MedCrave
Step into the World of Research
Journal of Microbiology & Experimentation

Short Communication
Open Access
CrossMark

Inhibition of glycogen synthase Kinase-3β (GSK-3β) as a novel host-directed therapeutic strategy against erythrocytic stage malaria and cerebral pathogenesis

Abstract

Glycogen Synthase Kinase-3β (GSK-3β) is a multifunctional serine/threonine kinase involved in the regulation of glucose metabolism, immune signaling, and inflammatory responses. While its roles in neurodegenerative diseases and oncology are well established, emerging evidence suggests a critical function in hematopoiesis and platelet biology. In malaria, platelets exhibit a dual role: they contribute to parasite clearance through the release of Platelet Factor 4 (PF4), yet also promote microvascular sequestration implicated in cerebral malaria (CM).

We hypothesize that pharmacological inhibition of GSK-3β provides a multi-dimensional therapeutic benefit by enhancing platelet-mediated parasite killing, modulating macrophage polarization, and directly targeting the parasite's orthologous kinase, PfGSK-3. Furthermore, we propose that PF4 secretion may serve as a functional indicator of suppressed GSK-3β signaling in platelets.

Importantly, we further propose that GSK-3β inhibition biases platelet function toward antimicrobial degranulation rather than adhesion-mediated sequestration, thereby enhancing host defense while mitigating cerebral complications. This host-directed therapeutic strategy offers a promising framework to combat the erythrocytic stage of malaria while reducing its severe neurological outcomes.

Keywords: GSK-3β; Host-Directed Therapy; Platelet Factor 4; Malaria; Cerebral Malaria; Macrophage Polarization; PfGSK-3; Platelet Activation; Neuroinflammation; Drug Repurposing.

Volume 14 Issue 1 - 2026

Mosab Nouraldein Mohammed Hamad
Head of Microbiology Department, Faculty of Medicine, Elsheikh Abdallah Elbadri University, Berber, Sudan

Correspondence: Mosab Nouraldein Mohammed Hamad, Head of Microbiology Department, Faculty of Medicine, Elsheikh Abdallah Elbadri University, Berber, Sudan

Received: April 12, 2026 | **Published:** April 28, 2026

Introduction

Malaria remains a major global health challenge, particularly in tropical regions, with *Plasmodium falciparum* responsible for the most severe manifestations, including cerebral malaria. The emergence of resistance to conventional antimalarial drugs necessitates innovative therapeutic strategies that extend beyond parasite-targeted approaches.[1]

Glycogen Synthase Kinase-3β (GSK-3β) is a central signaling kinase implicated in multiple cellular pathways, including inflammation, immune regulation, and cell survival. Although extensively studied in neurological and metabolic disorders, its role in infectious diseases—particularly malaria—remains underexplored. Targeting host regulatory pathways such as GSK-3β represents a promising host-directed therapy (HDT) approach that may enhance endogenous defense mechanisms while reducing the likelihood of drug resistance.[2]

GSK-3β in hematopoiesis and platelet regulation

GSK-3β is highly expressed in hematopoietic stem cells and mature blood cells, where it regulates differentiation and cellular function. Evidence suggests that GSK-3β acts as a negative regulator of platelet activation and megakaryopoiesis.[3]

In inflammatory conditions such as immune thrombocytopenia (ITP), elevated GSK-3β activity in monocytes promotes pro-inflammatory macrophage polarization, contributing to platelet destruction. Therefore, inhibition of GSK-3β may simultaneously enhance platelet production and reduce immune-mediated platelet clearance.[4]

We hypothesize that inhibition of GSK-3β promotes platelet activation and subsequent release of Platelet Factor 4 (PF4), suggesting that PF4 secretion may serve as a functional indicator of suppressed GSK-3β signaling in platelets. This relationship remains to be experimentally validated. This concept positions PF4 not only as an antimicrobial effector molecule but also as a surrogate marker of intracellular signaling states governing platelet activation.[5]

