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A Peptide-Based Checkpoint Inhibitor Therapeutically Rescues Mice from Lethal Malaria and Enhances Priming of T Cells Following Vaccination

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Checkpoint receptors are highly expressed on T cells from chronically-infected individuals, arguing T cell exhaustion contributes to pathogenesis and lack of immunity. Targeting checkpoint receptors has shown to improve outcomes in models of chronic infections. In malaria, increasing evidence suggests that inhibitory receptors (e.g., PD1, LAG3), mediate immune suppression. Studies have shown that PD1-deficient mice rapidly clear chronic *Plasmodium chabaudi* and develop sterile immunity. Moreover, PD1 mediates loss of long-term protection against *P. chabaudi*. These data argue that blocking PD1 may rescue T cell exhaustion in malaria-infected individuals. While mAb-based checkpoint therapeutics are efficacious in oncology, they are not ideal for infectious diseases. We created a platform for discovering short peptides and evolving these peptide scaffolds by *in silico* design. Our lead checkpoint inhibitor, LD01, inhibits both the PD1 and CTLA4 receptors and has shown efficacy in oncology models. We evaluated the LD01 checkpoint inhibitor in therapeutic and prophylactic malaria vaccine mouse models. In the lethal *P. yoelii* model 100% mortality occurs 10 days post-infection. Treatment with LD01, as late as 3 days post-infection, decreased clinical severity and induced 50% protection. Further, all of the LD01 treated surviving mice were protected after re-challenge, indicating long-lived memory. Studies in the *P. yoelii* model to elucidate immunological mechanism of action are ongoing. In a recombinant replication defective AdPyCS vaccine model, a significant increase in splenic PyCS-specific, IFN-γ^+ CD8 T cells was detected in mice treated with LD01 compared to AdPyCS alone. Overall, LD01 appears to mediate release of immune suppression and acts as a T cell focused adjuvant when co-administered with a vaccine antigen, supporting further studies to understand its potential as a therapeutic peptide-based checkpoint inhibitor or as part of a prophylactic vaccine regimen.