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Recent Progress in Preclinical HIV-1 Vaccine Research

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Introduction

Since isolation in humans in 1983 [1,2], HIV-1 has developed into a global pandemic. But an effective HIV-1 vaccine has not been succeeded despite multiple human vaccine trials performed [3,4]. Challenges to an effective vaccine arise from intrinsic virological and immunological features of HIV-1 [3-8]. For example, the envelope (Env) spike – composed of trimers of the receptor-binding subunit gp120 and the transmembrane subunit gp41, is the sole antigen available on the viral surface targeted by antibodies. However, the spike surface is shielded by an extensive glycan coat [7,9,10], which prevents most protein surface area from being recognized by antibody. The Env protein is also extremely unstable (e.g. frequent gp120/gp41 dissociation) [6,8,11] and evolves at an extremely fast rate [12,13], which frequently alters its immunogenicity to escape host immune surveillance [7]. Nonetheless, in the past 10 years, advanced technologies have been combined to reveal numerous aspects of HIV-1 interaction with the immune system, including but not limited to isolation of broadly neutralizing antibodies (bNabs) in natural infection coupled with structural characterization and/or neutralization profiling to identify sites of vulnerability [14-19], B cell repertoire sequencing of infected donors, and computational algorithms to characterize B cell response to HIV-1 and to identify determinants of affinity maturation of HIV-1 bNabs [20-27], *de novo* and grafted immunogen design and antigenicity enhancement [28-38], and genetically engineered animal models to evaluate immunogen efficacy [39-41]. The knowledge gained from these studies has revolutionized HIV-1 vaccine research. Recent studies on passive administration of bNabs showed efficacy for HIV prevention (reviewed in [4,42], indicating that the elicitation of bNabs by vaccination could in principle provide a long-term solution for HIV prevention. However, many HIV-1 bNabs have unusual features (e.g. high somatic hypermutation or long complementarity determining region 3 (CDR3)), which may require years of affinity maturation, and could thus form roadblocks for elicitation [3,4,15]. To conquer these potential barriers, new vaccine strategies have been developed such as vaccines designed to elicit antibodies against a specific site of vulnerability (epitope-based vaccine design) and to mature a specific antibody class (antibody lineage-based design) (reviewed in [5]). Here, we review recent progress in preclinical HIV-1 vaccine research.

Elicitation of Broadly Neutralizing Antibodies in Animal Models

Elicitation of bNabs, which prevent infection of diverse HIV-1 strains, particularly for hard to neutralize tier 2 and 3 strains, is critical for a universal HIV vaccine. To achieve this goal, a number of immunogens have been designed targeting prefusion Env protein [43,44] or conserved epitopes of Env (e.g. CD4 binding site [30,36], glycan-V3 supersite [32], trimer apex [31], and fusion peptide (FP) [35]). These immunogens are generally tested in animal models including mouse, guinea pig, and rhesus macaque or non-human primates (NHP) in various immunization regimens.

Recent studies in animal models showed that some immunogens and strategies could induce antibodies neutralizing autologous viruses and/or tier1 viruses and a few elicited modest to high autologous and/or heterologous tier 2 neutralization [10,14,35,40,41,44,45]. In particular, Xu and coworkers developed immunogens and regimens to elicit antibodies targeting the FP [35], a conserved critical component of the viral entry machinery and whose N-terminus is accessible to antibodies. A regimen that involves sequential immunization with FP peptide covalently coupled to Keyhole limpet hemocyanin (KLH) followed by a BG505 SOSIP trimer elicited cross-reactive sera neutralization titers in mouse, guinea pig, and NHP, with mouse monoclonal antibodies achieving up to 31% neutralization breadth against a 208 wild-type virus panel. Moreover, the best vaccine-induced NHP monoclonal antibody neutralizes 59% of 208 wild-type HIV-1 strains, better than FP-directed bNabs isolated from natural infection (manuscript submitted). Further characterization revealed that these vaccine-induced FP-directed antibodies do not require extraordinary somatic hypermutations, as many bNabs from natural infection do, suggesting affinity maturation may not be a barrier to re-elicitation. Thus, FP immunogens show significant promise for an effective HIV vaccine. While earlier studies had shown that Env trimer immunogens could induce broadly neutralizing antibodies in cows and llama [46,47], in each case the vaccine-induced neutralizing antibodies contained structural features not found in human repertoires including long heavy chain CDR3s (in cows, forming a protruding "knob" domain, while neutralizing llama antibodies were from heavy-chain-only antibody types). Neither of these features presents in human antibodies, so these immunization outcomes cannot be projected to humans.

Although most HIV immunogens are still at the proof-of-concept research stage, studies have consistently shown that sequential immunization has proven more effective at inducing neutralizing antibodies than immunogen cocktails [40,41,43].

Protection of HIV-1 challenge by vaccine-elicited neutralizing antibodies

A vaccine usually induces polyclonal antibodies with neutralization breadths ranging from bind-but-not-neutralize to broad neutralization (often defined as neutralization of >50% of the natural strain diversity) [48]. These antibodies could have different effector-function profiles and may act synergistically or competitively. The efficacy of vaccine-elicited neutralizing antibodies for protection and mechanisms of protection are still poorly understood. One approach to elucidate mechanisms of protection is to challenge NHP post vaccination with chimeric simian-human immunodeficiency virus (SHIV) [44,49-51]. Early studies showed that neutralizing antibodies induced by DNA-delivered gp120 immunization protected NHPs from tier 1 virus challenge [50,51]. A recent study by Pauthner and coworkers showed that neutralizing antibodies induced by BG505 SOSIP trimer can protect NHPs from autologous tier2 $SHIV_{BG505}$ infection [44]. More interestingly, the protection is correlated with high serum neutralizing antibody titer, but not antibody-dependent cellular cytotoxicity (ADCC) and T cell activities. This contrasts with the observation that non-neutralizing antibodies from the RV144 clinical trial protect vaccinees with modest efficacy by ADCC and other mechanisms [52]. Nonetheless, current studies are consistent in that neutralizing antibodies induced by Env immunogens are able to protect animal models from infection.

Conclusion

Proof-of-concept studies of the next-generation HIV-1 vaccine design, with the goal of eliciting bNabs for protection, are now revealing exciting progress in animal models. We anticipate that clinical trials of FP and Env trimer immunogens with animal models to be initiated in the next two years [35,43,44]. Further investigations in both animal models and humans are required to understand durability, efficacy, and other features of vaccine candidates and mechanisms of protection.

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