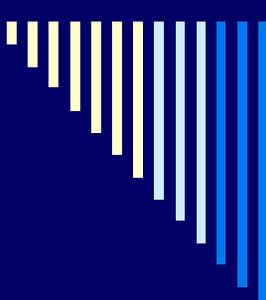


Human Papillomavirus Immunotherapy and the Vaccine Exemption Under *NIH Guidelines*

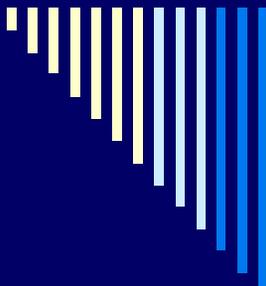
Recombinant DNA Advisory Committee
March 12, 2008





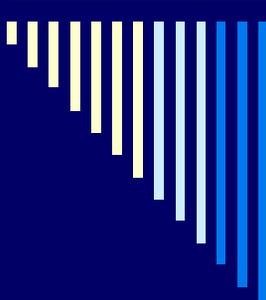
NIH Guidelines for Research Involving Recombinant DNA Molecules

- **Section M-VI-A** : Human studies in which induction or enhancement of an immune response to a vector encoded microbial immunogen is the major goal, such an immune response has been demonstrated in model systems, and the persistence of the vector-encoded immunogen is not expected, are exempt from **Appendix M-I, Requirements for Protocol Submission, Review and Reporting – Human Gene Transfer Experiments.**
-



History of Vaccine Exemption

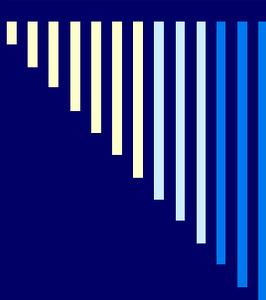
- Adopted in 1994.
 - Designed to foster the rapid development of vaccines against infectious agents with significant public health impact.
 - Adopted at a time when HIV was an emerging infection and concerns about speed of therapeutic options including vaccines was a public policy priority.
-



Examples of Studies that OBA has Determined Fall under Vaccine Exemption

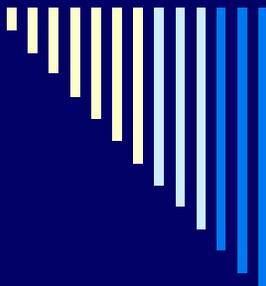
- *Phase I Study of the safety and Immunogenicity of rDEN3/4Δ30(ME), a Live Attenuated Virus Vaccine Candidate for the Prevention of Dengue Serotype 3*
 - attenuated virus
 - prevention of dengue infection

 - *A Phase I Clinical Trial to Evaluate the Safety and Immunogenicity of a Multiple Strain Ebola Plasmid Vaccine, VRC-EBODNA012-00-VP, in Adults Volunteers*
 - plasmid vector
 - prevention of infection by Ebola
-



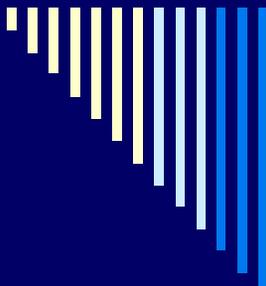
Examples of Studies that OBA has Determined Fall under Vaccine Exemption, cont...

- *A Phase I, Randomized, Double-Blind Study to Evaluate the Tolerability, Safety, and Immunogenicity of LC002, a DermaVir Vaccine, in HIV-1-Infected Subjects Currently Under Treatment with Highly Active Antiretroviral Therapy (HAART)*
 - plasmid vector
 - individuals infected with HIV
-



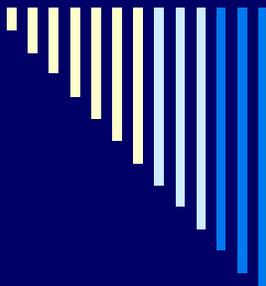
Human Papillomavirus Immunotherapy

- ❑ Transgene typically encodes polypeptides derived from the E6 and/or E7 genes of HPV strains 16 and/or 18.
- ❑ HPV 16 and 18 infection are responsible for the majority of cervical cancers worldwide
- ❑ The HPV transforming proteins, E6 and E7 have been shown to be the main contributors to the development of cancer of the cervix and cervical intraepithelial neoplasia (CIN)
- ❑ CIN 2 lesions may reveal low levels of E6 and E7 expression with replication episomally
- ❑ CIN 3 lesions (and invasive cancer) often display high levels expression of E6 and E7, more often with integration of viral DNA into the host genome



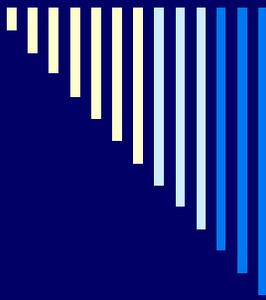
HPV Protocols Registered with OBA

- OBA 9904-307 A Phase I Trial of Immunotherapy with MVA-HPV-IL2 (TG4001) in Women with Cervical Intraepithelial Neoplasia (CIN) Grade 3.
 - ▣ Vector: Modified vaccinia Ankara poxvirus with mutation inactivated HPV 16 E6 cDNA and HPV E7 cDNA and interleukin 2 cDNA
 - ▣ Primary Endpoint: Evaluate safety and tolerability and MTD
 - ▣ Secondary Endpoint: Cellular and humoral response to E6/E7 and local immune response in dysplastic cervical tissues
 - ▣ Status: Completed
-



