

Lymph Node T-Cells Induced By Live Attenuated Vaccines Protect Against SIV

October 22, 2012

G Brennan

More than thirty years of effort have gone into the development of an HIV vaccine. Several vaccine candidates have been tested, including whole killed virus, expressed proteins, and recombinant virus vectors (a non-HIV virus expressing HIV genes). However, the most effective vaccine strategy tested to date, capable of complete protection in a rhesus macaque model, involves the use of a live attenuated virus (LAV) (Daniel et al., 1992).

In LAV vaccines, one or more viral genes are deleted to attenuate the virus, reducing both the pathogenicity and the ability of the virus to replicate. However, the protection afforded by LAV vaccines decreases as the viral attenuation increases. Because of this correlation, LAV vaccines are unlikely to be used in humans, because an effective vaccine would also have a high risk of mutating into a pathogenic virus. Understanding how LAV vaccines confer protection could help direct vaccine development to more closely mimic the vaccine targets and immune response that is so effective in LAV vaccines. To approach this question, Dr. Paul T. Edlefsen (Vaccine and Infectious Disease Division), along with collaborators, used a panel of LAV vaccines to correlate their elicited immune responses with vaccine efficacy.

Animals were vaccinated with one of five different LAVs of varying attenuation. These different viruses should result in varying immune responses and consequently diverse levels of protection, permitting statistical correlations between the immune response to each LAV and vaccine effectiveness. As expected, this vaccination strategy led to a spectrum of protection, and after challenge, 25 out of 32 animals were at least partially protected, and 19 were completely protected from subsequent SIV challenge.

Of the 11 immune parameters tested, only the magnitude of SIV-reactive CD4+ ($p=0.0036$) and CD8+ ($p=0.007$) T-cell responses in the lymph node statistically predicted the ability of the LAV vaccine to protect in this study. The authors also found that the level of LAV RNA in the lymph node was positively correlated with the magnitude of the T-cell response, suggesting that replicating LAV in the lymph node help stimulate and maintain LAV-specific T-cells in the lymph node. A microarray analysis found that the protected group upregulated T-cell receptor signaling genes and granzymes,

while the unprotected group did not, suggesting that the protected group had a higher and faster T-cell response in the lymph node than the unprotected group.

After the initial infection, HIV infects local white blood cells that then carry the virus through the blood to the lymph nodes. This study suggests that vaccination with a virus capable of replicating in these lymph nodes can prime and, importantly, maintain potent SIV-specific T-cells at this site. These activated cells may be able to intercept, control, and possibly clear virus at an early stage of infection. One can imagine that expressing HIV genes in a different virus backbone that also stimulates T-cell responses in the lymph node may provide a safe and effective alternative to a live attenuated HIV vaccine.

[Fukazawa Y, Park H, Cameron MJ, et al.](#) 2012. Lymph node T cell responses predict the efficacy of live attenuated SIV vaccines. *Nat Med.* 2012 Sep 9. Epub ahead of print, doi: 10.1038/nm.2934.

Also see: [Daniel, M.D., Kirchhoff, F., Czajak, S.C., Sehgal, P.K. & Desrosiers, R.C.](#) 1992. Protective effects of a live attenuated SIV vaccine with a deletion in the nef gene. *Science* 258, 1938–1941.

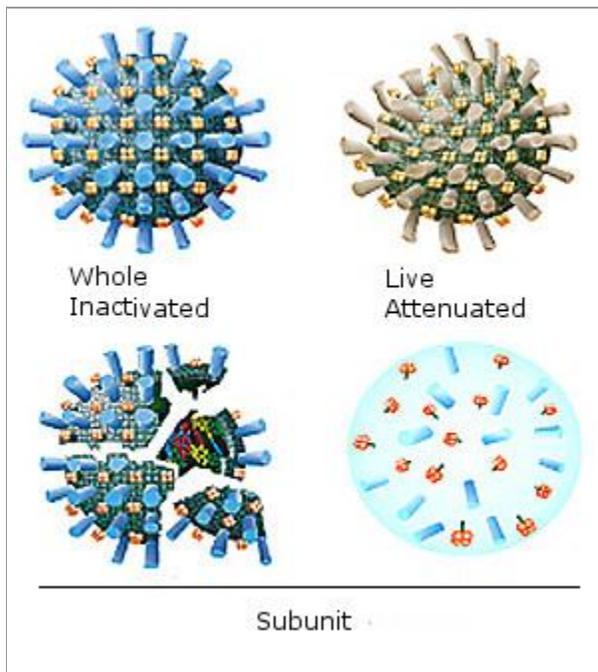


Image modified under CC-BY-SA license from Wikispaces

Schematic of various vaccine types. Whole virus may be inactivated by heat or chemicals, subunit vaccines may be generated by breaking open viruses or expressing specific proteins, and live attenuated viruses, the subject of this paper, may be generated by serial passage or mutation of specific genes to reduce the virus viability.