International Vaccine Design Center

Division of Mucosal Vaccines (New Dimensional Vaccine Design Team)
新次元ワクチンデザイン系・粘膜ワクチン分野

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To explore new avenues for mucosal vaccine development and immune-regulation, investigators have begun to employ novel adjuvants and targeting mucosal tissues and immune cells for vaccine delivery and elucidate the mechanisms of immune-regulation in the mucosal tissues. Despite recent advanced sciences, it remains to develop effective mucosal vaccines for human use. To this end, our main task is to define the effectiveness and safety of novel mucosal vaccines including adjuvant- and delivery system-development, and bring them from bench-top to practical applications.

1. Novel mucosal vaccine development for the induction of mucosal immunity in the aero-, digestive- and reproductive mucosa.

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It has been shown that oral antigen (Ag) plus adjuvant delivery for induction of immunity, as opposed to nasal delivery, is an effective non-invasive route. Further, it is well-tolerated and avoids the possibility of Ag and /or adjuvant uptake into the olfactory tissues with subsequent entry into the central nervous system (CNS). However, oral vaccines require relatively large amounts of Ag and adjuvant and are exposed to the proteolytic enzymes and lower pH of the stomach. Considerably, their efficacy limits the mainly gastrointestinal mucosa. In this regard, it is essential to develop a new generation of oral adjuvants which elicit mucosal immunity in the entire mucosal surfaces including respiratory and reproductive tracts. In order to accomplish this goal, we planned to discover novel molecules which could use

potential oral adjuvant for inducing global protective mucosal immunity by using a single-cell mRNA sequencing approach. We have successfully established several DNA libraries from nasopharyngeal-associated lymphoid tissues and Peyer's patches of naïve mice as well as mice given either oral or nasal vaccine. The sequence data have been analyzed using SHIROKANE supercomputer system and we have identified several unique molecules which preferentially upregulated in the NALT of mice given nasal vaccine when compared with those in Peyer's patches of mice given an oral vaccine. Our results showed that one of these molecules is indeed up-regulated in NALT and the reproductive tract. We showed that mice deficient with this molecule resulted in reduced levels of antigen-specific IgA antibody responses in the vaginal washes despite intact levels of serum IgG titers. Further, we are currently confirming these results at the cellular level. When we have assessed chemokine receptor expression which involved for the regulation of antigen-specific IgA responses, none of these receptors are essential for the regulation of mucosal IgA antibody responses.

2. Cationic-nanogel nasal vaccine containing the ectodomain of RSV-small hydrophobic protein induces protective immunity in rodents

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Respiratory syncytial virus (RSV) is a leading cause of upper and lower respiratory tract infection, especially in children and the elderly. Various vaccines containing the major transmembrane surface proteins of RSV (proteins F and G) have been tested; however, they either afford inadequate protection or are associated with the risk of vaccine-enhanced disease (VED). Here, we examined the potential of using the ectodomain of small hydrophobic protein (SHe), also an RSV transmembrane surface protein, as a nasal vaccine antigen. A vaccine was formulated using our previously developed cationic cholesteryl-group-bearing pullulan nanogel as the delivery system, and SHe was linked in triplicate to pneumococcal surface protein A as a carrier protein. Nasal immunization of mice and rats induced both SHe-specific serum IgG and mucosal IgA antibodies, preventing viral invasion in both the upper and lower respiratory tracts without inducing VED. Moreover, nasal immunization induced greater protective immunity against RSV in the upper respiratory tract than did systemic immunization, suggesting a critical role for mucosal RSV-specific IgA responses in viral elimination at the airway epithelium. Thus, our nasal vaccine induced effective protection against RSV infection in the airway mucosa and is therefore a promising vaccine candidate for further development.

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