

## 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 (Less than 70 words)

*Our laboratory focuses on the elucidation of host-pathogen interactions. We mainly work on malaria, but also cover several infectious diseases such as leishmaniasis and respiratory infections. We study both innate and adaptive immune responses against these diverse pathogens in order to develop successful vaccines against them.*

### 1. Adjuvant discovery and development platform

Adjuvants are considered essential vaccine components for enhancing vaccine responses. As a member of IMSUT International Vaccine Design Center (<https://vdesc.ims.u-tokyo.ac.jp/en/>), we have systematically screened innate and adaptive immune signaling molecules involved in the mode of action (MOA) of adjuvants and vaccines. Recently, we have been involved in the discovery of novel adjuvants as part of the AMED SCARDA project. One of the recent findings is to understand how the combination of TLR9 and STING agonists synergistically induce innate and adaptive responses to generate robust anti-tumor responses (Temizoz *et al.*, *International Immunology*, 2022). Our recent projects have focused on investigating B cell development and the pathways involved in germinal center (GC) formation for the generation of potent antibody responses against infections and during vaccination. We found that TBK1, the well-known innate immune signaling kinase that controls antiviral immune responses and nucleic acid-mediated type I interferon responses, is very important for the generation of GCs that confer sterile immunity to reinfection (Lee *et al.*, *J Exp Medicine*, 2022).

### 2. Elucidation of host-pathogen interactions

Our laboratory has investigated several aspects of

immunopathology caused by *Plasmodium* parasites. We have recently studied the immunopathology of cerebral malaria, the deadliest complication of human malaria infection, in the brain using the CUBIC clearance technique (Matsuo-Dapaah *et al.*, *Int Immunology*, 2021). The 3D reconstruction of malaria-infected brain showed that olfactory bulb is disrupted during experimental cerebral malaria. We have recently made significant progress in understanding new cell types that accumulate/reside in the olfactory bulb and interact with *Plasmodium* parasites. Chronic bone loss is an unforeseen complication of malaria which is mediated via MyD88 adaptor protein (Lee *et al.*, *Science Immunology*, 2017). We have been studying to address the crucial cell types important for MyD88-mediated bone loss. We also investigate bone marrow niches responsible for malaria-induced loss of memory.

### 3. Infection and Cancer

Previously, we investigated the role of Lipocalin 2 (LCN2, also known as siderocalin or neutrophil gelatinase-associated lipocalin (NGAL)) in malaria infection that bolsters innate and adaptive immune responses to malaria infection through modulation of iron metabolism (Zhao *et al.*, *Cell Host Microbe*, 2012). LCN2 expression is also increased in cancer. In carcinogenesis, in addition to the accumulation of so-

matic mutations, stroma-associated immunity is an important regulator of tumor growth. Tumor cells create a microenvironment by releasing various mediators to maintain their presence and spread. Due to the infiltration of monocytes and leukocytes against the tumor, it is hypothesized that the iron balance is disrupted by excessive iron consumption, possibly leading to increased expression of LCN2 as an intracellular iron transporter. We recently investigated the expressions of programmed cell death ligand-1 (PD-L1) and LCN2 in breast cancers with various molecular subtypes, along with their correlations with other

prognostic indicators, including Ki-67, lymph node metastasis, histological grade, tumor-infiltrating lymphocyte (TILs) accumulation, and necrosis. We found that there is an association of LCN2 with known prognostic factors and molecular subtypes. Moreover, significant elevations of LCN2 and PD-L1 expressions were observed in triple-negative and HER2-positive breast cancers. The findings from this research may contribute to the immunotherapeutic application of LCN2 and its prognostic significance in breast cancer management (*Ekemen et al., Breast Cancer: Targets and Therapy, in press*).

### Publications

Ekemen S, Bilir E, Soutan HEA, Zafar S, Demir F, Tabandeh B, Toprak S, Yapiçier O, Coban C. The Programmed Cell Death Ligand 1 and Lipocalin 2 Expressions in Primary Breast Cancer and Their Associations with Molecular Subtypes and Prognostic Factors. *Breast Cancer: Targets and Therapy*, 2023, *in press*.

Becker HJ, Ishida R, Wilkinson AC, Kimura T, Lee MSJ, Coban C, Ota Y, Tanaka Y, Roskamp M, Sano T, Tojo A, Kent DG, Yamazaki S. Controlling genetic heterogeneity in gene-edited hematopoietic stem cells by single-cell expansion. *Cell Stem Cell*, Jul

6;30(7):987-1000.e8. doi: 10.1016/j.stem.2023.06.002, 2023.

Ekemen S, Comunoglu C, Kayhan CK, Bilir E, Cavusoglu I, Etiler N, Bilgi S, Ince U, Coban C, Erden HF. Endometrial Staining of CD56 (Uterine Natural Killer), BCL-6, and CD138 (Plasma Cells) Improve Diagnosis and Clinical Pregnancy Outcomes in Unexplained Infertility and Recurrent IVF Failures: Standardization of Diagnosis with Digital Pathology. *Diagnostics*, 13(9):1557. doi.org/10.3390/diagnostics13091557, 2023.