instillation of 2% ePL (q.i.d for 1 week) or intrastromal injection of single dose 1% ePL decreased the fungal bioburden and prevented the adverse effects of the pathogenic fungi. Slit lamp examination, anterior segment–optical coherence tomography, and histological analysis indicated better recovery of the infected cornea when compared to the untreated cornea. Collectively these data suggest that ePL can be developed into a broad-spectrum antimicrobial polymer for vision threatening fungal infections.

Associate Professor Lakshminarayanan Rajamani is the Co-Head of the Ocular Anti-Infectives & Inflammation Research Group at the Singapore Eye Research Institute (SERI). He holds joint appointments at the Department of Pharmacy and Pharmaceutical Sciences at the National University of Singapore (NUS) as well as at the Academic Clinical Program in Ophthalmology & Visual Science program at the Duke – NUS. He received his PhD degree from the Department of Chemistry at the National University of Singapore in 2003. He received numerous awards such the prestigious Singapore Millennium Foundation - Post Doctoral Fellowship, ASEM-DUO Denmark Fellowship, Outstanding Postdoctoral Fellow and Outstanding Scientist Award. At SERI, he has been involved in translational research for treating bacterial and fungal infections of the eye. His major research interests include antimicrobial nanofibres, peptides & polymers, biophysics, nature-inspired polyphenol nanocoating, electrospinning of biopolymers for advanced wound dressings and personal protective equipment, mechanism of protein aggregation and functional amyloids. He has >150 publications that have an h-index of 57 and >9300 citations.

INVITED SPEAKERS

Professor Linqi Wang

**Institute of Microbiology,
Chinese Academy of Sciences,
Beijing, China**

Host-induced fungicide tolerance and persistence

Human pathogenic fungi pose a serious threat to human health and safety. Unfortunately, the limited number of antifungal options is exacerbated by the continuous emergence of drug-resistant variants. Recent studies have also highlighted the importance of other modes of fungal survival of antifungal treatment, including drug tolerance and persistence, pointing to the complexity of the fungal response to antifungal drugs. However, whether antifungal tolerance or persistence can be induced by host-derived factors during fungal diseases remains largely unknown. Through a systematic evaluation of metabolite-drug-fungal interactions in the leading fungal meningitis pathogen, Cryptococcus neoformans, we found that brain glucose induces fungal tolerance to amphotericin B (AmB) in mouse brain tissue and patient cerebrospinal fluid via the fungal glucose repression activator Mig1. Mig1-mediated tolerance limits treatment efficacy for cryptococcal meningitis in mice via inhibiting the synthesis of ergosterol, the target of AmB, and promoting the production of inositolphosphorylceramide, which competes with AmB for ergosterol. We also demonstrated that highly AmB-tolerant fungal persister cells can form during cryptococcal lung infections and identified the FDA drug with potent activity against fungal persister cells through a drug repurposing approach. Our group is now investigating the genetic basis that differentiates antifungal resistance, tolerance and persister.

INVITED SPEAKERS

Dr Louis Chia

**Division of Infectious Diseases,
National University Hospital,
Singapore**

Correlating bench versus bedside in determining novel susceptibility to invasive fungal infection

The past 2 decades have seen unprecedented bench advances in discovering and dissecting host recognition systems against pathogenic fungi extending from surface immune receptors, downstream canonical and non-canonical signalling pathways, immune cell characteristics as well as plasma moieties. While it is undoubted that all play roles in shaping the host response, it is acknowledged also that our immunity operates in a system of redundancy. To attempt to sieve out and highlight the most critical components among the myriad of signal moieties already described against fungal pathogens, we look to the patient with the extremes of presentation through whom mechanistic dissection in correlation with knowledge from the bench may pinpoint and validate specific susceptibilities most important to the human host.