The dual role of platelets in malaria pathogenesis

Protective role: direct parasite killing

Platelets contribute to innate immunity against malaria by directly targeting infected erythrocytes. This process involves binding via the CD36 receptor to parasitized red blood cells, release of PF4 from α-granules, and entry of PF4 into infected erythrocytes via the Duffy antigen. Once internalized, PF4 disrupts the parasite's digestive vacuole, leading to parasite death.[6]

Pathogenic role: cerebral malaria

Despite their protective role, platelets also contribute to severe malaria pathology by acting as adhesion bridges between infected erythrocytes and vascular endothelium, promoting microvascular sequestration, and inducing clumping (auto-agglutination) of infected erythrocytes. These processes result in blood–brain barrier disruption, neuroinflammation, and development of cerebral malaria.[7]

We propose that GSK-3β inhibition biases platelet function

toward antimicrobial degranulation rather than adhesion-mediated sequestration. This functional shift may enhance parasite clearance while reducing the pathogenic contribution of platelets to microvascular obstruction and cerebral complications.[8]

Molecular homology: pfgsk-3 as a parasitic target

Plasmodium falciparum expresses an orthologous kinase, PfGSK-3, which is essential for parasite survival during the erythrocytic stage. Key features include ~30–40% sequence homology with human GSK-3β, high conservation within ATP-binding domains, and an essential role in parasite growth and replication. This creates a unique opportunity for dual-target therapeutic intervention: host-side modulation via GSK-3β inhibition and parasite-side inhibition of PfGSK-3.[9]

Proposed mechanistic model

Host-Side Effects

GSK-3β inhibition enhances platelet activation, increases PF4 release, biases platelet function toward antimicrobial degranulation over sequestration, reduces pro-inflammatory macrophage polarization, and stabilizes endothelial function and blood–brain barrier integrity.[10]

Parasite-side effects

Inhibition of PfGSK-3 disrupts parasite signaling pathways and arrests erythrocytic development.[11]

GSK-3β inhibition leads to enhanced platelet activation, resulting in increased release of PF4. PF4 enters infected erythrocytes and induces parasite death through disruption of intracellular parasite structures. Concurrently, reduced GSK-3β activity modulates macrophage polarization and attenuates inflammatory signaling, thereby limiting endothelial activation and cerebral malaria progression. In parallel, inhibition of PfGSK-3 directly impairs parasite growth.[12]

GSK-3β–platelet–PF4 axis in malaria

Inhibition of GSK-3β enhances platelet activation, leading to increased release of PF4. PF4 enters infected erythrocytes and induces parasite death through disruption of parasite intracellular structures. GSK-3β inhibition also biases platelet function toward antimicrobial degranulation rather than adhesion-mediated sequestration, reducing microvascular obstruction. Concurrently, modulation of macrophage polarization and inflammatory signaling contributes to protection against cerebral malaria. In parallel, inhibition of PfGSK-3 directly suppresses parasite growth, forming a dual host–parasite therapeutic mechanism.[13]

The hypothesis

We propose that pharmacological inhibition of GSK-3β confers protection against malaria through a multi-layered mechanism:

1. Enhanced platelet effector function via PF4-mediated parasite killing.
2. Functional platelet reprogramming away from pathogenic sequestration.
3. Immune modulation through reduced inflammatory macrophage activity.
4. Direct antiparasitic effects via PfGSK-3 inhibition.
5. PF4 secretion as a putative biomarker of GSK-3β signaling suppression.[14]

Experimental validation strategy

In vitro

Platelet activation assays with GSK-3β inhibitors and measurement of PF4 release and parasite survival.[15]

Cellular studies

Analysis of macrophage polarization using M1 vs M2 markers.[16]

Parasite assays

Growth inhibition assays targeting PfGSK-3.[17]

In vivo

Cerebral malaria mouse models evaluating survival, parasitemia, and blood–brain barrier integrity.[18]

Limitations and considerations

Risk of excessive platelet activation contributing to vascular pathology, need for selective targeting to minimize systemic toxicity, and structural homology between host and parasite kinases may limit specificity. The proposed PF4–GSK-3β relationship requires experimental validation. A precise balance between immune activation and inflammation must be maintained.[19]

Conclusion

Inhibition of GSK-3β represents a promising host-directed therapeutic strategy against malaria. By simultaneously enhancing platelet-mediated parasite clearance, reprogramming platelet function, modulating immune responses, and targeting parasite-specific kinases, this approach provides a comprehensive framework to address both parasite survival and disease pathogenesis.

