Human Genome Center

Division of Metagenome Medicine
メタゲノム医学分野

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Abnormal compositions of the intestinal microbiota have been reported to be associated with a wide range of diseases. Our division analyzes both the intestinal bacteriome and virome across diverse pathological conditions to identify disease-associated pathobionts. By leveraging advanced bioinformatics approaches, we are constructing comprehensive analytical pipelines for microbiome research, conducting large-scale metagenomic analyses, and developing phage-based therapeutic strategies for the targeted control of pathobionts.

1. Development of a Novel Therapeutic Agent for GVHD

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Recent advances in genome analysis technologies have revealed that dysbiosis is implicated in a variety of diseases. In the context of hematopoietic stem cell transplantation, immune cells derived from donor stem cells may attack host tissues, resulting in graft-versus-host disease (GVHD). Previous studies have reported that GVHD is exacerbated by intestinal dysbiosis, particularly by an increase in Enterococcus species during treatment. We conducted metagenomic analyses of fecal samples from 46 allogeneic hematopoietic stem cell transplant patients at Osaka Metropolitan University Hospital. We identified not only an increase in *Enterococcus spp*. in 30 of the 46 patients, but also the presence of highly virulent Enterococcus faecalis strains associated with GVHD development. During transplantation, antimicrobial agents are routinely administered to prevent infection; however, we found that highly virulent *E. faecalis* evades antimicrobial pressure by forming biofilms in the intestinal tract, enabling its proliferation. Using gnotobiotic mouse models colonized with these virulent *E. faecalis* strains, we confirmed exacerbation of GVHD. We subsequently performed metagenomic analyses to identify bacteriolytic enzymes that specifically target *E. faecalis*. This effort led to the identification and synthesis of a novel endolysin that efficiently lyses *E. faecalis* and disrupts its biofilms both in vitro and in vivo. Oral administration of this endolysin to GVHD model mice significantly suppressed disease progression and improved survival. We are currently developing this endolysin as an oral therapeutic agent for GVHD, with ongoing efforts to improve its stability and pharmacokinetic properties.

2. Development of a Microbiome Digital Twin to Predict Disease States

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In collaboration with Fujitsu Limited, we are developing an AI-based digital twin capable of predicting disease states using intestinal microbiota metagenomic data and gene pathway analysis data as training datasets. We collected fecal samples from 10 patients with Crohn's disease and 18 patients with Parkinson's disease and performed comprehensive metagenomic analyses. These datasets were compared with metagenomic data from 100 healthy individuals. Beyond species-level compositional analyses, we visualized gene pathway analysis results and applied machine learning techniques. We further incorporated large-scale metagenomic datasets comprising several hundred patients with Crohn's disease and Parkinson's disease from the United States to refine and tune the prototype digital twin. Currently, we are validating the physiological relevance of characteristic pathway modules extracted by the digital twin, using generative AI to support efficient biological interpretation.

3. Development of Next-Generation Phage Therapy Against Multidrug-Resistant *Acinetobacter baumannii*

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Gram-positive bacteria possess a thick peptidoglycan layer that can be targeted by extracellularly administered endolysins. In contrast, Gram-negative bacteria are protected by an outer membrane composed of lipopolysaccharide (LPS), rendering them largely resistant to conventional endolysin-based approaches. Among these pathogens, *Acinetobacter baumannii* is particularly problematic due to its exceptional capacity to acquire antimicrobial resistance and its global impact as a major cause of nosocomial infections. In this project, we aim to comprehensively identify and characterize novel phage-derived enzymes capable of degrading the LPS layer of *A. baumannii*. By leveraging intestinal virome genome analyses and large-scale metagenomic databases, we seek to develop novel antimicrobial agents and to establish a comprehensive catalog of phage-derived enzymes targeting Gram-negative bacteria. This work aims to provide a breakthrough in phage-based therapeutic strategies against multidrug-resistant Gram-negative pathogens.

4. Establishment of Next-Generation Phage Therapy for Lifestyle-Related Diseases Associated with Chronic Dysbiosis

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Recent studies have demonstrated that intestinal overgrowth of *Thomasclavelia ramosa*, a Gram-positive bacterium, is associated with lifestyle-related diseases such as obesity and type 2 diabetes. Our research group previously generated gnotobiotic mouse models by transplanting fecal samples from obese individuals harboring *T. ramosa*, successfully recapitulating its intestinal expansion under a high-fat diet. Furthermore, oral immunization with a mucosal vaccine using freeze-dried *T. ramosa* cells as antigens induced *T. ramosa*-specific secretory IgA in the gut, resulting in reduced bacterial abundance and suppression of body weight gain and hyperglycemia. Building on these findings, we aim to elucidate the pathogenic mechanisms of *T. ramosa* and to develop *T. ramosa*-specific endolysins in combination with metabolic inhibitors. Unlike GVHD, which resembles an acute infectious process, *T. ramosa* is a commensal bacterium adapted to chronic dysbiosis, making eradication by endolysins alone challenging. We will therefore identify essential metabolic pathways through genomic and functional analyses and develop synergistic eradication strategies targeting both bacterial viability and metabolic dependence.

5. Development of Next-Generation Mucosal Vaccines Against Infectious Diseases

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There is a strong demand for next-generation vaccines capable of inducing both systemic and mucosal immunity. We previously demonstrated that intramuscular vaccination with CpG oligodeoxynucleotides and curdlan as adjuvants induces robust systemic antigen-specific IgG and IgA responses. Subsequent antigen boosting at target mucosal sites elicited high and long-lasting mucosal IgA responses and helper T-cell responses, including Th1 and Th17, effectively protecting against Streptococcus pneumoniae infection in mice. This vaccine strategy has been patented in Japan (2019), the United States (2020), and Europe (2021). We have further evaluated this approach using PspA, a universal pneumococcal anti-

gen, in both mice and cynomolgus macaques. Prime-boost immunization induced strong antigen-specific IgG in serum and IgA in bronchoalveolar lavage fluid, resulting in effective protection against pneumococcal infection. Based on these findings, we aim to develop novel emulsion-based adjuvants optimized for primates to further enhance mucosal IgA induction and advance this platform toward clinical application.

Publications

- 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.
- Otani K, Nakatsu G, Fujimoto K, Miyaoka D, Sato N, Nadatani Y, Nishida Y, Maruyama H, Ominami M, Fukunaga S, Hosomi S, Tanaka F, Imoto S, Uematsu S, Watanabe T, Fujiwara Y. Development of gastric mucosa-associated microbiota in autoimmune gastritis with neuroendocrine tumors. ***J Gastroenterol.*** 2025 Dec;60(12):1481-1495. doi: 10.1007/s00535-025-02298-w.