



**Supplementary information, Fig. S2: Interaction between the outer helices of HR2s and HR1 ( $\alpha 2$ ) with inner HR1 trimer ( $\alpha 1$ ,  $\alpha 3$ , and  $\alpha 4$ ).**

**a** Left: Electrostatic potential surface of the inner HR1 trimer ( $\alpha 1$ ,  $\alpha 3$  and  $\alpha 4$ ). Hydrophobic surfaces are colored in whitish gray, basic in blue, and acidic in red, the same in other panels. Each of two adjacent HR1 helices forms a hydrophobic groove, in which an HR2 (shown in cartoon representation and colored in orange) is embedded. Middle: Hydrophobic interactions between HR2 and the inner HR1 trimer. Key hydrophobic residues in an HR2 binding to the inner HR1 trimer are indicated by orange sticks and labeled. Right: HR2 hydrophobic residues involved in hydrophobic interactions with the inner HR1 trimer. **b** Hydrophilic interaction between an HR2 and an HR1 in the inner HR1 trimer. Residues that mediate the interaction of the HR1 and HR2 are indicated by sticks and marked aside. hydrogen bonds are labeled in dark grey lines. **c** Left: The HR1 ( $\alpha 2$ , colored in purple) shown in cartoon representation embedded in hydrophobic groove of the inner HR1 trimer. Middle: Hydrophobic interactions between the HR1 ( $\alpha 2$ ) and the inner HR1 trimer. Key hydrophobic residues in the HR1 ( $\alpha 2$ ) are indicated by purple sticks and labeled. Right: the HR1 ( $\alpha 2$ ) hydrophobic residues involved in hydrophobic interactions with the inner HR1 trimer. **d** Hydrophilic interaction between the HR1 ( $\alpha 2$ ) and two HR1s in the inner HR1 trimer. Residues that mediate the interaction of the HR1 and HR2 are indicated by sticks and marked aside. hydrogen bonds are labeled in dark grey lines. **e** Electrostatic surface on the two exposed surface grooves on the outer HR1 trimer of HR121. These two grooves are covered highly charged amino acid residues. The outer HR1 trimer of HR121 are surrounded by one HR1( $\alpha 1$ , colored in light greys) and two HR2s (colored in orange and dark orange, respectively). The right image is the result of rotating the left image 120° toward the viewer. Black arrows point to the possible HR2 or antibody binding grooves. **f** Electrostatic surface grooves on the HR1 trimer of SARS-CoV-2 6-HB. The two corresponding HR2s (which are lacked in HR121) in cartoon mode (colored in black) are embedded in the hydrophobic grooves in the HR1 trimer. The right image is the result of rotating the left image 120° toward the viewer.