

Department of Microbiology and Immunology

Division of Vaccine Science

ワクチン科学分野

| | |
|-----------------------------|------------------------------|
| Professor | Ken Ishii, M.D., Ph.D. |
| Associate Professor | Kouji Kobiyama, Ph.D. |
| Project Associate Professor | Misako Nakayama, M.D., Ph.D. |
| Assistant Professor | Burcu Temizoz, Ph.D. |
| Assistant Professor | Tomoya Hayashi, Ph.D. |

| | | | |
|-------|--------|-------|------|
| 教授 | 博士(医学) | 石井 | 健 |
| 准教授 | 博士(医学) | 小檜山 | 康司 |
| 特任准教授 | 博士(医学) | 仲山 | 美沙子 |
| 助教 | 博士(医学) | テミズオズ | ブルジュ |
| 助教 | 博士(薬学) | 林 | 智哉 |

Summary of Activity

Primary goal of our laboratory is to understand the immunological mechanisms of the intra- and inter-cellular signaling pathways that mediate the immunogenicity of successful vaccines, as well as biological responses to adjuvants. Such knowledge will enable us to develop novel concepts, modalities and next generation immunoprophylaxis and/or therapeutic agents against infectious diseases, cancer and allergy as well as other non-communicable diseases.

1. The development of vaccines for Emerging Infectious Diseases (EIDs) (COVID-19, Mpox vaccine, and others)

Supported by AMED, we contributed to the development of Japan's first LNP-mRNA vaccine (DS-5670, Daiichi Sankyo) and the first adjuvanted recombinant protein vaccine (S-268019, Shionogi Pharma) against SARS-CoV-2, approved in 2023 and 2024, respectively (doi: 10.1038/s41598-024-57308-3; doi: 10.1126/science.adh0968). We continue to investigate the molecular mechanisms of mRNA vaccines, while also collaborating with pharmaceutical companies on studies unrelated to mRNA—particularly to elucidate the mechanisms of novel adjuvants and advance next-generation vaccine design.

We also elucidated the immune mechanisms of the Mpox vaccine LC16m8, an attenuated vaccinia strain developed in Japan for smallpox, demonstrating robust and broad immunogenicity across MPXV clades. Using mouse, non-human primate, and human systems, LC16m8 was shown to induce strong neutralizing antibodies and cellular responses against outbreak-associated clade Ib and related strains. Comparative antigen profiling revealed distinct immunogenic hierarchies among viral proteins, provid-

ing insights for serological diagnostics and vaccine optimization. LC16m8 administration exhibited excellent safety, with only localized pox lesions and no systemic adverse effects. Overall, this cross-species analysis highlights LC16m8 as a safe, effective, and scalable platform for Mpox prevention and a useful framework for rapid vaccine development against emerging poxviruses (Kobiyama K. et al., EBioMedicine, 2025).

2. Innovative vaccine evaluation system for 100 days mission

Supported by AMED SCARDA (2022–), our laboratory leads a collaborative project with IMSUT, the National Institute of Infectious Diseases (NIID), and the National Institute of Biomedical Innovation, Health and Nutrition (NIBIOHN). The goal is to establish an innovative vaccine evaluation system capable of providing effective vaccines to the world within 100 days of the next infectious disease outbreak, epidemic, or pandemic. In line with the G7 “100-Day Mission,” this project integrates four essential research areas—pathogen biology, infection immunology, vaccine design, and animal model research—to build a robust framework for rapid, precise, and

high-level non-clinical evaluation of vaccine candidates, even under emergency conditions.

Through this initiative, we discovered that the pre-administration of certain adjuvants can induce broad and long-lasting protection against respiratory infections. We are currently advancing mechanistic studies to elucidate how this protective response is mediated. In parallel, we are expanding the scope of adjuvant studies by screening antiviral compounds that activate innate immunity through cell death-mediated pathways.

To further accelerate adjuvant development, we have also established the Adjuvant Database (ADB), a comprehensive and standardized multi-species transcriptomic resource encompassing 25 representative

adjuvants across multiple tissues, doses, time points, and animal species. Designed to be interoperable with the toxicogenomic platform Open TG-GATES (OTG), ADB enables integrated assessment of both adjuvant activity and toxicity using data-driven approaches. By applying machine learning, we identified previously unrecognized compounds with potential adjuvant activity and validated their effects experimentally. Together, these efforts aim to establish a data-driven, scalable foundation for the development of safe and effective vaccine adjuvants and immunomodulators to better prepare for future pandemics (Natsume-Kitatani Y. et al., *Cell Chem Biol*, 2025).

