Vaccines that Induce Broadly Neutralizing Antibodies against Human Papillomaviruses

Project #2
Bryce Chackerian, Ph.D. - Leader
Virus-like Particles (VLPs) are composed of viral coat proteins that, when overexpressed, spontaneously self-assemble into particles that are indistinguishable from infectious virus.

- VLPs can be derived from diverse virus types as highly effective vaccines against the virus from which they are derived.
- The dense, repetitive structure of VLPs confers high immunogenicity.
- VLPs can also be used as platforms for display of heterologous antigens.
- VLP display is so immunogenic it effectively targets self-antigens.
- We have used this strategy to induce high titer antibody responses against a wide variety of targets, including:
  - Short peptides, Full-length proteins, Glycans.
Displaying heterologous antigens on VLPs

Using VLPs derived from bacteriophage (MS2, Qβ, and PP7), we have developed a suite of technologies targeting diverse pathogens and self-antigen targets.

1) **Chemical Conjugation** of target antigens to the surface of preformed Qβ VLPs.
   - TNF-alpha (J Clinical Invest 2002)

2) **Genetic Insertion** of target peptides onto the surface of MS2 and PP7 VLPs
   - CCR5 (J Mol Biol 2008)
   - HPV L2 (unpublished data)

3) **Affinity Selection** of specific VLPs from a library of VLPs that display random peptides (i.e. phage display on VLPs).
   - HIV gp41 (funding from the Gates Foundation)
   - Anthrax Protective Antigen (unpublished data)
CENTRAL HYPOTHESIS: Current HPV vaccines only provide protection against 2 of at least 15 carcinogenic HPV genotypes. HPV L2 minor capsid protein contains inter-typic cross neutralizing epitopes for which immunogenicity can be enhanced using VLP-display technology

**AIM 1:** Rational design of peptide-displaying VLP-based vaccines targeting L2 neutralizing epitopes

**AIM 2:** Identification of novel candidate vaccines by genetic display of L2 epitopes on VLPs

**AIM 3:** Induction of mucosal and systemic immune responses against HPV vaccines – evaluation of aerosol delivery systems
Results Project #2
PP7 VLPs displaying a 16 aa epitope derived from HPV 16 L2

Mice immunized with:

L2 antibody responses

Serum Dilution (1:x)

OD 405
In Vivo Protection from Homologous and Heterologous Challenge with HPV Pseudovirus

In vivo challenge in collaboration with John Schiller’s laboratory, NCI
Project #2 Directions and Opportunities for Collaboration

• Promising possibilities for short timeline to initiate partnered GLP manufacturing, pre-clinical studies and phase I trials for novel broadly protective HPV vaccine

• Our technology and rapid progress may enable inclusion of potential strategies for combined prophylactic (L2) and therapeutic HPV vaccine strategies (E1,E2,E4, E5,E6,E7) – coupling of genetic & conjugate methods

• Our technology can be used to enhance the immunogenicity of vaccine candidates for a variety of STIs

• Our VLP phage display technology can be used to identify potential vaccines by affinity selection using monoclonal antibodies with specific activities