Effective HIV vaccine – Narrow path to broadly neutralizing antibodies

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The quest for a prophylactic vaccine against the human immunodeficiency virus is almost as old as the identification of HIV as the cause of the Acquired Immunodeficiency Syndrome (AIDS) in 1983 [1]. The eliciation of neutralizing antibodies (nAbs) by a vaccine is since believed to be imperative in either mediating sterilizing immunity or at least in preventing the establishment of latent reservoirs. Initial optimism was raised in the early 90s when it was reported that vaccination with antigen preparations including whole inactivated virus, purified recombinant envelope (Env) proteins and envelope-derived V3-specific peptides led to protection or a significant delay of infection of chimpanzees from a close to homologous i.v. challenge with a lab-adapted virus strain (HIV-1 IIIB) [2]. The clinical outcome was at that time attributed to sustained and high titers of virus neutralizing antibodies. These initial signs of hope, however, quickly gave way to fundamental sobering upon findings from numerous preclinical and clinical studies, including two phase 3 efficacy trials (VAX003 and VAX004), which proved that the neutralizing antibody responses induced by Env containing vaccine preparations such as the recombinant gp120s (AIDSVAX B/B and AIDSVAX B/E) used in the two phase 3 trials were largely strain-specific, lacked breadth and failed to neutralize primary isolates [3].

In this issue, 14 articles report about recent observations from large clinical cohort studies and vaccine trials. Special emphasis has been put on lessons learned from the plethora of broadly neutralizing monoclonal antibodies that were isolated from elite neutralizers over the last 5 years regarding their potential use in therapeutic and prophylactic settings, the ontology of envelope specific B cell development, the envelope immunogen design, and ultimately the development of knock-in mice producing human antibodies to support the testing of novel vaccine concepts.

The first contribution in this issue summarizes key findings from large clinical cohort studies analysis revealing that 10-30% of HIV infections result in some level of serum neutralization breadth. Only less than 10% of individuals seem to develop a greater breadth of neutralization warranting their classification as elite neutralizers [4]. This may in part be because of B cell abnormalities associated with the viremic phase of HIV infection that cause impaired B cell maturation and antibody responses. This topic is highlighted in a contribution on the critical role of germinal center (GC) B cells and follicular helper T cells (Tfh) for the generation of neutralizing antibodies - findings that will inspire the development of specific vaccination strategies for the stimulation of GC B cells and Tfh cells [5].

So far, human vaccine trials have unfortunately failed to elicit broad plasma neutralization of primary virus isolates [6]. Despite this limitation, some protection has been observed. Another article describes how the combined and comparative analysis of antibody responses from phase 2b and phase 3 efficacy trials has revealed various mechanisms by which non-neutralizing antibodies are presumed to have mediated protection [7]. Related to this, an article reviewing the B cell repertoire analysis and functional characterization of monoclonal antibodies isolated from vaccinees of such an HIV-1 vaccine trial with modest efficacy (RV144, RV305) [8,9] reports that vaccine boosts shifted the HIV-specific B cell repertoire and expanded pools of cells with long third complementarity determining regions in the

heavy chain, a characteristic of some bnAb lineages. The authors conclude that HIV vaccines should in principle be capable of inducing antibodies of a certain neutralization breadth [10].

Michel Nussenzweig and his colleagues demonstrated in a first-in-man dose escalation phase 1 clinical trial that 3BNC117, a potent human CD4 binding site antibody, reduced the viral load in HIV-1-infected individuals by a magnitude of 0.8-2.5 log10 and that viremia remained significantly reduced for 28 days [11]. Hence, it is fair to assume that the induction of bnAbs at sufficiently high titers could presumably protect humans against HIV infection. This is confirmed by several studies in non-human primates clearly demonstrating that the administration of broadly neutralizing monoclonal antibodies can provide sterilizing protection against viral challenges [12,13]. An article in this issue specifically addresses the role of mucosal IgA. The authors report that the dimeric IgA1 (dIgA1) form of a V3 specific neutralizing monoclonal antibody (HGN194 [14]) with its isotype-specific open hinge can prevent SHIV acquisition in rhesus macaques at a higher rate than dIgA2 and suggest "immune exclusion" through multimeric mucosal IgA to be a potent protective mechanism. Furthermore synergistic interactions at the mucosal level between the IgG1 and dIgA2 versions yielded complete protection are reported. In view of the outcome of the RV144 clinical trial that implied a negative effect of plasma anti-HIV Env on protection, the authors conclude that both, the localization as well as the antibody isotypes stimulated by active immunization strategies matter [15].

The isolation of more than 100 bNAbs from HIV-1-infected donors has led also to an unprecedented understanding of the sites of vulnerability that these antibodies target on the HIV-1 envelope [16]. Another contribution in this issue provides an elegant overview regarding the manifold ways by which selected panels of these bNAbs supported the characterization of the various sites of Env vulnerability. The authors highlight that these sites reside in the context of diverse envelope states required for HIV-1 entry, including a prefusion-closed state, a single-CD4-bound intermediate, a three-CD4-bound intermediate, a pre-hairpin intermediate, and postfusion states, and it seems not always clear which structural state optimally presents a particular site of vulnerability for vaccine elicitation [17].

