evasion from CD11b recognition (Eur J Immunol 2021, PMID 33728652), (3) Dendritic cells (DCs)-based vaccine induced lung resident memory Th17 cells and ameliorates *C. gattii* infection (Mucosal Immunol 2018, PMID 30279512), and (4) Neutrophil and opsonization can mediate fungicidal activity for cryptococcal cells (Med Mycol 2019, PMID 30668754). Based on these findings, we have inferred that induction of lung resident memory T cells (lung TRM) and TRM-driven myeloid cells including granulocytes is necessary for controlling this infection. Currently, we are developing new intranasal (IN) vaccines using highly immunogenic whole cell antigens and characterizing protective lung TRM induced by the vaccines. Just as with component vaccines, whole cell vaccines are also featured for cryptococcal infection because these are highly cross-reactive and protective against each serotype (Biol Pharm Bull 2020, PMID 32009111).

We developed two IN vaccines using whole cell antigen and adjuvant. Both vaccines induced IL-5-producing lung TRM and significantly reduced fungal burden in lungs and improved survival rates of mice following *C. gattii* infection, while not protective against *C. neoformans* infection. Although immune suppressive agent FTY720 can eliminate most circulating T cells and sustain tissue-resident subset, IN vaccines induced Th2-related immune response including eosinophils and IFN-γ independent granuloma, and reduced the fungal burden in lungs after the infection in the presence of FTY720. Vaccine-mediated protection was completely lost in the Rag-1 knockout mice deficient in T- and B-cells, while the fungal burden was reduced in the Rag-1 knockout mice after receiving the immunized CD4 + T cells in the adoptive transfer experiments. These results suggest that Th2-related lung TRM induced by IN vaccines are also protective against *C. gattii* infection as well as Th17-related counterparts induced by DC vaccine.

S7.4b
Microaerobic conditions enhance fungal pathogenesis in *Candida* spp.

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S7.4 Pathogenesis and host defense, September 23, 2022, 10:30 AM - 12:00 PM

Backgrounds. Fungal pathogen colonizing mucocutaneous membranes and indwelling medical devices is associated with invasive infections. Its pathogenetic mechanisms are poorly understood, although environmental oxygen levels have been recently suggested to alter pathogenic phenotypes in the human body. Our study aimed to compare the adhesion capabilities of *Candida* spp. depending on various oxygen levels and investigated the mechanisms contributed to pathogenic alteration.

Results and Conclusion: We observed significant differences in capabilities for cell adhesion and for biofilm formation of pathogenic yeasts in response to different oxygen levels. Under hypoxic conditions, the *C. glabrata* adhesion capability increased and the expression levels of several adhesion-related genes were up-regulated. Among these mutants, observed significantly lower adhesion capability for intestinal colonization than the wild-type in a murine model. Pathogenic yeasts showed different phenotypes in hypoxic conditions from ordinary aerobic circumstances, and those molecules which work on increased pathogenesis would be applied for novel therapeutic targets.

S7.4d
***Candida albicans* SR-like protein kinases regulate different cellular processes: Sky1 is involved in thecontrol of ion homeostasis, while Sky2 is important for dipeptide utilization**

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S7.4 Pathogenesis and host defense, September 23, 2022, 10:30 AM - 12:00 PM

Protein kinases play a crucial role in regulating cellular processes such as growth, proliferation, environmental adaptation, and stress responses. *Candida albicans* genome comprises of 108 predicted protein kinases, of which the exact role of nearly half of those kinases remains unknown. One family of protein kinases is serine-arginine (SR) protein kinases, which are highly conserved in eukaryotes and regulate fundamental processes such as constitutive and alternative splicing, mRNA processing, and ion homeostasis. The *C. albicans* genome encodes two (Sky1, Sky2) and the *C. glabrata* genome has one homolog (Sky1) of the human SR protein kinase 1, but their functions have not yet been investigated. We used deletion strains of the corresponding genes in both fungi to study their cellular functions. *C. glabrata* and *C. albicans* strains lacking SKY1 exhibited higher resistance to osmotic stress and toxic polyamine concentrations, similar to their ortholog Sky1 in Saccharomyces cerevisiae. Deletion of SKY2 in *C. albicans* resulted in impaired utilization of various dipeptides as the sole nitrogen source which was shown by utilizing a high-throughput phenotypic screen. Subsequent phosphoproteomic analysis identified the di- and tri-peptide transporter Ptr22 as a potential Sky2 substrate. Our data suggest that Sky2 seems to be involved in Ptr22 regulation since overexpression of PTR22 in the sky2Δ mutant restored the ability to grow on dipeptides and made the cells more susceptible to the dipeptide antifungals Polyoxin D and Nikkomycin Z. Altogether, our results demonstrate that *C. albicans* and *C. glabrata* Sky1 protein kinases are functionally similar to Sky1 in S. cerevisiae, whereas *C. albicans* Sky2, a unique kinase of the CTG clade, likely regulates dipeptide uptake via Ptr22.

P7
Banging your head against the (fungal) wall

Neil A.R. Gow
Plenary session 7, September 23, 2022, 2:00 PM - 3:00 PM

For a fungus, there may be nothing as biologically variable and highly regulated as its cell wall. This makes the wall intellectually and methodologically challenging to study, but worth the effort because they have the potential to reveal novel targets for antifungal drugs and the mechanisms that are important for immune recognition. Differences and adaptations to the cell wall composition can serve to resist chemotherapy and create a moving target for efficient immune recognition. 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. We show that the cell has a mechanism to maintain wall robustness within physiological limits. We also have 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. We have screened libraries of mutants with immune pattern recognition receptors (PRRs) to define the sub-set of fungal genes that assemble and regulate immune epitopes. This is revealing novel processes that are important for the assembly of the cell wall. These experiments demonstrate that the fungal cell surface is ordered, complex and dynamically changing, requiring immune recognition to mobilize the concerted action of multiple receptors operating singly and in combination. My presentation will focus on work that demonstrates and describes recent advances that have generated a scaler and dynamic model of the cell wall that illuminates mechanisms of immune recognition and cell wall homeostasis.

S8.1b
Is a search and destroy strategy still feasible for *Candida auris* in South Africa?

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S8.1 Tackling *Candida auris* in resource-limited settings, September 23, 2022, 3:00 PM - 4:30 PM

Candida auris was prospectively detected as a healthcare-associated pathogen in South Africa in 2014. However, a retrospective review of a culture collection from national laboratory-based surveillance for Candidaemia in 2009-10 showed that earlier cases had been missed owing to species misidentification. National surveillance, which was repeated during 2016-17, revealed that *C. auris* caused >10% of cases of Candidaemia in South Africa, with most (86%) cases detected in the Gauteng Province. We recommended all hospitals to passively monitor cases of *C. auris* disease and colonization by each maintaining a line list of culture-confirmed cases. Facilities were thus classified into three tiers. Tier 1 ('green status') included facilities with no prior known cases. Such facilities were requested to report their first cases for urgent intervention. This included active colonization surveys, isolation and/or cohorts of infected or colonized patients as well as intensified infection prevention and control and antifungal stewardship activities. Tier 2 ('orange status') included facilities with sporadic cases defined arbitrarily as fewer than 12 cases in the past 6 months and/or fewer than three units affected. Such facilities were requested to report any increase in the number of cases compared with a baseline, clinical units affected for the first time, or apparent case clustering within the facility for investigation. Tier 3 ('red status') included facilities with a relative endemicity defined as >12 cases and/or >3 units with cases in the last 6 months. Tier 3 facilities were only requested to report increases over a baseline or apparent clustering within the facility. Owing to limited resources, colonization screening of newly-admitted patients was not recommended in acute-care facilities in South Africa. During 2019-21, the proportion attributable to *C. auris* increased even further to 25% (of 12 959 national cases of Candidaemia), with a concomitant reduction in cases caused by *C. parapsilosis*. This suggested a concerning replacement of multidrug-resistant *C. auris* in an ecological healthcare niche previously occupied by azole-resistant *C. parapsilosis*. An epidemiological shift was also observed with an expanding number of acute healthcare facilities outside Gauteng Province reporting *C. auris* and large persistent healthcare-associated infection outbreaks in neonatal units, particularly in the under-resourced public health sector.

S8.2a
Trends in epidemiology of pediatric *Candida* infections

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S8.2 What is new in pediatric mycology?, September 23, 2022, 3:00 PM - 4:30 PM

Invasive *Candida* infections are a cause of increased morbidity and excessive mortality in immunocompromised and critically ill patients including premature neonates. In the pediatric setting, they are more frequent in the neonatal intensive care unit (ICU), in the pediatric ICU, and in the pediatric oncology/hematology departments. Its frequency in other pediatric departments, such as gastroenterology, surgery, and nephrology is less of a problem. *Candida albicans* remains the most frequent *Candida* species, whereas other non-*albicans Candida* spp. are less frequent. *Candida parapsilosis* is second in frequency, but in certain pediatric settings and countries, it may be first. While *C. albicans* is almost entirely susceptible to azoles, *C. parapsilosis* has started to manifest increasing resistance to fluconazole and this is of concern. However, due to improved infection control and prevention measures and to use of fluconazole prophylaxis in a number of neonatal ICUs, its incidence has been shown to decrease in a multi-state study conducted by the Centers of Disease Control and Prevention in the United States. Another large multinational study that was conducted in many European countries showed no changes in epidemiology over a number of years, and more non-*albicans Candida*, particularly *C. parapsilosis*, in South Europe. The epidemiology of *Candida* in pediatric ICU has been less studied. Similar epidemiology and risk factors exist in PICU as in neonates. Abdominal surgery and multi-site colonization with *Candida* of patients are risk factors for developing invasive *Candida* infections, mainly candidemia. In the patients with hematological malignancies, antifungal prophylaxis for mold infections is also active against *Candida*, therefore, the incidence of invasive candidiasis is relatively low. However, non-*Candida albicans* species with reduced susceptibility to azoles, such as *C. glabrata*, are found more frequently. In pediatric patients with solid organ transplantation, invasive candidiasis is the most frequent fungal infection, mainly in those with liver transplantation. *Candida* causes infection in the first weeks after transplantation earlier than other fungal infections.

S8.3b
How fungal cell wall glycans modulate the activation of platelets ?

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S8.3 How the fungal cell wall glycan can modulate the immune response?, September 23, 2022, 3:00 PM - 4:30 PM

Platelets are the first circulating blood cells that interact and adhere to vascular lesions. They play an important role in vascular repair and maintenance of blood homeostasis. Platelets are involved in the immune defense of the host against many infections caused by bacteria, viruses, and fungi. Following infection, these microorganisms can alter platelet function leading to platelet activation. During fungal infection, β-glucans, mannan, and chitin, are critical components of *Candida albicans*, an opportunistic pathogenic yeast of humans. These fungal glycans play an important role in the modulation of the host response. They are released into the bloodstream and can be detected up to 10 days before the onset of clinical signs of invasive candidiasis. However, their role in the modulation of platelet activities is unknown. In our studies, we observed that β -glucans and chitin decrease platelet activation and modulate the production of inflammatory mediators, mediated by TLR4 or TLR8 respectively. These glycans also reduce platelet adherence to *C. albicans* and to polynuclear neutrophils, suggesting a process by which *C. albicans* can escape from cells of innate immunity by releasing cell wall polysaccharides into the close environment or the blood circulation. This study provides evidence that fungal glycans play a role in the modulation of the immune response and how *C. albicans* can escape from the innate immune response.

S8.3c
Cell wall glycans as targets for the development of new antifungals

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S8.3 How the fungal cell wall glycan can modulate the immune response?, September 23, 2022, 3:00 PM - 4:30 PM

Being an extracellular organelle, the cell wall plays a crucial role in fungal life, by protecting fungal cells from a hostile environments and providing cells with mechanical strength. Exploiting the essentiality of this cell wall, available antifungal drugs target cell wall biosynthesis directly or by altering the fungal cell membrane. However, the emergence of resistance to antifungal drugs, new at risk-cohorts, and drug-drug interaction issue with antifungals demand new/alternative therapeutic strategy. In this regard, we have identified that surfactant protein-D (SP-D; a host humoral immune component) has growth inhibitory activity on *Aspergillus fumigatus*, a ubiquitous airborne opportunistic pathogen. SP-D, a soluble pattern recognition receptor of the collection family, targets galactosaminogalactan and galactomannan, the cell wall glycans of *A. fumigatus* hyphae, as the ligands. Hyphae grown in presence of SP-D show a significant decrease in the growth and are hyperbranched compared to control hyphae. SP-D treatment alters surface exposure of hyphal cell wall polysaccharides, thereby modifying hyphal immunoreactivity. SP-D pre-treatment increases the efficacy of the echinocandin and azole classes of antifungals against *A. fumigatus*. Interestingly, SP-D show hyphal growth inhibitory activity against multi-/pan-azole-resistant isolates of *A. fumigatus*. Overall, SP-D seems to target *A. fumigatus* cell wall glycans to execute its fungistatic activity. We are currently investigating the exact mechanism of anti-*A. fumigatus* activity associated with SP-D.