Destroying the human immunodeficiency virus before infection

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Human Immunodeficiency Virus (HIV) is the cause of a debilitating disease called AIDS. It poses global health problems and has resulted in approximately 40 million deaths. Apart from that, 39 million people are still living with AIDS, which imparts a significant economic burden and necessitates vaccine development. Antiretroviral therapy (ART) has prolonged the life span of AIDS-infected patients. However, it cannot eradicate the disease, and its reversal occurs once the medication stops apart from the occurrence of resistance in HIV and new variants arise due to selection pressure. To date, eight vaccines have been in late-stage clinical trials, and none but one called RV144 (a recombinant vaccine containing gp120) has shown moderate success.

HIV envelope (Env) protein is the only protein on the surface of HIV, hence the target of many broadly neutralizing antibodies (bNAbs). However, HIV has evolved a mechanism of immune evasion using multiple strategies, such as concealing the Env through heavy glycosylation and showing different conformational states during its entry into the host cells. Recently, an off-state called state 2A has been discovered, showing the potential for Antibody-dependent cell cytotoxicity (ADCC) and, hence, the target of inhibitors and vaccine design. However, the high-resolution structure of this state 2A is still lacking because of Env diversity among strains and its conformational heterogeneity. So, based on our previous studies, we have designed a few experimental approaches to attain high-resolution structures of the state 2A, using single particle cryo-EM and will show some of the preliminary results. The high-resolution structure of state-2A will inform the development of new strategies for utilizing the ADCC response, which may facilitate efficient vaccine design and prevention of AIDS.

Moreover, several studies have reported that survivors of chronic HIV-1 infection elicited bNAbs with long CDRH3 targeting state-1 (closed conformation) of HIV-1 Env. Our Collaborators have shown the generation of bovine bNAbs containing ultra-high CDRH3 regions on sequential vaccination of cows with various SOSIP trimers and sorted these ultrapotent bNAbs, targeting CD4-binding site. We aim to elucidate the epitopes of these bNAbs on HIV-1 Env structurally, which may pave the way for efficient vaccine design and AIDS prevention.