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Engineering Virus Like Particles Towards Directing Immunologic Responses

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**Engineering Virus Like Particles Towards Directing Immunologic Responses**

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**Introduction**

Virus like particles (VLPs) present a rich biomaterial architecture and platform for displaying antigens in a spatially controlled manner, either on the exterior and/or on the interior, which could be exploited to direct specific immune response pathways. The VLP derived from Salmonella typhimurium bacteriophage P22 has been shown to be a versatile platform for the incorporation of proteins on the VLP interior. Heterologous co-expression of a protein or peptide cargo of choice fused to the P22 scaffolding protein (SP) with P22 coat protein leads to assembly of the P22 VLP with the Cargo Protein-SF fusion protein incorporated on the interior. Utilizing this approach P22 VLPs containing the conserved nucleoprotein (NP) from influenza on the interior, in a biomimetic fashion, were shown to elicit a broadly protective CD8+ T cell response to influenza that provided multi-strain protection against 100 times lethal doses of influenza. These results provide strong evidence for utilizing our biomimetic approach, which is amendable to the quick production of vaccines to rapidly emerging pathogens. Investigations into a modular approach for attaching antigenic proteins to exterior of the P22 VLP, allowing display of antigens on the exterior or P22, is described. For proof of concept, green fluorescent protein (GFP) was utilized as a model protein for examining attachment of proteins to the exterior of the P22 VLP via sortase-mediated ligation. Results show that GFP can be effectively attached to the surface of P22, paving the way for attachment of other proteins, including antigenic proteins from pathogens. The ability to display antigens on the outside has the potential to activate alternate immunologic pathways, such as production of neutralizing antibodies that prevent pathogen infections. Tailoring the display of antigens has the potential to allow control over directing the specific immune pathway activated and responses generated.

**Biomimetic Display of Influenza Nucleoprotein**

- Biomimetic display of nucleoprotein (NP, green) within P22 is expected to generate a broadly protective CD8+ T cell response.
- Constructs containing full length NP were constructed by in vivo expression in E. coli (TEM image).
- SDS-PAGE, TEM, and size exclusion chromatography verified NP incorporation and homogeneous particle formation with high internal packaging of 145 copies of NP per capsid.

**Protection Generated Against Influenza by NP-P22 is NP-Specific**

- NP-P22 generates multi-serotype protection in mice treated with high doses (50 times lethal doses) of H1N1 (PR8) and H3N2 (X31).
- Weight data shows recovery by influenza infected mice immunized with NP-P22.
- TBE210 CD8+ T cell depletion combined with MHC I tetramer staining of CD8+ T cells indicate response is CD8+ dependent and NP specific.

**Future Directions**

- Further evaluate P22-GFP VLP materials constructed.
- Use sortase method to incorporate influenza antigen on exterior to provide broadly protective neutralizing antibody response.
- Explore how antigen display on interior vs. exterior modulates the response generated to antigens.

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