Pan-*Candida* monoclonal antibodies as novel immunotherapies to treat drug resistant life-threatening invasive candidiasis

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Fungal pathogens cause life-threatening invasive infections leading to 2.5 million deaths per annum with very limited antifungal therapy options. Effective treatment of infections is challenging due to increasing prevalence of drug resistant infections, drug toxicities and drug:drug interactions in often complex patients undergoing immunosuppressive therapies.

We have leveraged our expertise of the fungal cell wall to identify novel, surface-exposed peptide targets that are more abundant in drug-resistant fungi and become upregulated in response to treatment with current antifungals. The peptides belong to fungal cell wall proteins that we have shown are critical for cell wall remodelling and pathogenicity and are expressed during infection. The selected drug target Pga31 is pan-*Candida* and Utr2 is pan-fungal belonging to chitin:glucan crosslinking enzyme family, both are required for cell wall robustness.

A panel of Pga31 and Utr2- specific phage binders was isolated from a phage display antibody library and reformatted into human IgG1 anti-Pga31 and anti-Utr2 monoclonal antibodies (mAbs). All mAbs had a strong affinity to their target with EC50 values reaching around 300 pmol. The mAbs were cross-reactive to fungal cells across all major *Candida* pathogens with enhanced binding when cells were stressed with antifungal agents, caspofungin and fluconazole. Different binding patterns were observed on *Candida albicans* yeast and hyphal cells with preferential binding to the invasive hyphal morphology even without antifungal treatment. In addition, the anti-Pga31 antibody had localized binding to hyphal tips after antifungal challenge. Enhanced antibody-mediated opsonisation was detected, the binding of antibodies significantly induced phagocytosis of *C. albicans* by murine J774.1 macrophages compared with controls. Importantly the mAbs have proven in vivo efficacy in murine invasive candidiasis models that represent the immunocompetent and immunosuppressed status of patients. There is huge potential for unique, fungal-specific cell wall targeting mAbs with a novel mechanism of action as monotherapy or co-therapy with existing antifungals to improve clinical outcomes in complex patients and combat the AMR crisis.