Inducing Protective Antibody Response to HIV-1 with Inner Domain of gp120

Marzena Pazgier[1], William D. Tolbert[1], Neelakshi Gohain[1], Maxime Veillette[2], Jean-Philippe Chapleau[2], Chiara Orlandi[1], Andrés Finzi[2], George K. Lewis[1]

[1] Institute of Human Virology of University of Maryland School of Medicine; [2]Centre de Recherche du CHUM and Department of Microbiology, Infectiology and Immunology of Université de Montréal

Recent nonhuman primate studies and clinical trials suggest that antibody-mediated protection against HIV-1 will require anti-envelope (Env) humoral immunity beyond direct neutralization, to include Fc-receptor effector functions such as antibody-dependent cellular cytotoxicity (ADCC). In parallel, strong evidence points toward the transitional and non-neutralizing A32-like epitopes (Cluster A) of HIV-1 Env as major targets for potent ADCC responses. We were first to define these epitope targets at atomic level by describing structures of several A32-like antibodies in complexes with CD4-triggered gp120. Our studies mapped the A32-epitope into mobile layers 1 and 2 of the inner domain (ID) of CD4-triggered gp120. Here, we describe a stable molecule expressing the C1-C2 region epitopes within a minimal structural unit of HIV-1 Env. Through two phases of structure-based design we developed a construct, referred to as ID2, which consists of the inner domain of gp120 expressed independently of the outer domain and stabilized in the CD4-bound conformation by an inter-layer disulfide bond. Each phase of the design process was visualized and validated at the molecular level by structural analysis of ID variants complexed with anti-Cluster A antibodies as well as by functional testing. Our data indicate that ID2 expresses the C1-C2 epitopes involved in potent ADCC within the context of a CD4-triggered full-length gp120, but without the complication of other epitope regions. Thus, ID2 represents a novel candidate probe for the analysis and/or selective induction of antibody responses to the A32 epitope sub-region. We also present the crystal structure of ID2 complexed with mAb A32, the canonical antibody of the Cluster A region. This represents the first structural analysis of mAb A32 bound by its Env antigen defining its epitope.