Dr. Louis Chai is Senior Consultant Infectious Diseases Physician and Associate Professor in the University Medicine Cluster, National University Health System, Singapore, as well as Principal Investigator, Opportunistic Infections Group, Division of Infectious Diseases, NUHS. Dr Chai's interests lie in opportunistic and atypical infections in immunocompromised hosts, patients with altered immunity and host-pathogen interaction. These are also the themes of his research group. He remains deeply entrenched at the bedside in providing clinical service for general infectious diseases. Dr Chai is funded by the National Medical Research Council of Singapore and the National University Health System, Singapore.

INVITED SPEAKERS

Dr Naweed Naqvi

Temasek Life Sciences Laboratory, Singapore

Lipid signaling in fungal pathogenesis

The rice-blast fungus, Magnaporthe oryzae, offers an excellent model system to understand the cessation of vegetative growth prior to infection-related morphogenesis. Through mutant analyses, metabolomics and functional assays, we identified a key role for oxylipin signaling in such developmental transition and pathogenesis. Furthermore, lipid peroxides were essential for initiating Ferroptosis (a non-apoptotic cell death modality that requires iron) specifically in the spore while keeping the interconnected infection structure intact and viable. Such precise cell killing via lethal accumulation of lipid hydroperoxides leading to rupture of the plasma membrane. Autophagy and ferroptosis were functionally interdependent in regulating iron homeostasis and clearance of cell debris. Furthermore, selective autophagy-enabled degradation of mitochondria in the spores was an essential trigger for cell death and pathogenesis. Mitophagy regulated the accumulation of lipid peroxides and also helped maintain metabolically active mitochondria. Disruption of the electron transport chain or membrane potential led to mitochondrial fusion and inhibited ferroptosis, thus simulating the loss of mitophagy defects. Graded inhibition of Coenzyme Q biosynthesis in the presence or absence of Ferroptosis helped uncouple the antioxidant function from its roles in electron transport chain and mitochondrial membrane potential. Chemical genetic screens enabled the identification of a novel pentamethoxy flavone, Tangeretin, as a potent targeted fungicide that inhibits Ferroptosis and the ability of the pathogen to cause Blast disease.

INVITED SPEAKERS

Dr Thomas Dawson

A*STAR Skin Research Labs (A*SRL)
Agency for Science, technology and Research, Singapore

The importance of fungal inhabitants on the skin – both good and bad

The skin is our largest organ, providing protection and environmental interaction. Malassezia yeasts are the most frequently detected and abundant eukaryotic habitants of human skin, particularly on lipid-rich regions with high sebaceous activity. In a classic example of “hear no evil, see no evil, speak no evil”, most skin microbiome investigations focused on bacteria via 16S sequencing, with few studies inclusive of non-bacterial species. Even when employing metagenomics, the dearth of fungal genomes in common databases makes fungal community analyses challenging. Malassezia are obvious commensals, on all humans, and pathogens, causing multiple skin diseases, and mutualists in atopic dermatitis and prevention of C auris colonization. Recently, Malassezia have been shown to play roles outside a dermatological context, exacerbating inflammatory bowel disease via CARD9, accelerating pancreatic oncogenesis by migrating from gut to pancreas and activating the C3 complement cascade, and enhancing progression of breast cancer via the IL-17A/macrophage axis and induction of Sphk1 overexpression. Malassezia employ complex lipid metabolism in host/microbe communication, via evolutionarily conserved multi-kingdom mediators based on oxygenated polyunsaturated fatty acids (PUFA). In fungi and plants these communication mediators are referred to as “oxylipins”, while in human and animal biology as “eicosanoids”, which has led to research silos, poor communication, and a lack of collaborative research. Recent developments in Malassezia research are now yielding insight into human health across disciplines, and future work may lead to novel intervention points and impactful treatments.

