



Progress Towards Developing an Effective Vaccine Against HIV-1

by **A b r a h a m P i n t e r**

A critical requirement for halting the spread of the AIDS epidemic is the development of an effective vaccine against HIV-1, the virus responsible for this disease.

Despite a considerable worldwide effort, progress towards a protective vaccine has been slow and limited. A strong neutralizing antibody response is an essential component of a protective viral vaccine. Unfortunately, typical circulating strains of HIV-1 tend to be highly resistant to neutralization by antibodies commonly induced upon infection or vaccination. However, recent progress on several fronts has suggested for the first time that such a vaccine may be possible, and the Pinter lab has been in the forefront in exploring several of these key approaches.

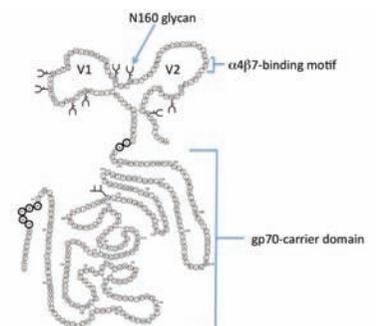
Several properties of HIV-1

contribute to the resistance of this virus to the immune system, and in particular, to neutralization by antiviral antibodies. Unlike most viral pathogens, HIV-1 causes a long-term chronic infection in which the virus keeps evolving for many years in the face of an active antibody response. This results in the elimination of viruses with highly

unusually high concentration of glycans which covers a large percentage of the exposed surface of virions, shielding many potentially immunogenic peptide targets. This is further exacerbated by the efficient utilization by the virus of conformational masking mechanisms that lead to the occlusion of sites that might otherwise act as sensitive targets.

domain as a vaccine target was limited because of its high variability and the limited cross-reactivity of many V1/V2-specific MAb. However, our interest in this region was sparked by our discovery and characterization, together with our former PHRI colleagues, Shermaine Tilley and Sujata Viji, of an interesting monoclonal antibody (MAb)

Figure Legend
Shown is the V1/V2 glycoprotein antigen used to identify the role of V1/V2-specific antibodies as a correlate of protection against HIV infection in the RV-144 vaccine trial carried out in Thailand (N. Engl. J. Med. 366;14, 2012). Highlighted are the gp70-carrier domain, the V1 and V2 regions, the N160 glycan that is a critical determinant of C108g and many of the QNE-specific broadly neutralizing antibodies, and the LDI tripeptide motif identified as a key $\alpha 4\beta 7$ binding determinant.



immunogenic sites that act as sensitive neutralization targets, leaving behind less immunogenic viral populations that are resistant to neutralization. Furthermore, HIV-1 Envelope proteins possess an

For a number of years an important focus of our research has been on characterizing the structure and immunological properties of the V1/V2 region of the HIV-1 Envelope (Env) protein. Interest in this

called C108g, whose target was localized to this domain. C108g came from a chimpanzee infected with HIV, and was particularly interesting because it was one of the strongest neutralizing antibodies known at that

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time. Another unusual property of C108g was its dependence on the presence of carbohydrate in Env, which we localized to a conserved glycosylation site at position 160 in the V2 region.

Despite its highly potent neutralizing activity, C108g did not generate much interest in the field because of its narrow breadth of reactivity; C108g reacted with the IIB strain of virus used to infect the chimp and one other natural HIV isolate named BaL, but not with other viral strains tested. However, we showed that the limited range of C108g was due to its dependence on an unusual substitution of glycine for the aspartic acid residue usually found at position 167 in V2, and that by introducing this single change we could introduce C108g reactivity into a number of different Env proteins. This demonstrated that other than the substitution of one atypical amino acid, the overall structure of the C108g epitope was highly conserved.

