No.	K24-3123	
Project Title	Immunopathology of, and Response to, Protozoan Parasites	
Principal Investigator	Mayda Gursel (Izmir Biomedicine and Genome Center・Professor)	
Project Member(s)	IMSUT Host Researcher	Cevayir Coban (The Institute of Medical Science, The University of Tokyo・Professor)
	Project Member (s)	Ihsan Gursel (Izmir Biomedicine and Genome Center・Professor)
	Project Member (s)	Jalal Alshaweesh (Malaria Immunology・Assistan Professor)
	Project Member (s)	Cevayir Coban (Malaria Immunology・Professor)
	Project Member (s)	Mayda Gursel (Izmir Biomedicine and Genome Center・Professor)
	Project Member (s)	Mariana Silva Almeida (Malaria Immunology・Postdoc)
	Project Member (s)	Irem EVCILI (Izmir Biomedicine and Genome Center・Researcher)
	Project Member (s)	Ibrahim TOKMAK (Izmir Biomedicine and Genome Center・Graduate Student)

(Form 2)

Principal Investigator
Prof. Mayda GURSEL

IMSUT International Joint Usage/Research Center Project <International>

Joint Research Report (Annual/Project Completion)

Project Completion Report

Report (April 1, 2024-March 31, 2026)

Project title: K24-3123-Immunopathology of, and Response to, Protozoan Parasites

Leishmaniasis, a vector-borne disease caused by Leishmania parasites, is undergoing significant epidemiological shifts due to factors like climate change, urbanization, and forced migration, enabling its resurgence in non-endemic regions such as Europe. Widespread resistance to antimony-based treatments emphasizes the urgent need for a better understanding of the mechanisms underlying both pathology and drug resistance. In collaboration with Prof. Coban and Prof. Sanjoba, we contributed to the diagnostic challenges that could be experienced in re-emergence zones such as Turkiye (Turkey) that cutaneous leishmaniasis have changed its clinical features and causative agent (*Ekemen et al., Frontiers in Medicine, 2024).* Currently, no human vaccine exists for leishmaniasis. Gursel Group recently investigated *Leishmania*-derived extracellular vesicles (EVs) as a vaccine platform. Immunization with EVs from *L. major* and *L. infantum* induced strong humoral and cellular responses, providing protection and cross-protection in susceptible BALB/c mouse models. Adjuvant selection significantly affected outcomes, highlighting its critical role in protection versus susceptibility. These findings support the potential of EV-based vaccines for leishmaniasis and other protozoan infections (*Yilmaz et al., J Extracell Vesicles. 2026 Apr;15(4):e70252. doi: 10.1002/jev2.70252*). We will further collaborate with Coban Group to extend these EV-based vaccines against Leishmaniasis.

We have expanded our collaboration to additional groups within IMSUT. In collaboration with the Ishii Group, we investigated the role of STING signaling in both autoinflammatory diseases and cancer. Our collaborative work demonstrated that SAVI pathology is partly driven by microbiome- and host-derived cyclic dinucleotides, linking dysbiosis to enhanced STING activation and identifying CDNs as potential biomarkers and therapeutic targets (*Shibahara et al., J Autoimmunity, 2025*). In parallel, we explored pharmacological modulation of STING, showing that DMXAA functions as a partial agonist in humans and developing a novel antagonist, HHMX. Notably, HHMX effectively suppressed aberrant STING activation in SAVI patient cells and mouse models (*Temizoz et al., Frontiers in Immunology, 2024*). Together, these findings highlight complementary mechanistic insights and therapeutic strategies for targeting STING-driven diseases.

Publication supported by Int. Joint Rece. Center of IMSUT(s):

1. Shibahara T, Temizoz B, Egashira S, Hosomi K, Park J, Surucu N, Björk A, Sag E, Doi T, Kisla Ekinci RM, Balci S, Versnel MA, Kunisawa J, Yamamoto M, Hayashi T, Ito S, Kamiyama Y, Kobiyama K, Katsikis PD, ***Coban C****,* ***Gursel M,*** *Ozen S, Nishida S, Kumanogoh A, Ishii KJ.* Microbial dysbiosis fuels STING-driven autoinflammation through cyclic dinucleotides. **J Autoimmun. 2025**, Jun;154:103434. doi: 10.1016/j.jaut.2025.103434. Epub 2025 May 6.

2. Ekemen S, Nalcaci M, Toz S, Sanjoba C, Demirkesen C, Cetin ED, Tecimer T, Yildiz P, ***Gursel M,*** *Ince U, Ozbel Y and* ***Coban C.*** Diagnostic challenges in cutaneous leishmaniasis due to atypical *Leishmania infantum*: pathologists' insights from re-emergence zones. **Frontiers in Medicine, 2024,** 11:1453211. doi:

10.3389/fmed.2024.1453211

3. Temizoz B, Shibahara T, Hioki K, Hayashi T, Kobiyama K, Lee MSJ, Surucu N, Sag E, Kumanogoh A, Yamamoto M, ***Gursel M,*** *Ozen S, Kuroda E,* ***Coban C,*** *Ishii KJ.* 5,6-dimethylxanthenone-4-acetic acid (DMXAA), a partial STING agonist, competes for human STING activation. ***Front Immunol. 2024*** *Mar 12;15:1353336.doi:10.3389/fimmu.2024.1353336.*

Related Publication(s):

1. Yilmaz IC, Tokmak I, Yildirim M, Yildirim TC, Ozkoc ES, Evcili I, Ipekoglu EM, Ayanoglu İC, Dunuroglu E, Caliskan D, Onler H, Arzum Z, Ulker C, Mert O, Orkut R, Tarman IO, Guler U, Salih B, Yazar V, Ozgun G, Birincioglu S, Ozbilgin A, Gungor B, Gursel I, ***Gursel M.*** Leishmania Extracellular Vesicles as a Preventive Vaccine Platform Against Leishmaniasis. ***J Extracell Vesicles. 2026*** *Apr;15(4):e70252. doi: 10.1002/jev2.70252.*