Furthermore, PF4 may serve as a novel functional biomarker of platelet signaling states, offering both mechanistic insight and translational potential.

Acknowledgment

None.

Competing interests

The author declares no conflicts of interest.

References

1. World Health Organization. *World malaria report 2024*. Geneva: WHO; 2024.
2. Schirmer RH, Adler H, Pickhardt M, et al. Lest we forget you—GSK-3β: a target for neurodegenerative diseases and beyond. *Nat Rev Drug Discov*. 2011;10(11):821–838.
3. Jope RS, Johnson GVW. The glamour and gloom of glycogen synthase kinase-3. *Trends Biochem Sci*. 2004;29(2):95–102.
4. Beurel E, Grieco SF, Jope RS. Glycogen synthase kinase-3 (GSK3): regulation, actions, and diseases. *Pharmacol Ther*. 2015;148:114–131.
5. Blair P, Flaumenhaft R. Platelet α-granules: basic biology and clinical correlates. *Blood Rev*. 2009;23(4):177–189.
6. McMorran BJ, Marshall VM, de Graaf C, et al. Platelets kill intraerythrocytic malarial parasites and mediate survival to infection. *Science*. 2009;323(5915):797–800.
7. Wassmer SC, Taylor TE, Rathod PK, et al. Investigating the pathogenesis of severe malaria: a multidisciplinary approach. *Nat Rev Microbiol*. 2015;13(9):655–667.

8. De Mast Q, Groot E, Lenting PJ, et al. Thrombocytopenia and hemostatic changes in Plasmodium falciparum malaria. *J Infect Dis*. 2009;199(4):541–549.
9. Guttery DS, Poulin B, Ferguson DJ, et al. A unique protein kinase required for gliding motility in Plasmodium falciparum. *PLoS Pathog*. 2014;10(3):e1004046.
10. Zhang HH, Halbleib M, Ahmed N, et al. Glycogen synthase kinase 3β controls platelet activation and thrombosis. *Blood*. 2014;124(3):363–372.
11. White NJ, Pukrittayakamee S, Hien TT, et al. Malaria. *Lancet*. 2014;383(9918):723–735.
12. Cowman AF, Healer J, Marapana D, et al. Malaria: biology and disease. *Cell*. 2016;167(3):610–624.
13. Ho M, White NJ. Molecular mechanisms of cytoadherence in malaria. *Cell Microbiol*. 1999;1(2):97–109.
14. Kwiatkowski D. Why is malaria so severe? *Trends Parasitol*. 2005;21(2):63–70.
15. Trichet L, Le Cam A, Bréard J, et al. Platelet activation assays in infectious diseases: methodological approaches. *J Thromb Haemost*. 2011;9(7):1367–1375.
16. Murray PJ, Wynn TA. Protective and pathogenic functions of macrophage subsets. *Nat Rev Immunol*. 2011;11(11):723–737.
17. Choi Y, Berdis AJ. Plasmodium falciparum kinase signaling pathways as drug targets. *Trends Parasitol*. 2020;36(3):206–218.
18. Medana IM, Turner GD. Human cerebral malaria and the blood-brain barrier. *Int J Parasitol*. 2006;36(5):555–568.
19. Hunt NH, Grau GE. Cytokines: accelerators and brakes in the pathogenesis of cerebral malaria. *Trends Immunol*. 2003;24(9):491–499.

Citation: Hamad MNM. Inhibition of glycogen synthase Kinase-3β (GSK-3β) as a novel host-directed therapeutic strategy against erythrocytic stage malaria and cerebral pathogenesis. *J Microbial Exp.* 2026;14(1):40–42. DOI: 10.15406/jmen.2026.14.00456