**Objectives**:

Immune tolerance is a critical determinant in the pathogenesis of non-HIV-associated cryptococcal meningitis (CM). While STING has been identified as a negative regulator of antifungal immunity, its mechanistic role in mediating immune tolerance remains unclear. This study aims to elucidate how STING interacts with glycolysis-related pathways to mediate immunometabolic suppression in non-HIV CM, identifying potential therapeutic targets to reverse immune tolerance.

**Materials & Methods:**

Peripheral blood monocytes were collected from non-HIV CM patients, pulmonary cryptococcosis (PC) patients and healthy controls. Subsequent multi-platform analyses were systematically conducted, including cytokine profiling (ELISA), STING pathway activation assessment (flow cytometry), and glycolytic flux quantification (targeted LC-MS metabolomics), to characterize disease-specific immunometabolic profiles. To validate STING’s functional role, an*in vitro*immune-tolerant cell model and a murine cryptococcal infection model were established, and STING genetic knockout and glycolytic rescue experiments were performed in this model to assess metabolic reprogramming and immune function. Finally, molecular docking simulation was used to predict interaction between STING and PFKFB3, a rate-limiting glycolytic enzyme, which were confirmed by co-immunoprecipitation (Co-IP).

**Results**:

Our clinical profiling revealed that monocytes from non-HIV cryptococcal meningitis (CM) patients exhibited significantly impaired TNF-α/IL-6 secretion compared to both healthy controls (HC) and pulmonary cryptococcosis (PC) cohorts (Fig 1A), indicative of pathogen-induced immune tolerance. Targeted metabolomics further demonstrated a marked reduction in glycolytic intermediates including fructose-1,6-bisphosphate, pyruvate, and lactate in CM monocytes (Fig 1B), highlighting glycolytic metabolism as a key contributor to immune tolerance pathogenesis. RNA-seq was used to investigate the transcriptomic profiling and uncovered pathological immune tolerance in CM monocytes, showing elevated STING protein expression compared to PC (Fig 1C). Mechanistically, persistent exposure to *Cryptococcus* glucuronoxylomannan (GXM) recapitulated this tolerogenic phenotype in monocyte-derived macrophages (MDMs) and bone marrow-derived macrophages (BMDMs), with cytokine suppression exhibiting strict GXM dose-dependency (Fig 1D). Further functional interrogation revealed that either pharmacological STING inhibition or genetic knockout restored cytokine production (Fig 2A). These findings were corroborated *in vivo*, where STING-/- mice exhibited superior survival and reduced fungal burden in brains post-infection compared to wild-type counterparts (Fig 2B). Molecular docking simulations identified a high-affinity interaction between STING and PFKFB3 (ΔG = -220.668 kJ/mol), with co-immunoprecipitation confirmed direct binding (Fig 2C). Finally, STING knockout reversed GXM-mediated PFKFB3 suppression, while PFKFB3 overexpression restored cytokine secration (Fig 2D). Together, these data delineate a pathogenic circuit whereby *Cryptococcus* exploits the STING-PFKFB3 axis to enforce glycolytic paralysis and immune tolerance, revealing actionable targets for metabolic checkpoint immunotherapy.

**Conclusions**:

Cryptococcal infection upregulates STING in monocytes, which directly binds to PFKFB3, suppressing glycolysis and inducing immune tolerance. Targeting the STING-PFKFB3 axis restores immunometabolic function and enhances antifungal responses. These findings establish STING as a master regulator of immunometabolic reprogramming in non-HIV CM and provide a novel therapeutic strategy.