Thomas L. Dawson, Jr., Ph.D. is director of the Singapore Asian Skin Microbiome Program, Deputy Executive Director of the A*STAR Skin Research Labs, and chair of the International Union of Microbiological Sciences section on Mycology and Eukaryotic Microbiology (IUMS-MEM). Prof Dawson earned his Ph.D. from the Univ. of North Carolina at Chapel Hill and did his post-doctoral fellowship in Pediatric Medical Genetics at the Duke University Medical Center. The A*STAR “Asian Skin Microbiome Program” seeks to define the healthy skin microbiome during human aging and menopause. Dr Dawson’s research is committed to improving skin health and retains his emphasis on Malassezia, including leading the global consortium on Malassezia research, the “Malassezia Research Consortium”. Prof Dawson is a strong advocate of training and mentorship for young scientists, gender equality, and STEM educational outreach. Tom is Past President of the Singapore Society for Skin Research, and Chair of the A*STAR SRIS Human Biomedical Ethics committee, Affiliated Professor at the Medical University of South Carolina, USA, and the CEO of an independent consulting company, Beauty Care Strategics.

INVITED SPEAKERS

Dr Winnie Lee

Singapore General Hospital, Singapore

Antifungal stewardship – the overlooked child in the family?

The use of antifungal agents has risen tremendously in the past decade along with increased complexity of healthcare interventions especially within the haematological-oncological space. Unfortunately, overprescribing of antifungal agents puts patients at greater risk for drug toxicities and drug interactions, and has the potential to select for resistant fungi. At the bedside, clinicians navigate this intricate balance daily between clinical benefit versus the potential risk of drug-related problems as well as selection pressure for resistant fungi.

The concept of stewardship was first coined in 1996 to address rising antimicrobial resistance. Since then, antibiotic stewardship is well-established as a tenet of best practice in accredited hospitals. Whilst antifungal stewardship is slowly gaining traction, most hospitals surveyed have yet to accord it the same level of attention as antimicrobial stewardship. This presentation aims to discuss the current state of practice for antifungal stewardship and identify barriers as well as opportunities for improvement.

Ms Winnie Lee is a Specialist Pharmacist in Infectious Diseases (ID) and an Assistant Director (Implementation Science) in the Division of Pharmacy, Singapore General Hospital. Over the years, she has had numerous ID research contributions and received awards e.g. SGH Young Investigator Award for Allied Health Division & Pharmaceutical Society of Singapore's Hospital Pharmacist of the Year. Winnie precepts resident pharmacists, nurses, and students under the National Residency Programs and affiliated universities. She is also incumbent Chairperson for the Pharmacy Specialists Accreditation Board (Ministry of Health, Singapore) responsible for defining and certifying speciality practice in Singapore.

INVITED SPEAKERS

Dr Yen Ee Tan

**Department of Microbiology,
Singapore General Hospital,
Singapore**

Medically important fungal pathogens in Singapore

Invasive fungal diseases (IFDs) are on the rise especially in the immunocompromised patient groups. However, the diagnostics and treatment for fungal infections remain challenging in many settings. This is worsened by the emergence of antifungal resistance. In 2022, WHO issued the first fungal priority pathogens list (FPPL) to address the importance of fungal research and development of new antifungal drugs and diagnostics. In this talk, Dr Tan will highlight some of the medically important fungi in local setting to bring an increased awareness of this underappreciated but important group of infectious diseases.

INVITED SPEAKERS

Professor Yong-Sun Bahn

Yonsei University
Seoul, Korea

Systematic functional analysis of essential transcription factors unveils a novel pathogenicity and developmental regulator in *Cryptococcus neoformans*

