Cautious optimism for HIV vaccine science

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Although there has been extensive clinical testing of HIV-1 vaccine candidates with almost 200 phase I trials started since 1987, only four vaccine regimens have been evaluated in phase III efficacy studies. Overcoming the challenge of viral diversity would be a huge coup in HIV-1 vaccine development. Having to contend with envelope amino acid sequence diversity amongst the nine HIV subtypes and complex intersubtype recombinant viruses as well as the error-prone replication of HIV-1 enabling escape from immune control [1] may appear to make this task almost insurmountable!

These complexities have driven a maturation of the global response to HIV-1 vaccine development over the past 30 years. The formations of public private partnerships that synchronize the efforts of government agencies, funders, scientists and pharmaceutical companies to address the challenges facing HIV vaccine science represent a critical evolution [2]. These partnerships focus our efforts to ensure successful product development pathways that can end in the licensure or registration and distribution of an efficacious vaccine. Being attentive to HIV vaccine clinical trial design and analysis has also optimized efficiencies in the conduct of clinical trials and has improved the understanding and interpretation of trial outcomes [3]. The use of nonhuman primate models, utilizing different viruses or host species, has contributed substantially to vaccine development through our understanding of simian immunodeficiency virus/simian human immunodeficiency virus pathogenesis and the performance of candidate vaccines in challenge studies [4]. We have developed increasingly sophisticated tools to measure and assess potential biomarkers of protection and susceptibility, with statistical and sequence analysis methods providing opportunities to exact mechanisms of vaccine efficacy [5]. This has been especially highlighted in the RV144 study, a pivotal study in Thailand showing the first evidence for acquisition efficacy in an HIV-1 vaccine study [6]. This has driven the field exponentially forward in delineating immune responses that correlate with, and may be involved in, the mechanism of observed protection, setting the scene for the next decade of HIV-1 vaccine science.

Fortunately too, the HIV vaccine field is plerthic with viral vector platforms for HIV vaccine delivery. Most advanced in development are the nonreplicating viral vectors [7] that have been studied extensively through to efficacy trials. Most notable of these is ALVAC, a canary-pox-based vaccine, studied as part of a prime–boost regimen in combination with a recombinant gp120 subunit vaccine in the RV 144 trial. ALVAC is now poised for testing further afield in high HIV incidence areas in southern Africa [1]. Further clinical research into other orthopoxvirus-based vaccines such as vaccinia (NYVAC, MVA) or fowlpox will expand our knowledge on the utility of these delivery systems. Extensive evaluation of the highly immunogenic adenovirus type 5-based vaccine platform in three proof-of-concept efficacy trials has definitively demonstrated the lack of efficacy of these candidates [8–10], making it unlikely that this vaccine delivery system will be utilized further. However, investigating other human adenovirus serotypes, such as Ad26 and Ad35, as well as nonhuman adenovirus viral vectors remain important strategies to refine our understanding of optimizing platform delivery in the nonreplicating viral vector realm.

Investing in live attenuated viral vaccines, which have been shown to induce durable, multi-component immunity thereby enabling the containment of highly contagious pathogens, make the approach of using replication-competent vector in HIV highly compelling. In particular, the advancement of live attenuated viral vectors capable of infecting mucosal surfaces and initiating replication on submucosal and lymphoid tissues for sexually acquired infections such as HIV is meritorious [11]. Advancing vaccine prototypes on the basis of vesicular stomatitis virus, vaccinia, measles and Sendai into clinical testing with optimal

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immunogen inserts will provide much needed information on the role of this approach in improving the magnitude and quality of immune responses.

However, the critical breakthrough for HIV vaccine science will probably be in the development of envelope immunogens capable of inducing durable, broadly neutralizing antibodies at optimal levels that will be associated with protection. It has been proposed that vaccines utilizing a combination of consensus and transmitter-founder envelopes may be capable of inducing neutralizing responses that are more potent and broader than single-envelope immunogens [12]. Further development of mAbs administered as biologics in passive immunization or as inserts in viral vectors may help to expand our immunogen portfolio. The identification of correlates of HIV-1 risk from the RV144 study has catalyzed research investigating envelope structure and host–pathogen interaction aimed at guiding the immune system towards susceptible sites on the envelope as well as improving existing envelope immunogens that may translate into more durable protection. Recent results from RV144 demonstrate that protection from HIV infection can occur in the absence of neutralizing antibodies or cytotoxic T-cell responses [13]. RV144 showed that qualitative differences in vaccine-induced humoral responses against the V2 loop, associated with low levels of IgA and high levels of antibody-dependent cellular cytotoxicity, may have contributed to the protection observed. Understanding the antiviral mechanisms of protection of nonneutralizing antibodies at the mucosal surface may provide an unprecedented breadth of approaches that aid immunogen design [14]. Hopefully, our current Achilles’ heel, the paucity of immunogens capable of inducing the spectrum of both broadly neutralizing and functional HIV-specific nonneutralizing antibodies, will soon be overcome.

In this Current Opinion series, state-of-the-art updates in HIV vaccine science are presented covering the recent explosion of knowledge that has been gained since RV144 and the realization that we will be expanding these findings in other regions of the world using an increasingly powerful arsenal of tools based on rational immunogen design and a deeper understanding of the protective immune responses required by HIV vaccines to realize the goal of a globally effective HIV vaccine.

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