Department of Microbiology and Immunology

Division of Vaccine Science
ワクチン科学分野

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***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 immuno-preventive and/or therapeutic agents against infectious diseases, cancer and allergy as well as other non-communicable diseases.*

The development of vaccines for COVID-19 (LNP-mRNA, Protein+adjuvant)

Supported by AMED, we contributed to the development of the firs LNP-mRNA vaccine in Japan by Daiichi Sankyo (DS-5670) and the first adjuvanted recombinant protein based vaccine by Shionogi Pharma (S-268019) against SARS-CoV2 virus approved in 2023 and 2024 respectively. doi: 10.1038/s41598-024-57308-3 doi: 10.1126/science.adh0968,

Innovative vaccine evaluation system for 100 days mission

Supported by AMED SCARDA, 2022-, our lab leads the project of the tile above with our colleagues in IMSUT, National Institute of Infectious Diseases (NIID) and National Institute of Biomedical Innovation, Health and Nutrition (NIBIOHN). The purpose of this research is to establish an innovative vaccine evaluation system to provide vaccines to the world in 100 days in the next outbreak, epidemic, or pandemic of infectious diseases. The pandemic of the new coronavirus showed the aspect of a simultaneous worldwide disaster and revealed the importance of global health coverage through international collaboration as well as the importance and urgency of research on vaccine development in one's own country. The G7 countries have set a goal to provide vaccines within the next 100 days. In Japan, the proposal for this research on infectious diseases, immunological research, and animal studies calls for the participation of Japan's top research institutes and their collaboration with CROs in order to ignite an innovation in non-clinical studies for vaccine R&D in Japan. With the ultimate goal of providing vaccines in 100 days, researchers in the four essential areas of pathogen research, infection immunology research, vaccine design research, and animal model research will work together in an organic manner at all times to achieve the ultimate goal of providing vaccines in 100 days. The team of researchers in the four essential areas of pathogen research, infection immunity research, vaccine design research, and animal model research will be organically integrated at all times during normal times, and an implementation system will be established to enable seamless, rapid, accurate, and high-level preclinical drug efficacy testing (humoral and cellular immunity) in the event of an emergency. https://www.amed.go.jp/content/000136233.pdf

5,6-dimethylxanthenone-4-acetic acid (DMXAA), a partial STING agonist, competes for human STING activation

5,6-dimethylxanthenone-4-acetic acid (DMXAA) is a mouse-selective stimulator of interferon gene (STING) agonist exerting STING-dependent anti-tumor activity. Although DMXAA cannot fully activate human STING, DMXAA reached phase III in lung cancer clinical trials. How DMXAA is effective against human lung cancer is completely unknown. Here, we show that DMXAA is a partial STING agonist interfering with agonistic STING activation, which may explain its partial anti-tumor effect observed in humans, as STING was reported to be pro-tumorigenic for lung cancer cells with low antigenicity. Furthermore, we developed a DMXAA derivative-3-hydroxy-5-(4-hydroxybenzyl)-4-methyl-9H-xanthen-9-one (HHMX)-that can potently antagonize STING-mediated immune responses both in humans and mice. Notably, HHMX suppressed aberrant responses induced by STING gain-of-function mutations causing STING-associated vasculopathy with onset in infancy (SAVI) in in vitro experiments. Furthermore, HHMX treatment suppressed aberrant STING pathway activity in peripheral blood mononuclear cells from SAVI patients. Lastly, HHMX showed a potent therapeutic effect in SAVI mouse model by mitigating disease progression. Thus, HHMX offers therapeutic potential for STING-associated autoinflammatory diseases. doi: 10.3389/fimmu.2024.1353336.

Tridecylcyclohexane in incomplete Freund's adjuvant (IFA) is a critical component in inducing experimental autoimmune diseases.

Incomplete Freund's adjuvant (IFA) has been used for many years to induce autoimmune diseases in animal models, including experimental autoimmune encephalitis and collagen-induced arthritis. However, it remains unclear why it is necessary to emulsify autoantigen and heat-killed Mycobacterium tuberculosis (HKMtb) with IFA to induce experimental autoimmune diseases. Here, we found that immunization with self-antigen and HKMtb was insufficient to induce autoimmune diseases in mice. Furthermore, IFA or one of its components, mineral oil, but not mannide monooleate, was required for the development of experimental autoimmune disease. Immunization with autoantigen and HKMtb emulsified in mineral oil facilitated innate immune activation and promoted the differentiation of pathogenic $CD4^+$ T cells, followed by their accumulation in neuronal tissues. Several water-soluble hydrocarbon compounds were identified in mineral oil. Of these, immunization with HKMtb and autoantigen emulsified with the same amount of hexadecane or tridecylcyclohexane as mineral oil induced the development of experimental autoimmune encephalitis. In contrast, immunization with HKMtb and autoantigen emulsified with tridecylcyclohexane, but not hexadecane, at doses equivalent to those found in mineral oil, resulted in neuronal dysfunction. These data indicate that tridecylcyclohexane in mineral oil is a critical component in the induction of experimental autoimmune disease. doi: 10.1002/eji.202350957

Publication

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