Cryptococcus neoformans causes fatal meningoencephalitis in humans. The limited range of current anti-cryptococcal treatments underscores the urgency to develop new therapeutics. In this regard, essential proteins necessary for growth are prospective drug targets. Our previous systematic functional survey of cryptococcal transcription factors indicated 17 genes as potential essential TFs, as evidenced by the inability to delete them. This study further seeks to pinpoint and assess the essential transcription factors (TFs) of C. neoformans. We engineered conditional expression strains for these putative essential TFs by replacing their native promoters with the copper-regulated CTR4 promoter. Under copper-replete repressive conditions, 14 conditional expression strains exhibited growth suppression. To confirm their indispensability, we constructed heterozygous mutants from a diploid strain and performed random spore analysis. Genotyping of the progeny from the selfing of these heterozygous mutants identified 15 essential TFs. Notably, Ezt1, which is evolutionarily distinct from other eukaryotic TFs, was significantly implicated in various functions: growth, antifungal drug susceptibility, stress responses, virulence factor production, sexual development, and overall virulence. Transcriptome and chromatin-immunoprecipitation sequencing analysis linked Ezt1 to key biological pathways, including metabolism, biosynthesis of secondary metabolites, and carbon utilization. Our research unveils many essential TFs in C. neoformans, offering valuable anti-cryptococcal targets.

Dr. Bahn is an Underwood Distinguished Professor in Biotechnology at Yonsei University and a Fellow of the American Academy of Microbiology (AAM). He earned his PhD from Ohio State University. Dr. Bahn has made significant contributions to the functional characterization of complex signaling pathways that govern growth, differentiation, stress responses, and virulence in human fungal pathogens, including Candida albicans, Candida auris, and Cryptococcus neoformans. His research utilizes molecular and genetic approaches to enhance our understanding of fungal pathogenesis mechanisms. Dr. Bahn's scientific contributions have been recognized with numerous academic achievement awards.

INVITED SPEAKERS

Assistant Professor Yuan Qiao

Nanyang Technological University, Singapore

Applying chemical biology tools to elucidate peptidoglycan fragments (PGNs)-induced *C. albicans* invasive growth.

Candida albicans is the major opportunistic fungal pathogen in humans. Normally residing in the host gut niche as a benign yeast state, C. albicans can transform into long filamentous hyphae that facilitate its mucosal penetration and bloodstream dissemination, causing deadly infections in the host. Among the numerous signals that trigger C. albicans hyphal growth, bacterial peptidoglycan fragments (PGNs) represent the most potent inducers. Thus, addressing the mechanistic details of PGN-induced C. albicans invasive growth may lead to novel insights to combat this deadly fungus.

In this talk, I will present our recent series of studies on gut microbiota-derived PGNs in triggering C. albicans hyphal growth. We developed versatile chemoenzymatic PGN probes with photoaffinity, bio-orthogonal, or fluorescent functionality to enable studies of PGN recognition in C. albicans. Recently, we uncovered that the surface sensing and cellular uptake of PGNs represent two distinct cellular processes in C. albicans, addressing long-sought-after questions in the PGN-induced C. albicans hyphal growth. These insights provide new opportunities to thwart C. albicans hyphal growth.

Yuan is currently a Nanyang Assistant Professor at School of Chemistry, Chemical Engineering, and Biotechnology (CCEB), NTU. Her research focuses on understating the structures and functions of gut microbiota-derived peptidoglycan fragments (PGNs) in hosts.

Yuan completed her Bachelor's degree in chemistry at Bryn Mawr College, and PhD in Chemical Biology at Harvard. She was a research fellow in Prof. Yue Wang's lab in IMCB, Singapore, where she got interested in understanding bacterial peptidoglycan in bacterial-fungal interaction. Yuan was a recipient of the A*STAR National Science Scholarship in Singapore, and a National Research Foundation Fellow (NRFF) Class of 2020.

SHORT TALK SPEAKERS

Dr Alicia Corbellini Piffer

Immunology of Fungal Infections,
Institut Pasteur, Paris, France

Deciphering key regulators of extracellular vesicle production in *Cryptococcus neoformans*

