Human monoclonal antibodies targeting novel, fungal cell wall proteins offer superior therapeutic efficacy in a preclinical model of infection.

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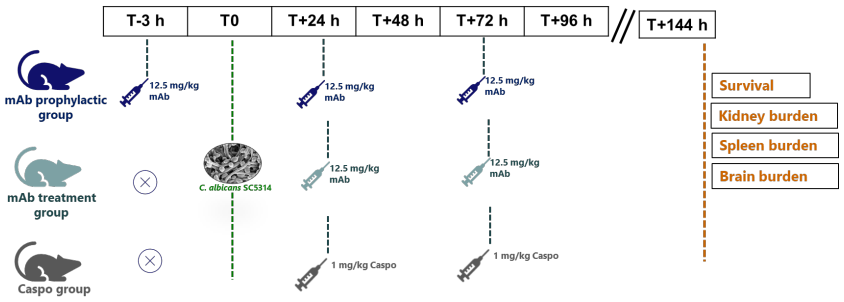
Monoclonal antibody (mAb) therapies are in their infancy in infectious diseases, specifically in systemic and deep-seated fungal infections with currently no licensed biologics drug available for patients at risk. Despite treatment, the mortality associated with invasive fungal infections remains as high as 40-50% due to the inherent limitations of current antifungals including: multidrug resistance, drug-drug interactions (DDIs) and toxicity. Treatment complications and failures are particularly high in critical care patients and those undergoing chemotherapy, transplant and complex abdominal surgeries. As the world begins to "run out" of anti-fungal drug options, the development of next generation alternatives remains a challenge by the need to kill a eukaryotic pathogen within a eukaryotic host.

Combining proteomic and transcriptomic based approaches, we have identified several cell wall proteins (CWPs) on the surface of fungal pathogens that are upregulated during *in vivo* infection in a mouse model of systemic candidiasis. These proteins are also present in higher abundance in drug resistant clinical isolates, including multidrug resistant *Candida albicans* and *C. auris* strains. Employing techniques to identify the surface exposed regions of CWPs, and applying conventional phage display technology, we have developed a proprietary platform to generate recombinant human mAbs binding well-defined peptide epitopes of fungal specific proteins that play key roles in infection and drug resistance.

These mAbs preferentially recognised *C. albicans* hyphal forms compared to yeast cells and an increased binding when the cells were grown in the presence of different antifungal classes. In J774.1 macrophage interaction assays, mAb pre-treatment resulted in a faster engulfment of *C. albicans* suggesting a role of the CWP antibodies as opsonising agents during phagocyte recruitment. Finally, in a series of clinically predictive, mouse models of systemic candidiasis, our lead mAb achieved an improved survival (83%) and several log reduction of fungal burden in the kidneys, similar to levels achieved for the fungicidal drug caspofungin, and superior to any anti-*Candida* mAb therapeutic efficacy reported to date.

The cell wall targeting mAbs have great potential to become a new class of antifungal drugs with improved safety and efficacy in high-risk patients where treatment choices are much-limited for life-threatening fungal infections.

A



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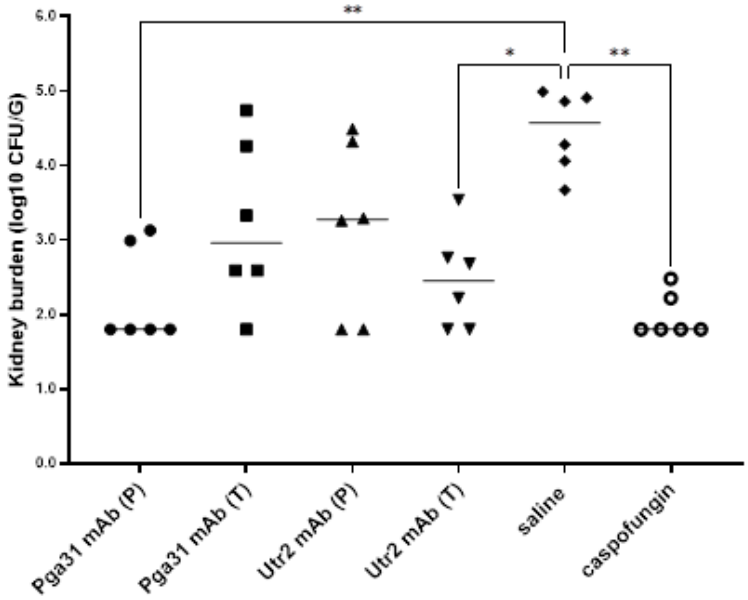

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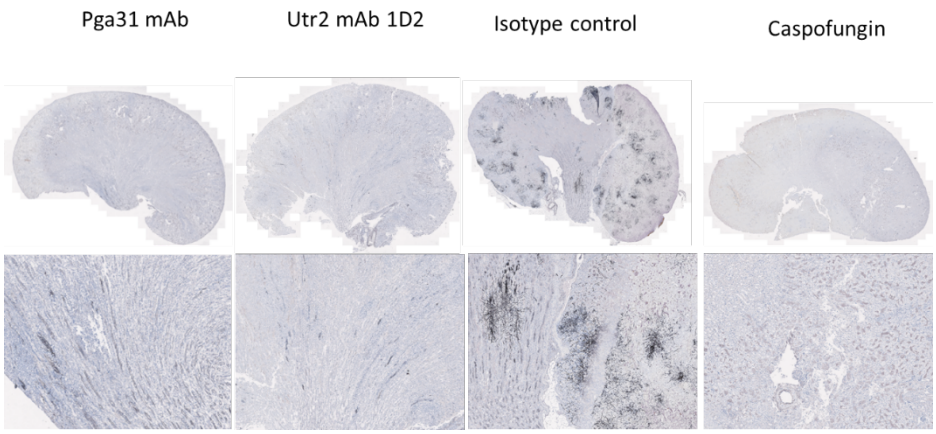

Figure 1: (A) Invasive candidiasis study plan (B) Fungal burden in various treatment groups using Utr2 and Pga31 mAbs (P) prophylactic arm, (T) treatment arm. Control groups included saline-only and caspofungin at 1 mg/kg body weight. Each symbol represents an individual mouse, and bars represent the mean kidney burdens in each group (C) Representative histopathological sections of kidneys of mice treated with Pga31 mAb, Utr2 mAb, isotype control IgG or caspofungin (1 mg/kg). Numerous fungal lesions are seen in the isotype control treated kidney (black staining) compared to kidneys from the mAb treatment groups and caspofungin group.