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Probing CD4-HIV-1 gp120 Glycoprotein Interaction

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CD4-gp120 interaction is the first step for HIV-1 entry into host cells. A highly conserved pocket in gp120 protein is an attractive target for developing gp120 inhibitors or novel HIV detection tools. Here we incorporate seven phenylalanine derivatives having different sizes and steric conformations into position 43 of domain 1 of CD4 (mD1.2) to explore the architecture of the 'Phe43 cavity' of HIV-1 gp120. The results show that the conserved hydrophobic pocket in gp120 tolerates a hydrophobic side chain of residue 43 of CD protein, which is 12.2 Å in length and 8.0 Å in width. This result provides useful information for developing novel gp120 inhibitors or new HIV detection tools. A fluorescently modified CD4 domain 1 (mD1) protein was also designed and elaborated in an *in vitro* expression system. This fluorescent probe contains a Förster resonance energy transfer (FRET) pair, which uses a tryptophan residue as the fluorescence donor and an acridon-2-ylalanine (Acd) as the acceptor. When excited at 260 nm, energy was transferred from tryptophan to the Acd residue of mD1 and emitted fluorescence at 420 nm. This fluorescence was quenched after Evans blue (EB) inhibitor or HIV-1 gp120 protein binding, presumably as a consequence of changes in the distance and dipole orientation between the donor and acceptor; the emission intensity at 420 nm decreased in a concentration-dependent fashion. This fluorescent CD4 probe could be developed into a novel tool for HIV-1 gp120 protein detection. It also could be used to screen small molecules that inhibit the gp120–CD4 interaction.

Biography

Poulami Talukder has her expertise in designing and synthesizing molecules as novel treatments for infectious diseases. As a graduate student at Biodesign Institute at Arizona State University, she successfully synthesized structurally optimized phenylalanine derivatives for incorporation into human CD4 protein to increase the binding affinity to HIV gp120 protein which provides useful information for developing novel gp120 inhibitors. She had also worked on developing a fluorescent CD4 probe as new HIV detection tool. While working as a postdoctoral fellow at UCSF School of Pharmacy she developed novel strategies for increasing the efficacy of known antibiotics against the gram-negative bacteria. She also worked on structure-activity relationship (SAR) of the antimalarial ozonides artefenomel (OZ439) and arterolane (OZ277) to improve their efficacies and ADME properties.

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