Another contribution in this issue reviews the development of soluble native-like HIV-1 Env-based gp140 trimer proteins, their impact in gaining atomic-resolution structural information and how this information has stimulated the guided design of several new and improved generations of such envelope proteins as antigens. Chemical crosslinking approaches have also contributed to trimer stabilization and the selection of particular conformational forms. Initial immunization experiments with such next-generation stabilized, closed conformation Env trimers revealed that whilst autologous bnAbs to Tier-2 virus envelopes are achievable, the reproducible elicitation of high titer bnAbs is not. Locking immunogens into a single stable conformation, as has been carried out in the context of respiratory syncytial virus vaccine development [18], is likely to be important to facilitate efficient B cell recognition [19].

Amongst the currently available bnAbs, the most potent and broadest representatives recognize epitopes within the membrane proximal external region (MPER) of the HIV-1 fusion protein subunit gp41 [20]. Another article summarizes new structural details, which reveal that the complex gp41 MPER epitopes are made up by specific lipids and extend into the transmembrane region. This recent insight is believed to spur new approaches to design gp41-MPER immunogens. Nanoparticle lipid compositions, for example, in which MPER peptides are incorporated via the trimeric transmembrane region and that are presented in a helical conformation, are suggested to help triggering broad, potent and sustained antibody responses [21].

Longitudinal sampling and analysis of diversifying virus and co-evolving B cells from time-of-infection provided deep insight into the immunological pathways, which antibody lineages follow to develop broad and potent neutralization [22]. The information on antibody footprints on the viral envelope along with the B-cell ontogenies has changed the view on immunogen design and vaccination strategies [17, 19]. This is also reflected by the development of several humanized knock-in transgenic mouse models, which are reviewed in this issue in greater detail. Such mouse models were equally

indispensable and invaluable to prove the concept that germline B cell receptor targeting followed by sequential immunization with carefully selected immunogens can engage the respective naïve precursor B cells and guide B cell receptor development towards broadly neutralizing reactivity [23].

Interactions of envelopes, even those that were engineered for improved binding, with germline BCRs are usually of low affinity most likely because of a general tendency of germline antibodies to be polyreactive [24]. Various formats are reported in another review article aiming towards the presentation of HIV envelopes in a repetitive manner on particle-based carriers. These encompass Gag-derived virus-like particles, bacteria-derived proteins that self-assemble into symmetrical nanoparticles, as well as liposomes assembled from membrane components. Such delivery formats are suggested to allow higher-avidity BCR-envelope interactions triggering affinity maturation and resulting in superior antibody responses characterized by improved breadth, potency and durability [25].

Apart from the challenge of inducing neutralization breadth, the induction of long-lived envelope specific antibody responses at high titers with defined Fc-effector profiles remains a major challenge in HIV vaccine development. Two contributions cover complementary approaches to modulate envelope specific antibody responses: A comparison of CD4+ T-cell responses in HIV infected individuals suggests that robust Gag-specific CD4+ T-cells may provide important T-cell help to Env-specific B-cells [26]. The impact of intrastructural T cell help on Env-specific IgG subclass distribution and glycosylation offers a new avenue in modulating Env-specific antibody responses [27]. Furthermore, new adjuvants with immune potentiating and effector modulating properties are described which are currently being tested in combination with recent HIV envelope-containing immunogens in prime-boost and subunit protein-only regimens. Probing the dynamics and molecular effects of complex adjuvant formulations with novel HIV-1 Env immunogens is critical for advancing candidate adjuvanted vaccine regimens to a level that allows induction of the desired immune response profiles [28].

Although we all hope that - based among others on the achievements reported in this issue - a prophylactic HIV vaccine is within reach, it may turn out that this task will remain utmost demanding. In the meantime, however, the discovery of highly potent broadly HIV-1 neutralizing antibodies may also provide new opportunities for successful prevention, treatment and possibly even cure of HIV-1 infection. In this context, another article describes humanized mouse models that have been developed and successfully used to demonstrate the antiviral efficacy of HIV-1 neutralizing antibodies *in vivo* [29]. Along these lines, the final contribution in this issue reports how this concept has been carried forward by developing entry inhibitors that can target multiple epitopes on Env, localize the inhibitor to the site of entry, or limit pathways of escape by binding conserved sites on Env. rAAV-vector mediated delivery of these inhibitors provided long-term protection from HIV-1 in the abovementioned mouse models and has thus been suggested to be in principle a viable alternative to passive administration - provided some safety and remaining efficacy issues will be solved [30].

Overall, impressive advances have been made within the last few years in the understanding of the interplay between HIV's envelope protein and antibodies, their developmental pathways, and functional differences. Various rational approaches build on this improved knowledge and have led to a number of promising vaccine concepts. It will be exciting to see within the next years whether such concepts can be translated into clinical studies and if they will eventually lead to a viable vaccine that is capable of eliciting broadly neutralizing antibody responses in humans that protect from infection with HIV.

Conflicts of Interest

None

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