Cryptococcus neoformans is a human pathogen classified by WHO as belonging to the critical group of the fungal priority pathogen list. As observed in all fungi species studied to date, C. neoformans secretes extracellular vesicles (EVs), lipid bilayer compartments that carry and transport various types of molecules, including lipids, polysaccharides, pigments, proteins and RNAs to the extracellular environment. Although their functions are still not fully understood, several studies suggest that they are associated with fungal pathogenicity. Despite their importance, the pathways involved in their biogenesis are poorly understood. To address this, we took advantage of the recently described relationship between EV biosynthesis and azole susceptibility and screened a library of knockout mutants for their sensitivity to fluconazole aiming to identify genes regulating EV production. One of the first fluconazole-resistant and low EV-producer mutant identified was a strain knockout for HAD1, a putative phosphatase previously described as a potential target of calcineurin in Cryptococcus. Using pharmacological inhibitors and genetic approaches, we confirmed that the calcineurin pathway positively regulates EV production in this yeast. In support to this, we have also shown that the chelation or addition of calcium in the culture medium alter EV production. In contrast, the transcription factor Crz1, which is one of the most studied targets of the calcineurin pathway in fungi, negatively regulates EV biosynthesis, suggesting a dual role of this pathway in coordinating EV production. Today, the function of Had1 and the mechanism by which it regulates EV generation in C. neoformans are still unknown but several biochemical and genetic approaches are being considered to address these questions.

SHORT TALK SPEAKERS

Dr Rajesh Patkar

Indian Institute of Technology Bombay, India

Engaged in community to enable change: A key morphological change induced by a novel protein during inter-species interaction

The talk will revolve around a novel and perhaps a unique Candida glabrata small protein that plays a key role during interaction with another species of candida. It is interesting to see how this species has evolved to use its mating signaling pathway to express and efflux this small protein. Importantly, this protein has a cryptic functional motif that is associated with the inducer activity. Given its uniqueness, this protein or its coding gene has a potential application in early diagnosis of mixed-species candidiasis.

SHORT TALK SPEAKERS

Dr Lingyu Ji

**Fudan University,
Shanghai , China**

Biology and genetic diversity of *Candida krusei* isolates from fermented vegetables and clinical samples in China

Candida krusei is an emerging non-albicans Candida species causing both superficial and deep-seated infections in humans. This pathogen is inherently resistant to the first-line antifungal drug, fluconazole, and is widely distributed in natural environments.
In our study, we collected 86 C. krusei strains from clinical settings and fermented foods from different areas of China. Comparing strains from different sources, clinical C. krusei exhibited a higher ability to undergo filamentation and biofilm development, whereas C. krusei from fermented foods showed higher resistance to several antifungal drugs including fluconazole, voriconazole, itraconazole, amphotericin B, and caspofungin. Whole-genome sequencing was performed, which unveiled genetic association between strains from clinical settings and fermented foods. Genomic analysis also showed that one-fourth of clinical strains and the majority of isolates from fermented vegetables are triploid, renewing previous understanding that C. krusei is a diploid organism. Additionally, we found six nucleotide substitutions at the promoter region of the ABC11 gene, encoding a multidrug efflux pump, could play a critical role in antifungal resistance in this species. Given the ubiquitous distribution of C. krusei strains in fermented vegetables and their genetic association with clinical strains, a One Health approach will be necessary to control the prevalence of this pathogen

SHORT TALK SPEAKERS

Dr Seong-Ryong Yu

Department of Biotechnology,
College of Life Science and Biotechnology,
Yonsei University, Seoul, Korea

Systematic elucidation of host-derived cues for the regulation of pathogenicity-linked transcription factors in fungal pathogen *Cryptococcus neoformans*

Cryptococcus neoformans is a causative agent of global fungal meningoencephalitis, responsible for over 180,000 annual deaths. In analyzing this pathogen, we performed in vivo transcription profiling to monitor 180 transcription factors (TFs) during infection. Our focus was on 12 TFs that were notably induced in host-mimicking conditions (HMC). To determine which host factors contribute to gene induction during infection, we dissected HMC signals into components of temperature, carbon, and nitrogen starvation. Remarkably, we identified three distinct cues significantly influencing gene regulation. Temperature upshift markedly induced the expression of six genes. Similarly, glucose starvation and nitrogen starvation highly induced the expression of six and nine genes, respectively. Furthermore, deleting MLN1 resulted in growth defects under carbon starvation conditions with alternative disaccharide carbon sources (maltose, trehalose, sucrose), excluding glucose. Also, in vivo studies using a mouse model demonstrated attenuated virulence and reduced brain fungal burdens in mice inoculated with mln1Δ. In conclusion, our systematic dissection of host-signaling cues provides deeper insight into the complex signaling pathways that modulate host-pathogen interactions in C. neoformans.

