Human Antibodies 14 (2005) 57–58
IOS Press

Editorial

Miroslaw K. Gorny*
New York University School of Medicine, c/o Veterans Affairs Medical Center, 423 East, 23rd Street, Room 18124N New York, NY 10010, USA

Despite the diagnosis of the Human Imuunodeficiency Virus (HIV)-1 as the cause of Acquired Immune Deficiency Syndrome (AIDS) more than two decades ago, the development of a potent vaccine capable of inducing a protective immune response against diverse HIV-1 isolates still remains a challenge to modern medicine. This has been due, in part, to the genetic diversity of the viral antigens, the inaccessibility of biologically relevant antigens, the lack of well-defined antigens which can elicit broadly protective antibodies (Abs), and/or specific effector cells in the hosts. While the virus continues to evade immune control through several known and unknown mechanisms, including its diversity and inaccessibility of its antigens by folding and masking, there is evidence that the host immune response has the ability to block infection and control virus replication. Such evidence comes from studies of acute HIV-1 infection, correlating declining viral load with increasing humoral and cellular immune responses, and from clinical trials of passive immunotherapy, when broadly neutralizing human monoclonal antibodies (mAbs) were shown to suppress viral replication *in vivo*. Further support of the beneficial role of Abs comes from passive immunization studies using neutralizing Abs that have shown a protective effect against HIV-1 challenge in various animal models.

As our understanding of the repertoire of neutralizing and protective Abs is limited, this gap in knowledge can be filled through studies that utilize new approaches to dissect the immune response during HIV-1 infection and identify viral immunogens that could be useful in vaccine design. This issue of the Journal brings together three review papers which include new concepts on how to induce protective Abs, and four original studies that analyze the natural humoral immune response during HIV-1 infection through examination of serum neutralizing Abs and the activities of selected mAbs.

Among the few human mAbs with broadly neutralizing activity against primary isolates, two, 2F5 and 4E10, are particularly unique in that although they bind to conserved regions of gp41, they also bind to host antigens. Haynes *et al*. (pages 59–67) presents and discusses a hypothesis of the recruitment of otherwise non-responsive B cells specific for auto-antigens and their possible role in producing safe, neutralizing Abs against the conserved regions of gp41.

A new concept utilizing the V3 region as an immunogen in vaccine design is presented by Susan Zolla-Pazner (pages 69–72). The strong immunogenicity of the V3 loop, the structural constraints imposed by its biological function, and the cross-neutralizing capacity of many human anti-V3 mAbs strengthens the case for the V3 loop as an epitope to include in candidate vaccines. Although V3 could serve as a good immunogen, the potency of the anti-V3 Abs induced could be limited by the masking of V3 that occurs in many virus isolates. The activity of V3 Abs against HIV-1 is further studied by Matsushita *et al*. (pages 81–88) who showed that a humanized anti-V3 mAb has the ability to neutralize *ex vivo* primary isolates derived from two patients in a dose-dependent fashion. The cross-reactive nature of anti-V3 mAbs is also discussed by Robyn Stanfield and Ian Wilson (pages 73–80). Their crystallographic analysis of the atomic interactions between various V3 peptides and Fab fragments of two human mAbs show that each mAb utilizes different strategies for cross-reactivity.

Kelly *et al*. (pages 89–99) demonstrates viral escape from the effects of neutralizing Abs in non-clade

*Tel.: +1 212 263 4156; E-mail: Mirek.Gorny@med.nyu.edu.

ISSN 1093-2607/05/$17.00

B chronically-infected individuals. Since neutralization of heterologous primary viruses is relatively weak, their findings suggest that neutralizing Abs generated during chronic infection could be isolate-specific. The specificity of neutralizing Abs in HIV-positive serum is still relatively poorly understood. Crooks *et al*. (pages 101–113) tested the activities of various reference mAbs, in several neutralization assays, for evaluating plasmas that may contain similar Abs. The study showed that 2F5/4E10-like Abs were absent in plasmas with broadly neutralizing activity and a few plasma samples exhibit neutralizing activities, suggesting that yet unidentified Abs can mediate neutralization. One of the intriguing riddles of the anti-HIV-1 immune response was explained by Robinson *et al*. (pages 115–121) who show that the CD4i epitopes are more immunogenic than was previously thought and that anti-CD4i Abs are the most dominant among several Abs found in the early phase of HIV-1 infection.