Publications

1. Kobiyama K, Utsumi D, Kaku Y, Sasaki E, Yasui F, Okamura T, Onodera T, Tobuse AJ, Sakkour A, Amiry AF, Hayashi T, Temizoz B, Liu K, Negishi H, Toyama-Sorimachi N, Kohara M, Sawasaki T, Takagi J, Sato K, Takahashi Y, Yasutomi Y, Ishii KJ. Immunological analysis of LC16m8 vaccine: pre-clinical and early clinical insights into mpox. *EBio-Medicine*. 2025 May;115:105703. doi: 10.1016/j.ebiom.2025.105703.
2. Shibahara T, Temizoz B, Egashira S, Hosomi K, Park J, Surucu N, Björk A, Sag E, Doi T, Kislá Ekinçi 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.
3. Utsumi D, Suzuki K, Matsuhara H, Kuroda E, Ishii KJ, Ohashi-Doi K. Enhancement of Immune Modulation by Toll-Like Receptor 9 Adjuvant Combination Subcutaneous Immunotherapy for Japanese Cedar Pollinosis. *Biol Pharm Bull*. 2025 August 8 ;48(8):1191-1198. doi: 10.1248/bpb.b25-00138. PMID: 40790815.
4. Matsuo-Dapaah J, Alshaweesh J, Lee MSJ, Hayashi T, Dash R, Kuroda M, Tainaka K, Ozawa M, Kuratani A, Yamamoto M, Liu K, Fukui R, Miyake K, Kobiyama K, Rénia L, Ishii KJ, Coban C. IFN- γ -inducible Gbp4 and Irgb6 contribute to experimental cerebral malaria pathology in the olfactory bulb. *mBio*. 2025 Aug 13;16(8):e0124925. doi: 10.1128/mbio.01249-25. Epub 2025 Jul 3. PMID: 40607809; PMCID: PMC12345229
5. Ono R, Tokuoka S, Tachibana M, Ishii KJ, Sakurai F, Mizuguchi H. Oncolytic adenovirus serotype 35 mediated tumor growth suppression *via* efficient activation of antitumor immunity. *J Immunother Cancer*. 2025 Jul 10;13(7):e006558. doi: 10.1136/jitc-2022-006558. PMID: 40639983; PMCID: PMC12258317.
6. Natsume-Kitatani Y, Kobiyama K, Igarashi Y, Aoshi T, Nakatsu N, Tripathi LP, Ito J, Nyström-Persson J, Kosugi Y, Allendes Osorio RS, Nagao C, Temizoz B, Kuroda E, Standley DM, Kiyono H, Nakanishi K, Uematsu S, Hamaguchi I, Yasutomi Y, Kunisawa J, Yamasaki S, Coban C, Yamada H, Mizuguchi K, Ishii KJ. An adjuvant database for preclinical evaluation of vaccines and immunotherapeutics. *Cell Chem Biol*. 2025 Aug 21; 32(8):1075-1088.e3. doi: 10.1016/j.chembiol. 2025. 07. 005.
7. Kaviani N, Kobiyama K, Ishii KJ, Coban C. Vaccine adjuvants as stand-alone immunoprophylaxis in strategies for 100-day rapid responses to future pandemics. *Int Immunol*. 2025 Aug 30:dxaf053. doi: 10.1093/intimm/dxaf053. Epub ahead of print. PMID: 40884464.
8. Mohri Y, Nie J, Morinaga H, Kato T, Aoto T, Yamanashi T, Nanba D, Matsumura H, Kirino S, Kobiyama K, Ishii KJ, Hayashi M, Suzuki T, Namiki T, Seita J, Nishimura EK. Antagonistic stem cell fates under stress govern decisions between hair greying and melanoma. *Nat Cell Biol*. 2025 Oct;27(10):1647-1659. doi: 10.1038/s41556-025-01769-9. Epub 2025 Oct 6. PMID: 41053225.
9. Hirayama T, Konaka H, Kato Y, Shibahara T, Nishizawa C, Tsujimoto K, Park J, Itotagawa E, Jo T, Nishide M, Nishida S, Shima Y, Narazaki M, Aoki W, Ishii KJ, Takamatsu H, Kumanogoh A. Identification of histone deacetylase inhibitor targeting type I interferon and B-cell abnormalities in systemic lupus erythematosus. *Arthritis Rheumatol*. 2025 Nov 14. doi: 10.1002/art.43434. Epub ahead of print. PMID: 41235819.
10. Kusaka M, Sakamoto K, Ikeyama Y, Kondo Y, Hayashi T, Ando A, Mori Y, Sato T, Matsushima M, Suzuki A, Fujita S, Shiraki Y, Kawabe T, Enomoto A, Ishii KJ, Hashimoto N, Ishii M. NOX2-Dependent Phagocyte Signaling Mediates Sili-

- ca-Induced Murine Lung Injury via Macrophage-Neutrophil Interactions. *Inflammation*. 2025 Dec 17;49(1):3. doi: 10.1007/s10753-025-02389-z. PMID: 41402658; PMCID: PMC12708739.
11. Nakayama T, Iwanami M, Sakakibara S, Mukasa R, Ota A, Furihata K, Honda Y, Ishii KJ. Immunogenicity, safety, and tolerability of a β -glucan-CpG-adjuvanted respiratory syncytial virus vaccine in Japanese healthy participants aged 60 to 80 years: A phase 2, randomized, double-blind, dose-finding study. *Hum Vaccin Immunother*. 2025 Dec;21(1):2489900. doi: 10.1080/ 21645515. 2025. 2489900.
12. Adachi T, Matsushita K, Yasuda K, Nakahira M, Imasaka M, Sugimoto M, Yang Z, Kobiyama K, Hayashi T, Ishii KJ, Yoshioka Y, Ohmuraya M, Shirasaki Y, Kuroda E. Resident alveolar macrophages are highly susceptible to the induction of RIPK1/RIPK3-mediated necroptosis which promote efficient pulmonary immune response. *Cell Death Dis*. 2025 Dec 22;16(1):919. doi: 10.1038/s41419-025-08372-8. PMID: 41429777; PMCID: PMC12749839.