SHORT TALK SPEAKERS

Dr Leovigildo Rey Alaban

Northern Iloilo State University, Philippines,
Microbiology Technology Institute
Lyon, France

Secreted metabolites profile of *Candida albicans* yeast to hyphae transition

Candidiasis, commonly caused by C. albicans, is one of the most fatal fungal infections. The C. albicans-induced infection is morphology dependent as the transition from yeast to hyphae is is considered as a virulence factor. While this morphology transition is increasingly shown to vary between isolates and clades, few information exists on the metabolites (small molecules) involved in this transition. Thus, we developed a simplified in vitro culture workflow to investigate the metabolic variations between isolates across clades. We induced hyphal transition of 24 isolates from five of the most represented clades and the unique clade (C. africana subspecies). These isolates, including the reference isolate (SC5314), were selected based on differential damage to a human cell line (TR146). We then used NMR (nuclear magnetic resonance) to quantify 38 of the secreted metabolites (exometabolites) in both morphologies. We observed that in the hyphae morphology, virulence is associated with the stronger consumption of proline and threonine. During energy replete conditions (yeast form), both metabolites enter the Krebs cycle. However, during hyphae transition when energy is depleted, both metabolites are used as carbon and nitrogen sources as the C. albicans shifts to glyoxylate cycle in an attempt to replenish the energy

SHORT TALK SPEAKERS

Dr Bing Zhai

CAS Key Laboratory of Quantitative Engineering Biology, Shenzhen Institute of Synthetic Biology, Shenzhen Institute of Advanced Technology, Chinese Academy of Sciences, Shenzhen, China

Antifungal heteroresistance causes prophylaxis failure and facilitates breakthrough *Candida parapsilosis* infections

Breakthrough fungal infections in patients on antimicrobial prophylaxis during allogeneic hematopoietic cell transplantation (allo-HCT) represent a significant and often unexplained cause of morbidity and mortality. Candida parapsilosis is a common cause of invasive candidiasis and has been classified as a high-priority fungal pathogen by the WHO. In high-risk allo-HCT recipients on micafungin prophylaxis, we show that heteroresistance – the presence of a phenotypically unstable, low frequency subpopulation of resistant cells (~1 in 10,000) – underlies breakthrough bloodstream infections by C. parapsilosis. By analyzing 219 clinical isolates from North America, Europe, and Asia, we demonstrate widespread micafungin heteroresistance in C. parapsilosis. Standard antimicrobial susceptibility tests, such as broth microdilution or gradient diffusion assays, which guide drug selection for invasive infections, fail to detect micafungin heteroresistance in C. parapsilosis. To facilitate rapid detection of micafungin heteroresistance in C. parapsilosis, we constructed a predictive machine learning framework that classifies isolates as heteroresistant or susceptible using a maximum of ten genomic features. These results connect heteroresistance to unexplained antifungal prophylaxis failure in allo-HCT recipients and demonstrate a proof-of-principle diagnostic approach with the potential to guide clinical decisions and improve patient care.

SHORT TALK SPEAKERS

Dr Dazhi Zhang

CAS Key Laboratory of Quantitative Engineering Biology, Shenzhen Institute of Synthetic Biology, Shenzhen Institute of Advanced Technology, Chinese Academy of Sciences, Shenzhen, China

Antifungal strategies against drug-resistant fungi: new targets, new mechanisms and novel compounds

Antifungal azoles are facing more and more serious drug resistance. We have focused on the strategies including: 1) new targets, novel mechanisms and structure optimization of several kinds of sensitizers which can synergize antifungal azoles to kill or inhibit drug-resistant fungi; 2)research on novel azole antifungals against drug-resistant fungi.

