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Development of respiratory syncytial virus vaccine using HBc virus-like-particles to induce mucosal immunity

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Background: Respiratory syncytial virus (RSV) is recognized as one of the most important viral pathogens leading to severe lower respiratory tract diseases and it causes an estimated 33.8 million RSV infections, resulting in 160,000 to 199,000 deaths per year worldwide. Currently there is no safe vaccine in clinical use. One of the most important factors for the development of RSV vaccine is the induction of Th1-biased immune response.

Material/methods: Using optimal codons for *Escherichia coli* expression, we have successfully constructed and expressed HBc virus-like particles (VLPs) and heptad region of RSV fusion protein containing antigenic site Ø, 2 and 4 (HRØ24). Intranasal immunisations have been applied in C57BL/6 mice to test the immunity of the vaccine candidates. In order to enhance the immunity of the vaccine candidates, CpG adjuvant has been investigated.

Results: Our results showed that HBc VLPs mix with HRØ24 is able to induce serum total IgG, IgG1 and IgG2a against HRØ24, RSV site Ø and RSV site 2. Bronchoalveolar lavage fluid (BALF) from immunised mice also showed significant higher HRØ24-specific secretory IgA. The effect of using CpG as mucosal adjuvants is not significant. The results from splenocytes re-stimulation indicated that the immune response induced by HBc VLPs/ HRØ24 mixture is Th1 biased. Challenge results showed significantly lower lung viral load from mice immunized with HRØ24/HBc mixture and suggest that this vaccine candidate provides a better protection to prevent mouse weight lost and RSV-induced illness.

Conclusions: Taken together, results in this study suggest that uniquely combined HBc VLPs/ HRØ24 mixture can induce both systemic and mucosal antibody responses specific for RSV. Mice immunized with HBc VLPs/ HRØ24 mixture showed protection against RSV without causing lung disease. HBc VLPs/ HRØ24 mixture did not over stimulating lymphocytes compared to FIRSV in a

mouse model and offer as a potential safe RSV vaccine candidate. Further studies will test the immune responses of our vaccine candidates in cotton rat model which is 100-fold more permissive to infection with RSV. Sequential immunization studies will be included for the possibility to improve our current dosing regimen. Innate lymphoid cell will be analyzed to determine the HBc adjuvant effects.

Key words:RSV, mucosal immunity, virus-like particle, HBc antigen, adjuvant