PRESS RELEASE

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NUS Medicine scientists identify potential therapy and diagnostic markers for cerebral malaria

Singapore, 22 December 2025 – Malaria continues to place a substantial burden on many emerging economies, contributing to significant loss of life, long-term disability, and economic disruption. According to the World Health Organization, the disease accounts for about 600,000 deaths each year, with the highest impact in low- and middle-income regions where access to prompt diagnosis and treatment remains limited. *Plasmodium falciparum* is the most dangerous malaria parasite that infects humans and can cause severe malaria, including cerebral malaria, where infected red blood cells clog small blood vessels in the brain. Infection can progress rapidly, leading to coma, brain swelling, and death if not treated promptly. Even in survivors, there can be persistent cognitive and motor impairment caused by the infection.

In a study published in *Nature Communications*, researchers from the Yong Loo Lin School of Medicine, National University of Singapore (NUS Medicine), together with international collaborators, examined whether methylene blue could mitigate brain injury during severe malaria, and whether a practical set of blood biomarkers could help clinicians identify cerebral malaria early and track how patients respond to treatment.

Assistant Professor Benoit Malleret, Department of Microbiology and Immunology, and Immunology Translational Research Programme (TRP), NUS Medicine, said, “Cerebral malaria develops quickly and leads to severe consequences, but there remains a lack in practical diagnostic tools or targeted therapies. Our findings show that methylene blue can reverse many of the infection-induced molecular changes in the brain, which is encouraging for a compound that is already inexpensive and widely accessible.”

In the study, the researchers applied methylene blue intravenously in laboratory models with *Plasmodium coatneyi* after severe symptoms appeared. *P. coatneyi* closely resembles *P. falciparum* as it has extremely similar symptoms, and is widely used as a stand-in in laboratory and preclinical studies. The team then analysed which genes were switched on or off during infection. They used these data to identify patterns in the blood that reliably signalled when cerebral malaria was present. They found that methylene blue was able to reset many of the abnormal genetic changes in the brainstem, the part of the brain most affected during cerebral malaria. It also reduced clear signs of brain injury, such as pigment deposits from infected red blood cells, small bleeds, and swelling. Many gene activity changes caused by the infection

returned close to normal, and the tissue samples showed improvements that matched the molecular results.

By comparing results across datasets, the researchers identified a nine-gene blood signature: *MAG, IL1RN, LCN2, S100A8, S100A9, CD177, CHIT1, MMP9* and *NFE2*. This set of genes consistently separated cerebral malaria from milder malaria and from healthy individuals. As the pattern appeared stable across both adults and children, it raises the possibility of developing a single, standardised blood test to help doctors diagnose cerebral malaria, assess its severity, and track patient recovery. Several of these genes are linked to neutrophils, a type of white blood cell, suggesting that neutrophil-driven inflammation contributes to brain swelling and damage during the disease.

Asst Prof Malleret added, “The biomarker signature we identified was remarkably consistent. This suggests that a simple blood test could be developed to differentiate cerebral malaria from other severe conditions, enabling earlier intervention and clearer treatment decisions.”

Another important finding was the improved understanding of immune processes involved in brain injury. Neutrophils, which were not previously considered central to cerebral malaria, appeared repeatedly across the biomarker and immune-cell analyses. This provides new clues about how inflammation damages the blood–brain barrier and how neurological symptoms arise. While methylene blue showed encouraging effects, the researchers noted that timing may be key, as earlier treatment appeared more beneficial. Clinical trials will be needed to determine the best dosing, timing, and safety when used together with current antimalarial drugs. The nine biomarkers will also need to be tested in larger and more diverse patient groups, and translated into a practical, field-ready test.

The team ultimately hopes to develop a rapid, reliable blood test for cerebral malaria and to evaluate methylene blue as an affordable supportive treatment. By clarifying how the brain becomes inflamed during malaria, the study lays groundwork for better diagnostics, treatments, and patient monitoring in regions where the disease remains a major health concern.

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Our multidisciplinary and real-world approach to education, research and entrepreneurship enables us to work closely with industry, governments, and academia to address crucial and complex issues relevant to Asia and the world. Researchers in our faculties, research centres of excellence, corporate labs and more than 30 university-level research institutes focus on themes that include energy; environmental and urban sustainability; treatment and prevention of diseases; active ageing; advanced materials; risk management and resilience of financial systems; Asian studies; and Smart Nation capabilities such as artificial intelligence, data science, operations research, and cybersecurity.

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Through a dynamic and future-oriented five-year curriculum that is inter-disciplinary and inter-professional in nature, our students undergo a holistic learning experience that exposes them to multiple facets of healthcare and prepares them to become visionary leaders and compassionate doctors and nurses of tomorrow. Since the School's founding in 1905, more than 12,000 graduates have passed through our doors.

In our pursuit of health for all, our strategic research programmes focus on innovative, cutting-edge biomedical research with collaborators around the world to deliver high impact solutions to benefit human lives.

The School is the oldest institution of higher learning in the National University of Singapore and a founding institutional member of the National University Health System. It is one of the leading medical schools in Asia and ranks among the best in the world (Times Higher Education World University Rankings 2025 by subject and the Quacquarelli Symonds (QS) World University Rankings by subject 2025).

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