Based on our previous study on the lead compounds including baicalein, berberine, and curcumin, which can significantly enhance the susceptibility of fluconazole against fluconazole-resistant Candida albicans, a series of novel derivatives were designed, synthesized, and evaluated for their in vitro and in vivo synergistic activity in combination with fluconazole. Photo affinity probes and chemical genetic techniques have been employed to investigate their targets.

Based on the genetic recombinant Saccharomyces cerevisiae with overexpression of drug-resistant elements inluding MDR1, CDR1 or ERG11 mutations, novel azole antifungal agents have been designed, synthesized and evaluated for their antifungal activity against fungi, especailly drug-resistant fungi.

A series of novel sensitizers have been obtainded to promote antifungal azoles to kill drug-resistant fungi. Compound SPH8740, at a concentration of 0.5 μg/mL, can enhance the susceptibility of fluconazole against fluconazole-resistant C. albicans from >64.0 μg/mL to 0.125-0.5 μg/mL. Moreover, SPH8740 in combination with fluconazole can also exibit synergistic antifungal activity against Cryptococcus neoformans, Candida glabrata, and Candida tropicalis. Their synergistic fungicidal activity has been well investigated both in vitro and in vivo.

Eno1 in C. albicans has been identified as a potential target of baicalin based on photo affinity probes.

Based on the chemical genetic techniques, Erg251 has been identified to be the target of CZ66 which can promote antifungal azoles to kill drug-resistant fungi.
A series novel azoles have been obtained to have potent and broad-spectrum antifungal activity.

Erg251 and Eno1 have been identified to be new targets to exert their antifungal synergistic effect, which deserve further resarech for new approches to combat fungal drug resistance.

Two azole antifungal candidates are under pre-clinical research and development.

SHORT TALK SPEAKERS

Dr Sanhita Roy

**LV Prasad Eye Institute,
Hyderabad, India**

Membrane targeted antimicrobial peptides as an alternative therapeutics for corneal infections

Fungal keratitis is a leading cause of corneal infections associated with poor prognosis that leads to blindness or loss of vision and often termed as “silent epidemic”. The increase in resistance to existing antifungals often makes the treatment more complex and difficult. The commonly used antifungal, amphotericin B, has limited efficacy and is associated with neurotoxicity and nephrotoxicity. The situation demands extensive research on alternative interventions to combat infection and antimicrobial resistance. The antimicrobial peptides (AMPs) are considered as the most potent next generation therapeutics to battle antimicrobial resistance. In the current study, our work on AMPs is highlighted, we have shown that the peptide inhibits the growth and biofilm formation of Fusarium spp. and Candida spp., two major organisms responsible for corneal infections in India and globally. Microscopy and biophysical experiments including NMR spectroscopy have been performed to study the interaction of the peptides with fungal membrane or mimics and they show that the peptide binds to and perturbs the membrane. The peptide also affects expression of fungal genes and exhibit protective role and reduces fungal burden in our in vivo murine model of corneal infections. The peptides are also non-cytotoxic, non-irritant and non-haemolytic in nature. Thus, these peptides possess potential to be studied further for the development of targeted therapeutics against fungal keratitis.

SHORT TALK SPEAKERS

Dr Ying Xie

Institute for Systems Genetics, New York University Langone Medical Center,
New York, United States

Polysome collapse and RNA condensation fluidize the cytoplasm: a possible stress adaptation strategy adopted by fungi pathogen *Candida glabrata*

