Poster

Structural perspective into rabies virus neutralization

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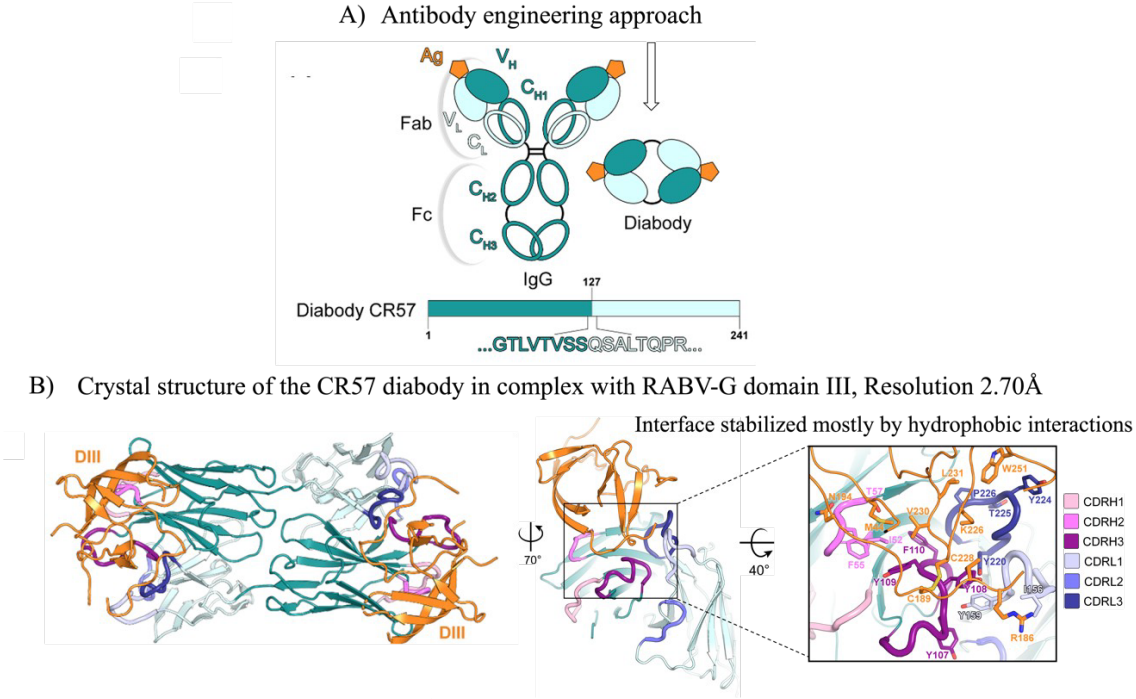
Rabies virus (RABV) is a lethal neurotropic virus which causes approximately 60,000 deaths annually [1, 2]. The trimeric glycoprotein (G) spikes of RABV are the only surface-exposed proteins on the virion and mediates receptor recognition and host cell entry [3, 4]. RABV-G displays several epitopes which are targeted by antibodies, including neutralizing monoclonal antibodies (mAb) that have been proposed as effective alternatives to traditional polyclonal rabies immunoglobulin treatment [5-7]. In this study, one such neutralizing antibody, CR57, was engineered into a diabody to enable crystallization in complex with the targeted domain from rabies G. Here, we report the crystal structure of the RABV-G domain III in complex with the CR57 diabody at 2.7 Å resolution. The structure reveals the antibody epitope, where key interactions are targeted at a 6-residue hydrophobic peptide on RABV-G. We present an antigenic mapping of all known epitopes on the spike, which reveals two predominant sites of vulnerability to neutralization. Based on a structural analysis, we postulate two possible mechanisms for CR57-mediated neutralization: steric occlusion of receptor binding and of the fusogenic conformational changes. Our results provide a molecular description for rabies inhibition by one of the most potent antibodies against diverse rabies strains. This study also showcases the importance of the diabody as a crystallization scaffold for challenging targets.

Figure 1. A) Schematic representation of the design of CR57 diabody. Antigen (Ag) binding sites are denoted. B) Crystal structure of the CR57 diabody



in complex with RABV-G domain III, resolved at 2.7Å resolution, and a magnified view of the CR57 diabody– RABV-G domain III interface, where key interacting residues are labelled and shown as sticks with oxygen atoms in red and nitrogen atoms in blue.

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