*Department of Microbiology and Immunology*

# Division of Malaria Immunology
## マラリア免疫学分野


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***Summary of Activity***

*Our laboratory investigates host-pathogen interactions that drive immunopathology in severe infectious diseases, with a focus on cerebral malaria. Using transcriptomics and genetic models, we recently identified a few key regulators of early cerebral malaria pathogenesis in the olfactory bulb. In parallel, we advance vaccine adjuvant discovery for pandemic preparedness by developing data-driven, transcriptomics- and machine-learning–based platforms to enable rapid, safe, and effective vaccine and immunotherapeutic design.*


### 1. Understanding host-pathogen interactions in the context of cerebral malaria

**IFNγ-inducible Gbp4 and Irgb6 contribute to experimental cerebral malaria pathology in the olfactory bulb.** Cerebral malaria (CM) is a severe and often fatal complication of *Plasmodium falciparum* infection. Although much progress has been made in understanding CM, the precise pathogenesis remains elusive. The olfactory bulb (OB) has emerged as a critical site of immunopathology in experimental cerebral malaria (ECM) models, but its contribution to disease progression is not fully understood. To investigate the molecular mechanisms driving early ECM pathogenesis, we conducted transcriptomic profiling of the OB to identify key genes associated with disease onset. Our analysis revealed significant early upregulation of interferon (IFN)-inducible GTPases, particularly Irgb6 and Gbp4, effectors downstream of IFN-γ but not IFN-α/β signaling, suggesting their involvement in ECM pathology. Using *Gbp4*$^{-/-}$, *Irgb6*$^{-/-}$, and double knockout (*Irgb6*$^{-/-}$ *Gbp4*$^{-/-}$) mice, we identified a pathological role for these GTPases. Mechanistically, we found that double-knockout mice exhibited increased infiltration of CD4$^{+}$ and CD8$^{+}$ T cells into the brain but with reduced T cell functionality and impaired antigen presentation by endothelial cells, leading to enhanced parasite accumulation in the OB. This disruption in immune regulation ultimately conferred improved survival in the *Irgb6*$^{-/-}$ *Gbp4*$^{-/-}$ mice and indicated the pathological impact of Gbp4 and Irgb6 in ECM. These findings reveal that Gbp4 and Irgb6 play important roles in the early immunopathogenesis of ECM by modulating antigen processing and presentation in the OB, thereby shaping immune cell dynamics. Our work shows the dual role of Irgb6 and Gbp4 GTPases in host defence and immunopathology and offers new insights into ECM mechanisms and antigen presentation. Importance of these findings: Cerebral malaria (CM) arises from an excessive inflammatory response and blood-brain-barrier (BBB) dysfunction in *Plasmodium*-infected hosts, but the precise mechanisms driving early-stage pathogenesis remain unclear. Through RNA sequencing of the olfactory bulb (OB) in a murine experimental cerebral malaria (ECM) model, we identified the early upregulation of interferon (IFN)-inducible GTPases, Irgb6 and Gbp4, key effectors downstream of IFN-γ signaling. Our results demonstrate that Gbp4 and Irgb6 synergistically contribute to ECM pathology by

regulating antigen cross-presentation in endothelial cells. This dysregulation leads to abnormal parasite burden and alters the accumulation of CD4+ and CD8+ T cells in the brain via the OB, further perturbing inflammation. Our findings suggest a novel mechanism in CM and emphasize the pivotal roles of Gbp4 and Irgb6 in promoting cell-autonomous immune responses that, in turn, escalate pathological inflammation. Our study offers insights into how dysregulated immune responses drive CM progression and suggests potential therapeutic targets to mitigate fatal outcomes ***(Matsuo-Dapaah et al., mBio, 2025)***.

## 2. Adjuvant discovery and development for 100 days mission

**Vaccine adjuvants as stand-alone immunoprophylaxis in strategies for 100-day rapid responses to future pandemics.** The COVID-19 pandemic accelerated vaccinology progress, driving rapid vaccine development for infectious and non-infectious diseases. However, challenges persist: malaria, HIV, and dengue lack fully effective vaccines, whereas influenza and tuberculosis face waning efficacy. Emerging pathogens and drug-resistant strains further highlight the need for improved vaccines, particularly those offering rapid deployment, broad immunogenicity, and durable protection against variants. Adjuvants can play a dual role in this context: as new stand-alone tools for an early response to a pandemic -aiming at the 100-days mission objective- and for prevention of anti-microbial resistance (AMR); and as traditional components enhancing the efficacy and breadth of vaccines. The understanding of their mechanisms of action and novel usage could address critical gaps in pandemic preparedness, especially for vulnerable populations like children and the elderly ***(Kavian et al., International Immunology, 2025)***.

**An adjuvant database for preclinical evaluation of vaccines and immunotherapeutics.** Adjuvants are immunostimulators used to enhance vaccine efficacy against infectious diseases. However, current methods for evaluating their efficacy and safety are limited, hindering large-scale screening. To address this, we developed a prototype Adjuvant Database (ADB) containing transcriptome data, generated using the same protocols as the widely used Open TG-GATEs (OTG) toxicogenomics database, covering 25 adjuvants across multiple species, organs, time points, and doses. This enabled cross-database integration of ADB and OTG. Transcriptomic patterns successfully distinguished each adjuvant regardless of organs or species. Using both databases, we built machine learning models to predict adjuvanticity and hepatotoxicity. Notably, we identified colchicine's adjuvant activity and FK565's liver toxicity through data-driven analysis. Overall, ADB combined with OTG offers a framework for transcriptomics-based, data-driven screening of adjuvant candidates ***(Natsume Kitatani et al., Cell Chemical Biology, 2025)***.

## Publications


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