Polyanhydride nanovaccine and cyclic dinucleotide based formulations stimulate innate immunity and modulate immune response


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Statement of Purpose: Yersinia pestis, the causative agent of plague-related diseases, due to its ease of spread through aerosolized droplets and the ability to easily introduce antibiotic resistance, is considered to have the potential to be used as a biological weapon. Despite this, and the fact that plague is still endemic in many regions globally, no commercial vaccine against Y. pestis is available. A polyanhydride nanovaccine based on F1-V, an F1 and LcrV fusion protein, has recently been demonstrated to provide protective immunity against lethal challenge with pneumonic plague. This nanovaccine formulation provided 100% protection against challenge with CO92 Y. pestis, with both soluble protein alone and protein adjuvanted with MPLA failing to elicit a protective immune response. These results suggest the potential for an efficacious single dose vaccine against Y. pestis.

In order to elicit protective immunity at very early time points after administration, a vaccine formulation must effectively engage innate immune mechanisms as well as develop a potent adaptive immune response. Cyclic dinucleotides (CDNs), which are bacterial second messengers based on DNA nucleotides, have been shown to stimulate the innate immune system through interactions with STING, which induces the expression of type 1 interferons. Herein, these molecules are utilized to elicit a rapid induction of the immune response after vaccination.

Methods:
A 5 µg dose of F1-V was tested by subcutaneously administering nanovaccine formulations consisting of 2.5 µg F1-V encapsulated into polyanhydride nanoparticles at a 0.5% loading delivered with 2.5 µg of soluble F1-V plus CDNs. Antibody titers were measured weekly through five weeks and protective immunity at extended time points was investigated through immunization and challenge with a lethal dose of CO92 Y. pestis at six weeks post-immunization.

Results:
We have demonstrated that through the addition of CDNs to the polyanhydride nanovaccine formulation, the innate immune response can be stimulated and high titers can be elicited at early time points (Figure 1).

Additionally, we demonstrate a shift of the immune response from IgG1-dominated phenotype to a balanced IgG1/IgG2 immune response with the addition of CDNs to the nanovaccine formulation (Figure 2).

Conclusions:
Herein we demonstrated the modulation of the immune response at early time points after administration of cyclic dinucleotides to stimulate the innate immunity and shape the antibody response and isotype profile. We conclude that the addition to CDNs to nanovaccine formulations leads to the development of robust antibody responses at early time points after administration and a balanced immune response., both of which are beneficial for efficacious vaccine development against plague.

References: