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Non-neutralizing Antibody Functions for Protection and Control of HIV in Humans and of SIV and SHIV in Non-human Primates

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The search for a vaccine to prevent infection with HIV began with the isolation of the virus [1, 2]. While much of the effort in HIV vaccine development has been devoted to inducing T cell immune responses, and while T cell immunity is still a desired participant in preventing and controlling HIV infection, the focus of HIV vaccine research has pivoted towards antibody (Ab) responses since a correlation was reported in the RV144 clinical trial between reduced infection and specific Ab levels in non-infected vaccinees [3-5]. In parallel with the RV144 results, there was a technological revolution in the production of human monoclonal antibodies (mAbs) which has led to the isolation and characterization of a large number of potent and broadly reactive neutralizing Abs (bnAbs) [6-9]. Induction of these exceptional Abs with vaccine candidates has been the overarching goal of most HIV vaccine researchers, although the obstacles are enormous given that these bnAbs are found in a very small proportion of HIV-infected individuals and are characterized by extensive somatic hypermutation [10, 11]. To date, no vaccine tested in man or animals has induced bnAbs, and the modest but significant protection in RV144 was achieved in the absence of any detectable bnAbs. Indeed, in RV144 there was no correlation between neutralizing Abs and reduced infection rates [3].

Increasingly, Ab-mediated protective immunity has been associated with non-neutralizing, Fc-mediated Ab functions. Non-neutralizing Abs play a role in protection from a number of viral pathogens including influenza, herpes, alphaviruses, flaviviruses, respiratory syncytial virus, and CMV [12-15]. In addition, in RV144 there was a correlation with Ab-dependent cell mediated cytotoxicity (ADCC) and high levels of specific Abs when the level of IgA HIV-specific Abs was low [3, 16, 17]. Other non-neutralizing Ab-dependent activities have been implicated in protection and control of HIV in humans as well as SIV and SHIV in non-human primates [3, 16-27].

In this issue of *AIDS*, immunogens are described that induced non-neutralizing Abs that may play an important role in protection. Initially, this group showed that rhesus macaques infected intravenously with SIV_{mac239} nef induced plasma cells in the submucosa and ectopic tertiary lymphoid follicles of the ectocervix and vagina; these cells produced IgG Abs reactive with gp41 trimers (gp41t) which were concentrated in the path of virus entry by neonatal Fc receptors (FcRn) in the vaginal epithelium [28, 29]. Now, Voss *et al.* have designed and tested SIV gp41t immunogens. Upon immunization of rhesus macaques, gp41t-specific Abs were induced which were detectable in serum and found complexed with FcRn+ cervical vaginal epithelium [30]. These data add to those previously published by other groups showing that non-neutralizing Abs in general [27, 31, 32], and gp41-specific

Abs in particular [33–36], can mediate Fc-dependent biologic functions associated with anti-viral effects and protection. Of note, two of the mAbs used in the latter studies of Fc-mediated effects (gp41-specific human mAbs 240-D and 246-D) were members of a category of human mAbs, Cluster I anti-gp41 mAbs, which targets the immunodominant region of the gp41 ectodomain and reacts with trimeric gp41 [37–39].

The data indicating a protective role of gp41 Abs also suggest an explanation for how an early vaccine candidate, live, attenuated SIV_{mac239} nef, may have provided robust protection against subsequent challenge with SIV. Importantly, the data reported in this issue may provide a significant alternative approach to the development of an HIV vaccine. While this approach certainly does not rule out a role for neutralizing Abs, it extends the many other studies cited above indicating that the exceptional bnAbs which have been the Holy Grail of HIV vaccine research may not be an absolute requirement for protection, and that other “conventional” Abs, which are more readily induced than bnAbs may be adequate to provide protection against HIV. What remains is still a daunting task: to demonstrate conclusively that non-neutralizing Abs such as the ones described in Voss *et al.* can protect, or participate in protection. Such a demonstration would need to explain why non-neutralizing Abs, such as the gp41t Abs described in this issue (which are present in the majority of HIV-infected individuals), do not protect HIV+ individuals from superinfection.

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