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Efficient, adjuvant-free mucosal vaccination via IgA feedback loop

Keywords: mucosal vaccination, vaccine conjugate, IgA binder, IgA feedback loop, retro-transcytosis, adjuvant-free, infection, cancer

INVENTION NOVELTY

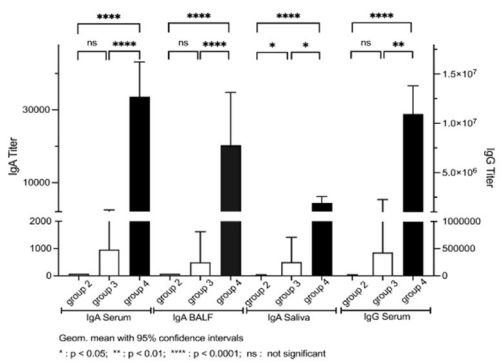
The human body is constantly exposed to a myriad of pathogens and toxins, with the mucosa of the skin, respiratory system, and intestinal tract serving as the primary interface between the environment and the body's sterile interior. This barrier, spanning several hundred square meters, is the first line of defense against most potential threats. Thus, inducing immune responses directly in the mucosa would offer several advantages over conventional vaccination strategies. However, the epithelium is naturally designed to prevent foreign substances from entering, making it difficult for vaccines to activate the mucosal immune cells situated behind this barrier. Despite numerous strategies developed to overcome these challenges, the clinical application of mucosal vaccines remains limited due to their restricted efficacy, the necessity for repeated vaccinations, and the use of strong, potentially harmful adjuvants. The present invention exploits the natural IgA feedback loop to transport an antigen-containing vaccine conjugate without adjuvant through the epithelium to the mucosal immune cell, where it elicits a strong IgA response.

VALUE PROPOSITION

The invention provides a platform technology that can be easily adapted for vaccination against different pathogens or cancers. It effectively addresses the challenges associated with current mucosal vaccination methods by utilizing the natural IgA feedback loop for transepithelial transport. It eliminates the need for costly recombinant IgA by utilizing a small IgA-binder, and does not require an adjuvant, thereby avoiding issues such as toxicity, unspecific induction of immune responses, and adverse reactions.

TECHNOLOGY DESCRIPTION

The IgA feedback loop is a natural regulatory mechanism of the mucosal immune system, whereby a portion of sIgAs patrolling the lumen is continually re-internalized by retro-transcytosis through the epithelium to the submucosal lymphatic tissue. If these sIgAs are loaded with an antigen, they are recognized as an immunostimulatory signal, leading to the production of further sIgAs and IgGs against the antigen. Previous mucosal vaccination methods that exploited retro-transcytosis have relied on externally produced sIgAs, which are effective on a small scale but cost-prohibitive on a larger scale. The present invention leverages the vast pool of naturally occurring sIgAs present in the mucosa by utilizing a vaccine conjugate consisting of an IgA-binder and the antigen of choice. The IgA-binder can be either an antigen against which most (if not all) individuals have sIgAs (e.g., SARS-CoV2 spike protein), or a universal IgA-binder that recognizes the IgAs' conserved Fc-portion. The former approach offers high affinity and specificity, while the latter approach may have weaker and less specific binding but utilizes the entire pool of sIgAs present.



Mucosal/nasal vaccination against SARS-CoV2 spike protein in mice. *IgA und IgG titer in saliva, BALF and serum; group 2: control; group 3: OVA-SARS conjugate w/ adjuvant and w/o pre-exiting OVA immunity; group 4: OVA-SARS conjugate w/o adjuvant and w/ pre-exiting OVA immunity (Frey et al., unpublished).*

Upon binding of the vaccine conjugate to the sIgAs, a portion of the newly formed sIgA::vaccine complex is transported to the mucosal immune cells, where it triggers a robust immune response against the antigen of interest. *In vivo* proof of concept has been demonstrated in mice vaccinated against the SARS-CoV2 spike protein (alpha vs. omicron). In both cases, the highest IgA and IgG titers were found in saliva, BALF, and serum (refer to Fig.). Notably, the IgA and IgG titers achieved with the present invention were consistently higher than those achieved with a standard protocol that employs an adjuvant.

DEVELOPMENT STATUS

The practicability of the novel mucosal vaccination strategy was demonstrated *in vivo*, and some universal IgA-binding peptides have been developed. Further studies are underway to proof the concept and the universality of the approach.

COMMERCIAL OPPORTUNITY

The innovative mucosal vaccination system is available for in-licensing.

PATENT SITUATION

The European priority patent application EP23213600.2 was recently filed.

FURTHER READING

Frey et al. (2024) Manuscript in preparation.

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