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

A squalene-based emulsion adjuvant, induces T follicular helper cells and humoral immune responses via α-tocopherol component

Adjuvants are chemical or biological materials that enhance the efficacy of vaccines. A-910823 is a squalene-based emulsion adjuvant used for S-268019-b, a novel vaccine against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that is currently in clinical development. Published evidence has demonstrated that A-910823 can enhance the induction of neutralizing antibodies against SARS-CoV-2 in humans and animal models. However, the characteristics and mechanisms of the immune responses induced by A-910823 are not yet known. To characterize A-910823, we compared the adaptive immune response profile enhanced by A-910823 with that of other adjuvants (AddaVax, QS21, aluminum salt-based adjuvants, and empty lipid nanoparticle [eLNP]) in a murine model. Compared with other adjuvants, A-910823 enhanced humoral immune responses to an equal or greater extent following potent T follicular helper (Tfh) and germinal center B (GCB) cell induction, without inducing a strong systemic inflammatory cytokine response. Furthermore, S-268019-b containing A-910823 adjuvant produced similar results even when given as a booster dose following primary administration of a lipid nanoparticle-encapsulated messenger RNA (mRNA-LNP) vaccine. Preparation of modified A-910823 adjuvants to identify which components of A-910823 play a role in driving the adjuvant effect and detailed evaluation of the immunological characteristics induced by each adjuvant showed that the induction of humoral immunity and Tfh and GCB cell induction in A-910823 were dependent on α-tocopherol. Finally, we revealed that the recruitment of inflammatory cells to the draining lymph nodes and induction of serum cytokines and chemokines by A-910823 were also dependent on the α-tocopherol component. This study demonstrates that the novel adjuvant A-910823 is capable of robust Tfh cell induction and humoral immune responses, even when given as a booster dose. The findings also emphasize that α-tocopherol drives the potent Tfh-inducing adjuvant function of A-910823. Overall, our data provide key information that may inform the future production of improved adjuvants.

Dendritic cell proliferation by primary cilium in atopic dermatitis

Atopic dermatitis (AD) is a common allergic ecze-

ma that affects up to 10% of adults in developed countries. Immune cells in the epidermis, namely, Langerhans cells (LCs), contribute to the pathogenesis of AD, although their exact role(s) in disease remain unclear. We performed immunostaining on human skin and peripheral blood mononuclear cells (PBMCs) and visualized primary cilium. Result and discussion: We show that human dendritic cells (DCs) and LCs have a previously unknown primary cilium-like structure. The primary cilium was assembled during DC proliferation in response to the Th2 cytokine GM-CSF, and its formation was halted by DC maturation agents. This suggests that the role of primary cilium is to transduce proliferation signaling. The platelet-derived growth factor receptor alpha (PDGFRα) pathway, which is known for transducing proliferation signals in the primary cilium, promoted DC proliferation in a manner dependent on the intraflagellar transport (IFT) system. We also examined the epidermal samples from AD patients, and observed aberrantly ciliated LCs and keratinocytes in immature and proliferating states. Our results identify a potential relationship between the primary cilium and allergic skin barrier disorders, and suggest that targeting the primary cilium may contribute to treating AD.

Challenges in developing personalized neoantigen cancer vaccines

The recent success of cancer immunotherapies has highlighted the benefit of harnessing the immune system for cancer treatment. Vaccines have a long history of promoting immunity to pathogens and, consequently, vaccines targeting cancer neoantigens have been championed as a tool to direct and amplify immune responses against tumours while sparing healthy tissue. In recent years, extensive preclinical research and more than one hundred clinical trials have tested different strategies of neoantigen discovery and vaccine formulations. However, despite the enthusiasm for neoantigen vaccines, proof of unequivocal efficacy has remained beyond reach for the majority of clinical trials. In this Review, we focus on the key obstacles pertaining to vaccine design and tumour environment that remain to be overcome in order to unleash the true potential of neoantigen vaccines in cancer therapy.

The 100 Days Mission: how a new medical-countermeasures network can deliver equity and innovation

As shown during the response to COVID-19, the faster we can develop safe, effective and affordable vaccines, therapeutics and diagnostics for an escalating infectious disease, the more lives we can save. As the scientific advisory member for CEPI as well as IPPS and STEG for G7, Ken Ishii is committed to contribute to the 100 days mission. The goal of the 100 Days Mission is to prepare as much as possible so that within the first 100 days that a pandemic threat is identified, the following interventions can be made available, safe, effective, and affordable:

Accurate and approved rapid point of care diagnostic tests
An initial regimen of therapeutics
Vaccines ready to be produced at scale for global deployment

In June 2021, G7 Leaders welcomed the "100 Days Mission'' (100DM) in Carbis Bay, building on the collaborative scientific efforts which led to the development of Diagnostics, Therapeutics, and Vaccines (DTVs) for COVID-19. The 1st 100 Day mission report was authored by scientific, governmental and industry experts drawn from within and beyond the G7. It proposed 25 recommendations to harness scientific innovation and strengthen public and private collaboration that will reduce the time from discovery to deployment of DTVs within 100 days of the next pandemic threat.

In order to deliver on these ambitions, G7 scientific advisers called for the establishment of an International Pandemic Preparedness Secretariat ('the Secretariat') to support implementation and catalyse scientific exchange on the progress of the 100DM.

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