Bridging Vaccine-Induced HIV-1 Neutralizing and Effectors Antibody Responses in Rabbit and Rhesus Macaque Animal Models

Justin Pollara

<u>Abstract</u>

Studies in animal models are essential prerequisites for clinical trials of candidate HIV vaccines. Small animals, such as rabbits, are used to evaluate promising strategies prior to further immunogenicity and efficacy testing in nonhuman primates. Our goal was to determine how HIV-specific vaccineelicited antibody responses, epitome specificity, and Fc-mediated functions in the rabbit model can predict those in the rhesus macaque (RM) model. Detailed comparisons of the HIV-1-specific IgG response were performed on serum from rabbits and RM given identical modified vaccinia virus Ankaraprime/gp120-boost immunization regimens. We found that vaccine-induced neutralizing antibody, gp120-binding antibody levels and immunodominant specificities, antibody-dependent cellular phagocytosis of HIV-1 virions, and antibody-dependent cellular cytotoxicity (ADCC) responses against gp120coated target cells were similar in rabbits and RM. However, we also identified characteristics of humoral immunity that differed across species. ADCC against HIV-infected target cells was elicited in rabbits but not in RM, and we observed differences among subdominantly targeted epitopes. Human Fc receptor binding assays and analysis of antibody-cell interactions indicated that rabbit vaccine-induced antibodies effectively recruited and activated human natural killer cells, while vaccine-elicited RM antibodies were unable to activate either human or RM NK cells. Thus, our data demonstrate that both Ec-independent and Fc-dependent functions of rabbit antibodies can be measured with commonly used in vitro assays; however, the ability of immunogenicity studies performed in rabbits to predict responses in RM will vary depending on the particular immune parameter of interest.

IMPORTANCE: No neutralizing antibody functions have been associated with reduced infection risk, or control of virus replication, for HIV-1 and related viruses. It is therefore critical to evaluate development of these responses throughout all stages of preclinical testing. Rabbits are conventionally used to evaluate the ability of vaccine candidates to safely elicit antibodies that bind and neutralize HIV-1. However, it remained unexplored how effectively rabbits model the development of nonneutralizing antibody responses in primates. We administered identical HIV-1 vaccine regimens to rabbits and rhesus macaques and performed detailed comparisons of vaccine-induced antibody responses. We demonstrated that nonneutralizing HIV-specific antibody responses can be studied in the rabbit model and have identified aspects of these responses that are common, and those that are unique, to rabbits and rhesus macaques. Our findings will help determine how to best utilize preclinical rabbit and rhesus macaque models to accelerate HIV vaccine candidate testing in human trials.

KEYWORDS: ADCC, ADCP, antibody Fc functions, HIV-1 vaccines, rabbit model, rhesus macaque

Justin Pollara Department of Surgery, Duke University School of Medicine, Durham, North Carolina, USA E-mail: justin.pollara@duke.edu