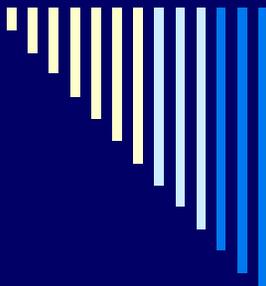
HPV Protocols Registered with OBA

- OBA 595:A Phase I/II Clinical Trial of pNGVL4a-Sig/E7(detox)/HSP70 for the Treatment of Patients with HPV16+ Cervical Intraepithelial Neoplasia 2/3 (CIN2/3)
 - Vector: DNA plasmid with HPV 16 E7 cDNA with 2 point mutation to generate non-functional protein
 - Primary Endpoint: Evaluate feasibility and toxicity of vaccine
 - Secondary Endpoint: Evaluate changes in lesion size, HPV viral load and cellular and humoral immune response to vaccine
 - Status: Ongoing



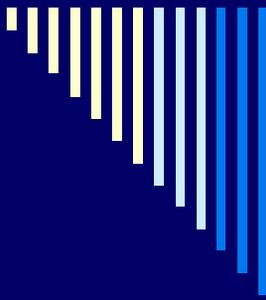
Protocols Registered with OBA

- OBA 592: A Phase I Study to Determine the Safety and Immunogenicity of Vaccination with *Listeria monocytogenes* Expressing Human Papilloma Virus type 16 E7 for the Treatment of Progressive, Recurrent and Advanced Squamous Cell Cancer of the Cervix
 - Vector: *Listeria monocytogenes* containing cDNA for HPV 16 E7
 - Study Population: Patients with progressive, recurrent or advanced SCC of cervix that is metastatic or unresectable
 - Primary endpoint: Safety and feasibility
 - Secondary endpoint: Type of immunity induced and relationship to the number of organisms delivered in the vaccine and to monitor for survival
 - Reviewed publicly by the RAC in December 2003
-



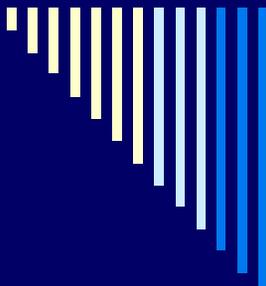
Goals of the HPV Vaccine in Subjects with Cervical Dysplasia

- ❑ Generation of immune response to treat dysplastic, precancerous lesions
 - ❑ Subjects are only eligible if they have cervical Intraepithelial Neoplasia 2/3 (CIN2/3) lesions
 - ❑ In addition to safety and tolerability, efficacy to be measured by regression of these precancerous lesions
 - ❑ Potential alternative to surgical excision/prevention of cervical cancer
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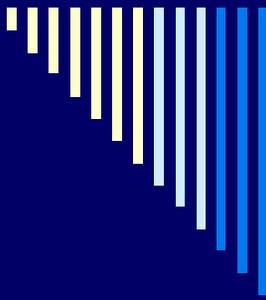
What is the Major Goal of these Protocols?

- Human studies in which induction or enhancement of an immune response to a vector encoded microbial immunogen is the major goal . . .
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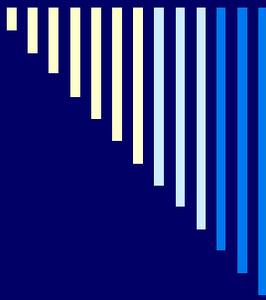
RAC Working Group Conclusion

- The primary goal is to generate an immune response to an antigen
 - However, because the transgene is derived from a known viral oncogene and the major goal is to treat precancerous lesions, these protocols are analogous to cancer vaccines and do not fall within the intent of the Vaccine Exemption under Section M-VI-A of the *NIH Guidelines*
-



Vaccine Working Group

- Howard Federoff, M.D., Ph.D.
 - Steve Dewhurst, Ph.D.
 - Hildegund Ertl, M.D.
 - Louis Kirchhoff, M.D.
 - Richard Vile, Ph.D.
 - John Zaia, M.D.
-



References

- Paavonen, J., Human papillomavirus infection and the development of cervical cancer and related genital neoplasias, *Intl. J. of Infect. Dis.* 2007;11 (Supp. 2): S3-S9
 - Hebner, C.M., Laimins, L.A., Human papillomaviruses: basic mechanisms of pathogenesis and oncogenicity, *Rev. Med. Virol.* 2006; 16:83-87
 - Narisawa-Saito, M., Kiyono, T., Basic mechanisms of high-risk human papillomavirus-induced carcinogenesis: Roles of E6 and E7 proteins, *Cancer Sci.* 2007; 98(10):1505-1511.
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