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Protection and antibody responses induced by a four-peptide antifungal vaccine against *Candida* in mouse models

Candida species are commensal fungi that colonize the oral cavity, gastrointestinal tract, and genitourinary tract of many healthy individuals. However, these otherwise harmless members of the human mycobiome can become pathogenic in the setting of microbiota dysbiosis, epithelial barrier disruption, or immunocompromise, causing diseases ranging from mucosal candidiasis to life-threatening invasive candidiasis (IC). IC affects an estimated 1.5 million people worldwide each year and is associated with nearly 1 million deaths. Together with rising antifungal resistance—particularly in the multidrug-resistant, WHO critical-priority pathogen *Candida auris*—and persistently high mortality despite treatment, these challenges underscore the urgent need for preventive strategies. Yet no licensed vaccine currently exists for *Candida* or any fungal pathogen.

Previous studies from our laboratory demonstrated protection in mouse models using a *Candida* vaccine displaying the conserved cell-surface peptides Fba and Met6 on a spontaneous nanoliposome antigen particle (SNAP). This platform has since been expanded into a four-peptide, lyophilized SNAP vaccine that incorporates two additional epitopes Pkg1 and Hwp1, in a formulation design for improved stability during storage and transport. To characterize and compare antibody responses between the two- and four-peptide formulations, peptide-specific IgG titers and IgG1/IgG2a subclass ratios were measured by ELISA using serum collected after primary and secondary immunizations. These comparisons assessed whether adding Pkg1 and Hwp1 altered the antibody responses to Fba and Met6, and whether there was evidence of immune enhancement or interference among the peptide antigens. ELISAs demonstrated robust IgG responses to Fba and Met6, that were predominantly IgG1, consistent with a Th2-biased response.

Because antibody responses alone do not establish protection, protective efficacy was evaluated in immunocompetent BALB/c mice and in FK506 (tacrolimus)-treated C57BL/6 mice, which model the immunosuppression associated with solid-organ transplantation. Following intravenous challenge with *Candida albicans*, mice were monitored for survival. At death or humane endpoint, kidneys and brains were harvested, homogenized and plated to quantify fungal burden (CFU); comparison of fungal burden between vaccinated and control groups is ongoing. Together, these studies characterize the antibody response to the four-peptide SNAP vaccine and its protective efficacy in both immunocompetent and immunosuppressed hosts. Completion of the fungal burden analysis will further define the vaccine's potential as a storage-stable antifungal vaccine candidate for high-risk, immunocompromised populations.