SPECIFIC AIMS

Protective vaccines and cure strategies for human immunodeficiency virus type 1 (HIV-1) that causes Acquired Immune Deficiency Syndrome (AIDS) are global health priorities, but have been elusive. In 2020, there were approximately 37.6 million global HIV-1 diagnoses and 1.5 million new infections (UNAIDS). Even wide and sustained implementation of combined antiretroviral therapy (cART) will require decades before eradication of the latent reservoir can be achieved (1-4). Potent broadly neutralizing monoclonal antibodies (bNAbs) have provided proof of concept that passive bNAb administration can prevent HIV-1 infection in animal models (5-7). The potency of bNAbs has also been evident in pre-clinical and clinical treatment studies that demonstrated their ability to control virus replication (8-11) and impact the size of virus reservoirs ((12-14) also reviewed in (15). Additionally, vaccine-induced potent autologous neutralizing antibodies (NAbs), with shared characteristics of bNAb precursors can prevent simian-HIV (SHIV) infection in non-human primates (NHP) (16), and have also been elicited by our group (see FOCUS 1 preliminary data). Lastly, NHP studies from multiple investigators have established the important role of HLA-class I-restricted CD8 T cell responses in preventing and controlling virus infection (recently reviewed in (17)).

In this UM1, building upon recent advances in HIV immunology and vaccine clinical research, we hypothesize that a vaccine strategy capable of inducing both polyfunctional NAbs and CD8 T cell responses would be the optimal regimen to both prevent and cure HIV-1. The in vivo mechanistic studies proposed in this application will reveal the extent to which NAbs and CD8 T cell responses will contribute to prevention and eradication of HIV-1 infection. We will build upon our development of our vaccine strategy that can induce protective NAb responses in NHPs by exploring innovative mRNA constructs for immunogen delivery that can elicit both NAb and CD8 T cell responses. The vaccine regimen will ultimately represent a novel approach for prevention as well as treatment of HIV-1 infection. For treatment, we will evaluate the ability of this vaccine regimen to act in concert with the latest generation of latency reversing agents (LRA) that has been recently described as potent and successful in the NHP model (14, 18) in addition to novel anti-HLA-E/ VL9-peptide complex mAbs that can block NKG2A-HLA-E/VL9 interactions to enhance the cytotoxic activity of CD8 and NK cells, and as well, enhance NK cell antibody dependent cellular cytotoxicity (ADCC) (19-21).

Research FOCUS 1: Vaccine-induced NAb protection from HIV-1 infection (leaders: Williams and Haynes): we will evaluate the ability of vaccine-induced polyfunctional NAbs to protect NHPs from an autologous SHIV challenge and determine their impact on selection of escape variants that seed the latent reservoir (Aim 1). In addition, we will test our previous strategy of recombinant soluble stabilized (SOSIP) trimer induction of protective NAbs, and our improved strategy using multimeric SOSIP nanoparticles (NPs) to generate higher levels of protective NAbs. Based on the unprecedented success of mRNA-based vaccines for prevention of COVID-19, with Drew Weissman, we will design mRNA vaccines to induce NAb responses in conjunction with CD8 T cell responses to improve protection in NHPs (Aim 2). Analysis of sequences from breakthrough SHIV isolates and the latent reservoir will be used to design new immunogens to explore the protective action of a novel priming and boosting vaccine strategy developed to induce breadth of NAbs against autologous SHIV escape variants (Aim 3).

Research FOCUS 2: Therapeutic vaccine regimen in association with LRA and cellular cytotoxic licensing mAb for eradication of latent reservoir (leaders: Ferrari and Betts): we will evaluate the impact of therapeutic vaccine-induced NAbs and cellular responses combined with LRAs from David Margolis at UNC and Richard Dunham of Viiv to reduce and/or eliminate HIV-1 latent reservoirs. We will evaluate the ability of NAbs as vaccine-induced responses and as passive infusions of IgG collected from vaccine-induced protected animals in FOCUS 1 to reduce the latent reservoir (Aim 1). We will also evaluate the ability of humoral and cellular responses elicited by the newly designed T+B cell vaccine in FOCUS 1 to reduce or eliminate the latent reservoir following administration of effective LRAs (Aim 2). The newly designed priming and boosting vaccination strategy (FOCUS 1) will also be tested with LRAs in combination with novel anti-HLA-E/ VL9-peptide complex mAbs (Aim 3) recently identified in collaboration with our colleagues at Oxford University (22).

NHP-SHIV Centralized Research Resources (CRR): Design of barcoded-SHIV for a latency model and conduct NHP studies (leaders: Santra and Bar): we will produce appropriate SHIV stocks that are barcoded as described by Fennessey et al. (23) to investigate the diversity of the virus reservoir. The NHP-SHIV CRR will produce the new challenge stocks designed to represent breakthrough isolates from FOCUS 1-Aims 1-2 and FOCUS 2-Aim 1 studies to evaluate the efficacy of the new prime-boost regimen. Moreover, the NHP-SHIV CRR will process and distribute samples from all NHPs.

Expected outcomes: We will test our previously protective B cell-based HIV-1 vaccine and compare to a mRNA-based vaccine strategy, which has been widely used to ameliorate the COVID-19 pandemic, to enhance protection from HIV-1 acquisition by inducing B and T cell immunity. Successful completion of the studies in this proposal will demonstrate a role for protective HIV-1 vaccines in curing HIV/AIDS, thus providing a roadmap for eradicating HIV-1 using vaccine-induced protective polyfunctional responses and novel therapies.