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Editorial

Combating HIV with bNABs

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Since the discovery of the HIV as the causative agent for AIDS, many attempts have been directed towards a vaccine or prophylactic measure. Our immune system has evolved to attack foreign molecules, but viruses like HIV have found ways to hide their unique parts and masquerade as human molecules. One of the mechanisms involves carbohydrate masking. Surface glycoproteins of viruses are synthesized in infected cells; therefore they are made up of the same sugar chains that cover proteins in humans. This provides them with an effective camouflage, burying the actual functional sites of the viral protein deep within these sugars and making it difficult for antibodies of the immune system to reach the target. In addition to this, the viruses have developed error-prone replication machinery. This generates a great diversity in the viral glycoproteins over few generations. So even though the immune system eventually succeeds in making the correct antibodies to neutralize the infecting agents, future generation of viruses rapidly mutate to change the site that is recognized. Amazingly, the immune system in a few select individuals is able to fight back. Some people develop broadly neutralizing antibodies (bNAbs) to combat viral infection. The term "broadly" signifies that the antibodies attack many strains of the virus, and "neutralizing" indicates ability to bind key functional sites in the virus. There is now rising promise that bNAbs will pave the path forward for AIDS treatment and vaccine development.

Towards a vaccine

Ever since the discovery of HIV-1 [1,2] and the subsequent appreciation that the viral genome expresses a unique viral surface exposed envelope glycoprotein (env) [3], much research has been focused on developing a vaccine for AIDS prevention and treatment by exploiting this target [4,5]. These efforts had success in that they were able to induce high levels of antigen-specific antibody responses. But the antibodies failed to neutralize most of the circulating strains of HIV-1[6]. These vaccines did see the light of clinical trials but a well-conducted human efficacy trial failed to show decrease in plasma viral loads or any preventive benefit [7]. For various reasons covered in great detail elsewhere [8,9],initial gp120 based vaccines turned out to be a complex and difficult task.

The good news is that in recent years our understanding of the atomic-level structure of several regions of HIV-1 Env has reached the point where we can rationally design vaccine immunogens [10,11]. In addition in recent years due to the increasing efforts from proteomics and genomics studies, many bNAbs, have been isolated from HIV-1 infected donors. These antibodies have been exhaustively categorized and their efficacy and therapeutic effects observed in several animal models [12,13,14].

During HIV-1 infection, many broadly neutralizing antibodies are generated. Of special interest has been the antibodies of the VRC01-class [15]. Because this antibody recognizes a specific and unusual target, it is an unusually structuredantibody. The antibody VRC-01 (PDB entry 4nco), has an unusually long extension to one of its loops, which makes it protrude like a finger through the glycoproteins and into a conserved site of the viral antigen. The rest of the antibody also has dozens of mutations that each are responsible for the interaction with surrounding proteoglycans and peptides of the viral coat [16]CD4, with gp120. Here, we extended the investigation of the VRC01-gp120 core interaction to the biologically relevant viral spike to better understand the mechanism of VRC01-mediated neutralization and to define viral elements associated with neutralization resistance. In contrast to the interaction of CD4 or the CD4bs monoclonal antibody (MAb.The IgG V region of VRC01 is responsible for binding to the gp120. From an affinity and activity stand point, VRC01 has proved to be highly advantageous as a therapeutic agent. VRC01 neutralizes about 90% of diverse virus strains with a geometric mean 50% inhibitory concentration (IC50) of 0.33 mg/ml and IC80 of 1.0 mg/ml [17,18]. Thus, making VRC01 extremely potent and broadly reactive. Furthermore, VRC01 and its clonal variants have demonstrated complete protection against infection in several animal model [19,20]. As a therapeutic agent, VRC01 has demonstrated the ability to suppress virus replication during acute SHIV infection [21]. The VRC01 drug product was developed by the Vaccine Research Center (VRC), National Institute of Allergy and Infectious Diseases (NIAID) at the National Institutes of Health (NIH) and has been found to be safe in healthy, uninfected adults [22]. Currently, the HIV Vaccine Trials Network and the HIV Prevention Trials Network are carrying out a large scale study to determine the efficiency of VRC01 in preventing HIV infection in the general population.http://ampstudy.org/about#sthash.tPl4dwJY.Kd6qrJ3y.dpuf

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Discovery of Broadly Neutralizing Antibodies (bNAbs) has given a great boost to HIV vaccine research. Not only is there a potential to immediately use available bNAbs as a prophylactic measure in the war against AIDS. We also have a template in the form of existing bNAbs to ultimately design the elusive HIV vaccine. For that reason a number of bioinformatics resources exist for bNAbs. One such database EDB-3D (www.iedb.org) [23] that provides experimentally determined structures. The LANL (http://www.hiv.lanl.gov/content/index) resource offers a 'Summary of Best Neutralizing Antibodies' table with links to papers, Ab sequences and structures, notes on breadth of neutralization, and references to the tables and figures in original publication, as well as list of Ab contacts or key residues. In addition a new bioinformatics tool has been developed to help the research community bNAber (broadly neutralizing antibodies electronic resource) [24]user-friendly access to detailed data on the rapidly growing list of HIV bNAbs, including neutralization profiles, sequences and three-dimensional structures (when available provides access to raw data on broadly neutralizing HIV antibodies. Third party software is integrated to help biologists perform certain analysis for sequence alignment and understanding neutralization data using heat maps. Users in the research community may contribute newly identified bNAbs and support the ultimate goal to provide immunogen design for the development of an HIV/AIDS vaccine. The broader scope of such databases is that they could be of interest to researchers developing vaccines to other diseases, including influenza, hepatitis C, dengue and West Nile viruses [25].

Recent advances in the understanding of bNAbs role in immune response, have once again spurred the possibility that an HIV vaccine can be designed. Better understanding of the structural uniqueness and more information on key residues interacting with Env structures nudges us closer to identification of vaccine candidates and the Increasing availability of bNAbs structure will hopefully usher in a convergence of virologists, geneticists, and basic B cell biologists towards breakthroughs in our fight against AIDS.

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