The cell interior is packed with macromolecules of mesoscale size, and this crowded milieu significantly influences cellular physiology. Cellular stress responses almost universally lead to inhibition of translation, resulting in polysome collapse and release of mRNA. The released mRNA molecules condense with RNA binding proteins, to form membraneless RNA-protein (RNP) condensates known as processing bodies and stress granules. Here, we show that polysome collapse and condensation of RNA transiently reduces elastic confinement in the cytoplasm; coarse grained molecular dynamic simulations support this as a minimal mechanism for the observed biophysical changes. Increased mesoscale diffusivity correlates with the efficient formation of Q-bodies, membraneless organelles that compartmentalize misfolded peptides during stress. Synthetic, light-induced RNA condensation also fluidized the cytoplasm. Together, our study reveals a functional role for stress-induced translation inhibition and formation of RNP condensates in modulating the physical properties of the cytoplasm to enable efficient response of cells to stress conditions. Currently, I am expanding the research on stress-induced condensates and physical properties study in the human fungal pathogens Candida glabrata, hypothesizing that these condensates serve as a physical mechanism to enhance the fitness of Candida glabrata pathogens, leading to immune evasion in the human host.

SHORT TALK SPEAKERS

Dr Cheryl Leong

A*STAR Skin Research Labs (A*SRL)
Agency for Science, technology and Research,
Singapore

Prolonged in vitro azole exposure drives cross-resistance in commensal malassezia

Malassezia are commensal lipid dependent yeasts and opportunistic pathogens that cause superficial mycoses and systemic infection. Azoles target cell wall ergosterol synthesis and are the first line of antifungal treatment. However, they may become ineffective if the strain has had prior azole exposure.

To determine the effect of sustained treatment with clotrimazole, ketoconazole, and fluconazole on the MIC values of other antifungals and identify physiological and molecular drivers underlying cross resistance, we maintained the cells in media containing sub-MIC concentrations of clotrimazole, ketoconazole, and fluconazole for 4 weeks. Antifungal susceptibility testing (AFST) was performed weekly as described by Leong et. al. 2017.

We observed that prolonged Malassezia furfur treatment with sub-MIC ketoconazole or clotrimazole resulted in increased MICs for other azoles and terbinafine, but not amphotericin B. Fluconazole treatment had minimal effect on susceptibility to other antifungals. RNAseq analysis of drug transporters such as PDR10 showed an increase in expression during treatment which remained high in some conditions after drug withdrawal.

Elucidating the relationship between susceptibility and exposure is valuable, as commensal Malassezia are frequently exposed to topical over-the-counter antimicrobials, and this may serve as a reservoir and drive the evolution of resistant strains.

SHORT TALK SPEAKERS

Dr Won Hee Jung

Department of Systems Biotechnology, Chung-Ang University, Anseong, Korea

Exploring the gut mycobiome in ulcerative colitis patients using culturomics analysis

The human gut is colonized by diverse microorganisms, including bacteria, viruses, protozoa, and fungi. Several studies have suggested that the gut fungal microbiome (mycobiome) impacts host immunity and the development and progression of human diseases. However, most gut microbiome studies have focused exclusively on bacteria, and the mycobiome in the organ has largely been unexplored. Here, we established a culturomics platform to isolate the fungal strains from fecal samples of a cohort of patients with ulcerative colitis (UC) and compared the fungal community structure with those of healthy subjects (HT). Our analysis revealed that the majority of identified fungal colonies belonged to the phylum Ascomycota followed by Basidiomycota in both HT and UC. Interestingly, we observed differences in the relative abundance and diversity of the gut mycobiome between UC patients and healthy individuals. Particularly, the fungal diversity was found to be decreased in UC patients compared to HT, suggesting a potential correlation with active inflammation. Furthermore, we conducted growth assays on fungal isolates under conditions mimicking the gut environment to distinguish true colonizers from transient ones that may originate from environmental sources such as food. Moreover, we collected some Candida albicans isolates, which was one of the most dominant fungal species in the fecal samples. The phenotypic characteristics of the C. albicans isolates from fecal samples were analyzed and compared with those of the same fungal species isolated from the different niches such as the gut mucosal layer and blood. The results of the comparisons between the different C. albicans isolates are presented. Finally, our study emphasizes the importance of the gut mycobiota and provides useful information on C. albicans residing in the human gut.

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