

A Trip Down B Cell Memory Lane for the HPV Vaccine

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Human papillomavirus (HPV) vaccines protect against the types of HPV that cause anogenital and oropharyngeal cancers (HPV 16 and 18). The quadrivalent HPV (qHPV) vaccine is also effective against the types of HPV that cause genital warts (HPV 6 and 11). Most vaccines prevent infections by generating antibodies (Abs), yet it has been unclear why some vaccines provide long-term or even life-long protection, while others such as the tetanus toxoid vaccine (TT), require boosters. The qHPV vaccine is an example of a subunit vaccine where, rather than using the pathogen in its entirety, only part of the pathogen is used. Subunit vaccines typically have fewer adverse reactions and are ideal for pathogens where use of live, attenuated or inactivated pathogens presents safety concerns. The qHPV vaccine is highly effective, and previous studies have shown sustained Ab levels up to 5 years post-vaccination and a boost in Ab responses upon re-vaccination. While this is consistent with HPV vaccination eliciting plasma cells (cells that secrete Abs for long periods of time) and memory B cells (Bmem; cells that can rapidly differentiate into Ab-secreting plasmablasts upon antigen re-exposure), HPV-specific Bmem had never been characterized.

A recent Fred Hutch study, conducted in the lab of Dr. Denise Galloway in the Human Biology Division, and published in the journal *PLOS Pathogens*, sought to understand the immunological memory evoked by a successful vaccine in the absence of pre-existing immunity. "Our study is the first to characterize the memory B cells elicited by HPV vaccination. It's really just a starting point for understanding what immune responses make the HPV vaccine so effective", said lead author Dr. Erin Scherer.

The authors first needed to develop a strategy to isolate HPV-specific Bmem. To achieve this, the investigators first purified B cells from peripheral blood samples obtained from 12 qHPV vaccine recipients at one month post-vaccination. They then used a flow cytometry-based method to discriminate HPV 16-specific Bmem. A particular combination of cell surface markers was used to identify classic Bmem (CD27+, IgD-). To distinguish HPV 16-specific Bmem, fluorescently labeled HPV16 pseudoviruses (psV) served to label antigen receptors on the surface of HPV 16-specific Bmem. These psV are composed of two capsid proteins, L1 and L2, where L1 is the antigen in the qHPV vaccine. Fluorescently labeled bovine papillomavirus (BPV) psV were included as a control. Importantly, HPV16+ Bmem, but not BPV+ Bmem, were detected. The authors then cloned Abs from

singly sorted HPV16+ Bmem and found that these were predominantly IgG in nature, and exhibited moderate levels of somatic hypermutation, comparable to that observed for Abs cloned from healthy donors or TT vaccinees, rather than the high levels observed for certain broadly-neutralizing HIV-1 Abs. Finally, the authors demonstrated that 8 out of 12 Abs cloned from single HPV16+ Bmem potently neutralized HPV16 psV. Collectively, these data show that the authors' labeling method selectively identified antigen-specific HPV16+ Bmem and is consistent with the emerging view that somatic hypermutation is not a prerequisite for potent neutralizing activity by Abs.

"We hope to use such information as a benchmark for vaccine development against other infectious agents. We will also use this strategy to evaluate whether fewer doses of the expensive HPV vaccine generates comparable memory responses. Such considerations are particularly relevant to the distribution of this vaccine in developing countries." , explained Dr. Scherer.

[Scherer EM, Smith RA, Simonich CA, Niyonzima N, Carter JJ, Galloway DA. 2014. Characteristics of memory B cells elicited by a highly efficacious HPV vaccine in subjects with no pre-existing immunity. *PLoS Pathog*, 10\(10\), e1004461. PMID: PMC4199765.](#)

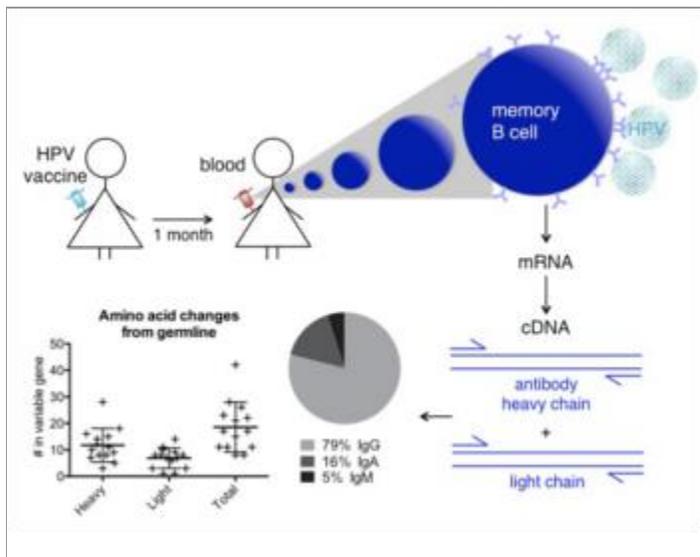


Image provided by Dr. Erin Scherer

In order to characterize the immunological memory generated by the qHPV vaccine, blood was collected from girls (aged 9-13 years) and young women (aged 18-26 years) one month after receiving their final vaccine dose. HPV16-specific memory B cells were isolated from these samples using flow cytometry methods, and full-length antibodies were cloned from these cells. These antibodies were then characterized for their sequence characteristics and anti-viral activity.