

Structural basis for HIV-1 Env recognition of the unmutated common ancestor of the CH235 antibody lineage

In this project we are interested in investigating the structural basis for the development of HIV-1 neutralization efficacy in an antibody lineage isolated from an HIV-1-infected individual. We have determined structures at 4.2 Å, of the unmutated common ancestor, which is an early progenitor with very limited neutralization breadth, in complex with an HIV-1 Env immunogen designed to enable binding to this early lineage member. This structure has recently been published in Plos Pathogens (PLoS Pathog. 2019 Sep 17;15(9):e1008026.)

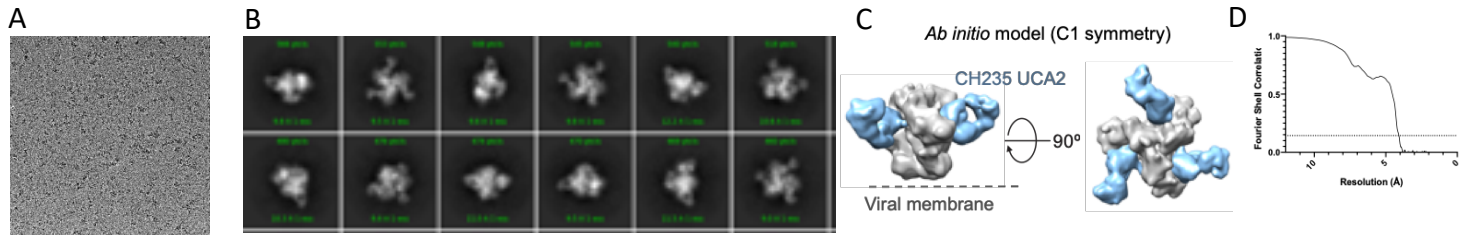


Figure 1. Structural determination of Fab CH235UCA in complex with HIV-1 Env at 4.2 Å resolution. (A) Representative micrograph. (B) 2D class averages. (C) *Ab initio* model showing CH235UCA in blue and HIV-1 Env in gray. (D) Fourier shell correlation curve of final refined map with C3 symmetry. The dotted line indicates FSC_{0.143}.

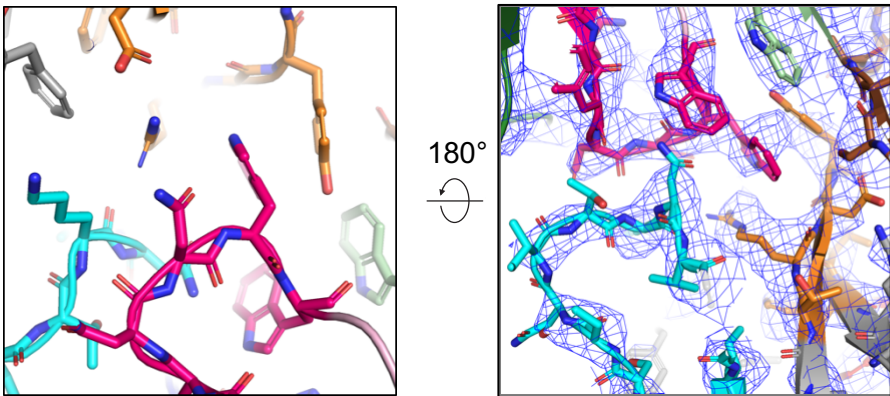


Figure 2. Details of CH235 UCA interaction with HIV-1 Env immunogen Man₅-enriched CH505.N279K.G458Y.SOSIP. (Left) The cryo-EM structure reveals a critical interaction between the complementarity determining loop 3 (CDR L3) (magenta) with loop V5 (orange) and loop D (cyan) of HIV-1 Env gp120. (Right) A 180° rotated view showing the cryo-EM density as blue mesh.

The goal of this study and its next steps are to determine structures of the CH235UCA without the loop mutations. While antibody binding affinity may be reduced, these structures will allow us to understand the barriers faced during maturation of the CH235 lineage. We also aim to solve structures of the same set of Envs with the mature CH235.12 antibody to understand the structural transition between the UCA and the mature.

The list of structures we need to determine are as follows:

Env	Antibody	Scientific question
CH505TF SOSIP/complex glycans	CH235UCA	Interaction of UCA and mature antibodies with the transmitted founder Env
	CH235.12	
CH505.N279K SOSIP/complex glycans	CH235UCA	Interaction of UCA and mature antibodies with unmutated loop V5
	CH235.12	
CH505.N279K SOSIP/ Man ₅ -enriched glycans	CH235UCA	Interaction of UCA and mature antibodies with unmutated loop V5, shorter glycans
	CH235.12	
CH505.G458Y SOSIP/complex glycans	CH235UCA	Interaction of UCA and mature antibodies with unmutated loop D
	CH235.12	
CH505.G458Y SOSIP/ Man ₅ -enriched glycans	CH235UCA	Interaction of UCA and mature antibodies with unmutated loop D, shorter glycans
	CH235.12	

For all these complexes (total 10), we have screened grids ready for data collection. All these grids have well-dispersed particles and robust 2D class averages similar to what is shown in Figure 1.