Several years later, we showed that the same V2 region recognized by C108g was also a critical determinant of a very different type of MAb called 2909, isolated by our collaborators Miroslav Gorny and Susan Zolla-Pazner at the NYU Medical School. 2909 was the prototype for an important new class of antibodies that recognize so-called quaternary neutralization epitopes (QNEs) that are preferentially expressed on trimeric Env complexes and are dependent on residues in both the V2 and V3 domain. This antibody, and a related class of MAbs isolated from monkeys infected with SHIV-SF162P4 (SHIVs are chimeric viruses formed between HIV-1 and simian immunodeficiency virus that replicate in monkeys) possessed unusually

potent neutralizing activity for the SF162 strain, but not for any other strains. Further studies in our lab showed that the restricted reactivity of these MAbs was due to their dependence on a rare substitution of lysine at position 160, in place of the asparagine-linked glycosylation site required by C108g. Further in contrast to C108g, 2909 reacted preferentially with the consensus residue at position 167. The fact that both C108g and the QNE-dependent mAbs mapped to allelic variants in the same region in V2 suggested

that the interaction between HIV-1 and this receptor may be important for transmission of virus through the mucosal barrier, a critical step in infection. A second discovery came from the analysis of correlates of protection in the recently concluded RV144 vaccine trial conducted in Thailand, the first HIV vaccine trial that resulted in some protection against infection. Protection in this trial was shown to correlate with an increased titer of antibodies that bound to a V1/V2 fusion protein that we had developed, but not to any

important in protection against infection by applying recently developed methods for cloning MAb genes directed against targets of interest from single memory B cells isolated from HIV-infected people who express broadly neutralizing antibodies. We are fortunate that several of our long-term research interests have recently proven to be particularly important for HIV vaccine design, and hope that our continued efforts in these areas will lead to important contributions towards the development of an effective anti-HIV vaccine. ■



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that this region was highly exposed on the viral surface and was a highly sensitive neutralization target.

Our findings led us to hypothesize that sequences that combined the conserved N-linked glycan at position 160 required by C108g together with the typical residues at position 167-169 required by 2909 would also be immunogenic, and would be recognized by a class of broadly neutralizing antibodies. This hypothesis was recently proven true with the isolation of a series of potent and broadly neutralizing MAbs targeting a class of quaternary epitopes that were dependent on precisely these sites in the V2 region.

Two additional recent discoveries kindled further interest in the V1/V2 domain as an important vaccine target. One was the demonstration by the Fauci lab that a small conserved sequence in the V2 domain interacted with $\alpha 4\beta 7$ integrin, the mucosal homing receptor for activated T cells, and that this interaction strongly enhanced infection of those cells. This suggested

other factor analyzed, including avidity and titers of Env-specific IgG and IgA, viral neutralizing activity or levels of Env-specific CD4+ T cells. These results suggested that V1/V2-specific antibodies may be critical for protection in this study.

A current focus of our research is on learning more about the structures of broadly conserved QNEs and developing immunogens and vaccine strategies for inducing such broad and potently neutralizing antibodies. One approach we are using is inserting these epitopes into SHIVs, and examining the immune response of animals infected with these viruses. We are also continuing to characterize the structure and functional activities of the V1/V2 domain and to study potential antiviral activities of V1/V2-specific antibodies. Finally, we are seeking to identify new antibodies and targets that could be

Abraham Pinter has dedicated his career to understanding the structure, function and immunological properties of viral surface glycoproteins. He earned a PhD in chemistry from Columbia University, and after a postdoc in the Animal Virology lab at Rockefeller University, he joined the Viral Oncology lab at Memorial-Sloan Kettering Cancer Center, where he first studied the properties of the Envelope proteins of retroviruses, a class of virus that causes cancer in animals. In 1985, he joined the Public Health Research Institute, where he turned his research program towards the study of HIV-1, which had just been shown to be the etiological agent responsible for the AIDS epidemic. His current research is focused on understanding the structural and immunological properties of the HIV-1 surface proteins, and applying this information towards the development of an effective vaccine against this virus.

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