

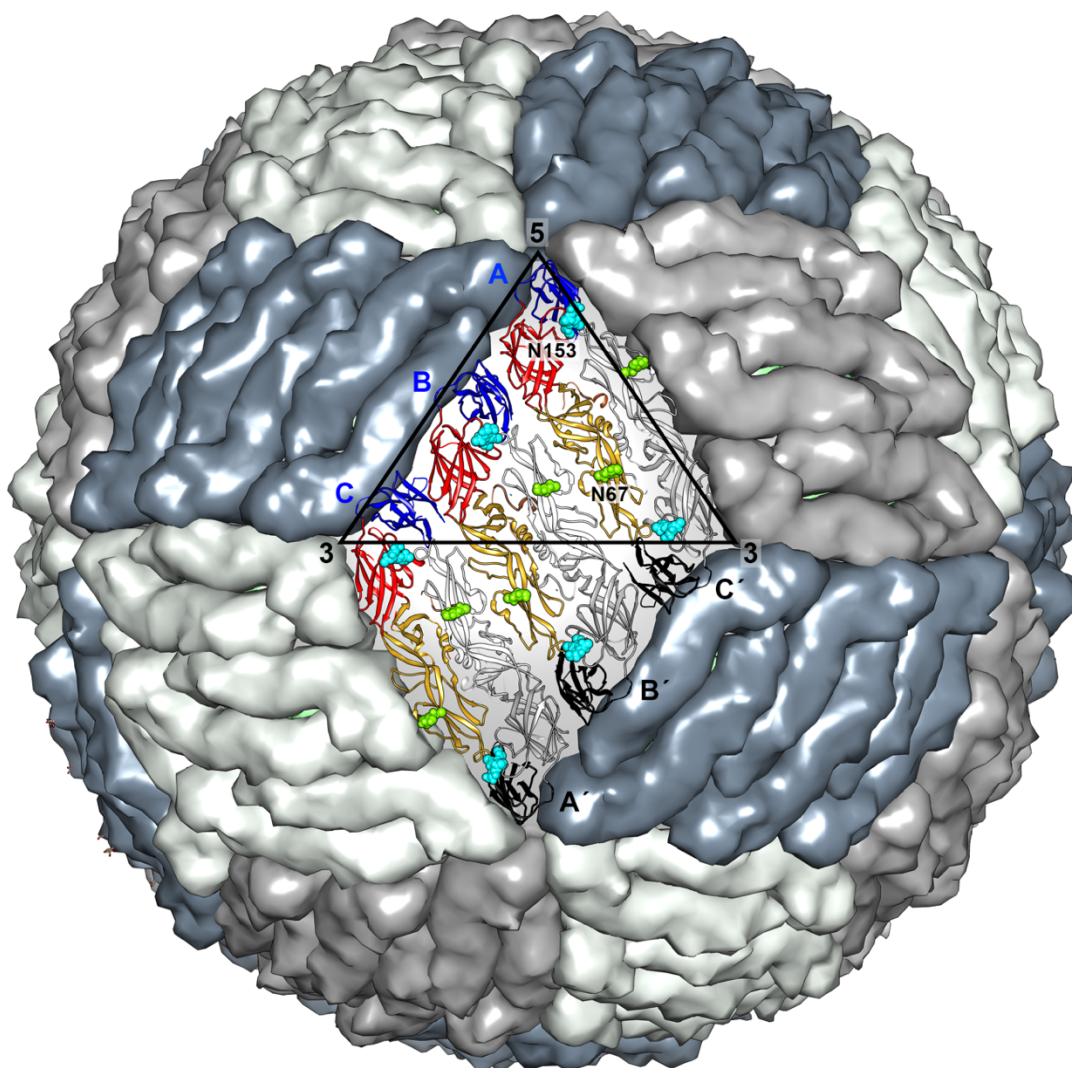
Supplementary Text

The binding orientations of Fabs 2D22 and C10 on DENV2 WT and the N153Q mutant

The binding axes of Fabs 2D22 and C10, when bound to their respective epitopes on the E proteins of DENV2 WT and N153Q, are shown in **Fig. 6**. There are two groups of Fab 2D22 binding axes, the first group consists of Fab bound to epitopes near 2- and 3-fold vertices of DENV2 WT and N153Q mutant, and the second group consists of Fab bound to epitopes near the 5-fold vertices (**Fig. 6A**). Since the majority of the epitopes residues for Fab 2D22 are located on the DII of one E protein in a dimer (**Fig. 5A, and Tables S3-S5, S8-S10**), the presence of these two distinct groups of binding axes indicates there are two structurally different epitope on E protein dimer. These two epitopes differ based on the relative position of DII of one E protein and the DIII of the other E protein and/or adjacent E protein. Even though there are differences in the local structures of the epitopes, Fab 2D22 was still able to bind all epitope suggesting the flexibility of Fab paratope in recognizing the epitope residues. Notably, the distance between axes of the three Fab 2D22 binding sites on DENV2 N153Q is closer than those on the DENV2 WT indicating the N153Q reduced the local structure differences between the three epitopes on the virus (**Fig. 6A**). This resulted in similar Fab 2D22 occupancy at the three epitopes near to 2-, 3-, and 5-fold vertices in the DENV2 N153Q mutant, with occupancy level of 0.79, 0.72, and 0.75, respectively.

Different from Fab 2D22, Fab C10 binds to the epitopes near the 2-, 3-, and 5-fold vertices of DENV2 WT and the N153Q mutant in a more unified manner. The interacting residues in the epitope of Fab C10 are distributed almost equally on DII of one E protein and DII/DI-DII hinge region/DIII of the other E protein (**Fig. 5B, Tables S6-S7, S11-S13**). The Fab C10 binding axes are clustered into a single group, indicating a stricter structural requirement of the epitope for Fab binding (**Fig. 6B**). The epitope located near the 5-fold

vertices of DENV2 WT likely does not fit the structural requirement, hence there is no Fab C10 binding at this epitope. However, this epitope on DENV2 N153Q mutant was able to adopt a conformation that permitted Fab C10 binding. Superposition of the DII of E protein structures of uncomplexed and Fab C10-complexed DENV2 WT and N153Q near the 5-fold vertices showed that the DIII of the E protein in DENV2 N153Q mutant has a different conformation, moving away from the Fab C10 bound position (**Fig. S6B**). This suggests that DENV2 N153Q exhibits higher structural flexibility compared to DENV2 WT, allowing such movement and accommodating the Fab C10 binding at this epitope.



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38 **Figure S1. The arrangement of E proteins on a mature DENV particle.** Each E protein
 39 consists of three domains: DI, DII, and DIII. Two E proteins form a head-to-tail dimer, and
 40 three of these E protein dimers are arranged parallel to each other, forming a raft structure. A
 41 total of 30 E protein rafts are present on the DENV surface, arranged in a herringbone pattern.
 42 The E protein rafts are depicted in different shades of grey. One E protein raft is represented in
 43 ribbon form, with DI, DII, and DIII of E protein molecules A, B, and C colored in red, yellow,
 44 and blue, respectively. The corresponding domains of molecules A', B', and C' are depicted in

various shades of grey. Glycosylation at residues N67 and N153 is shown as light green and cyan spheres, respectively. The black triangle indicates an icosahedral asymmetric unit.

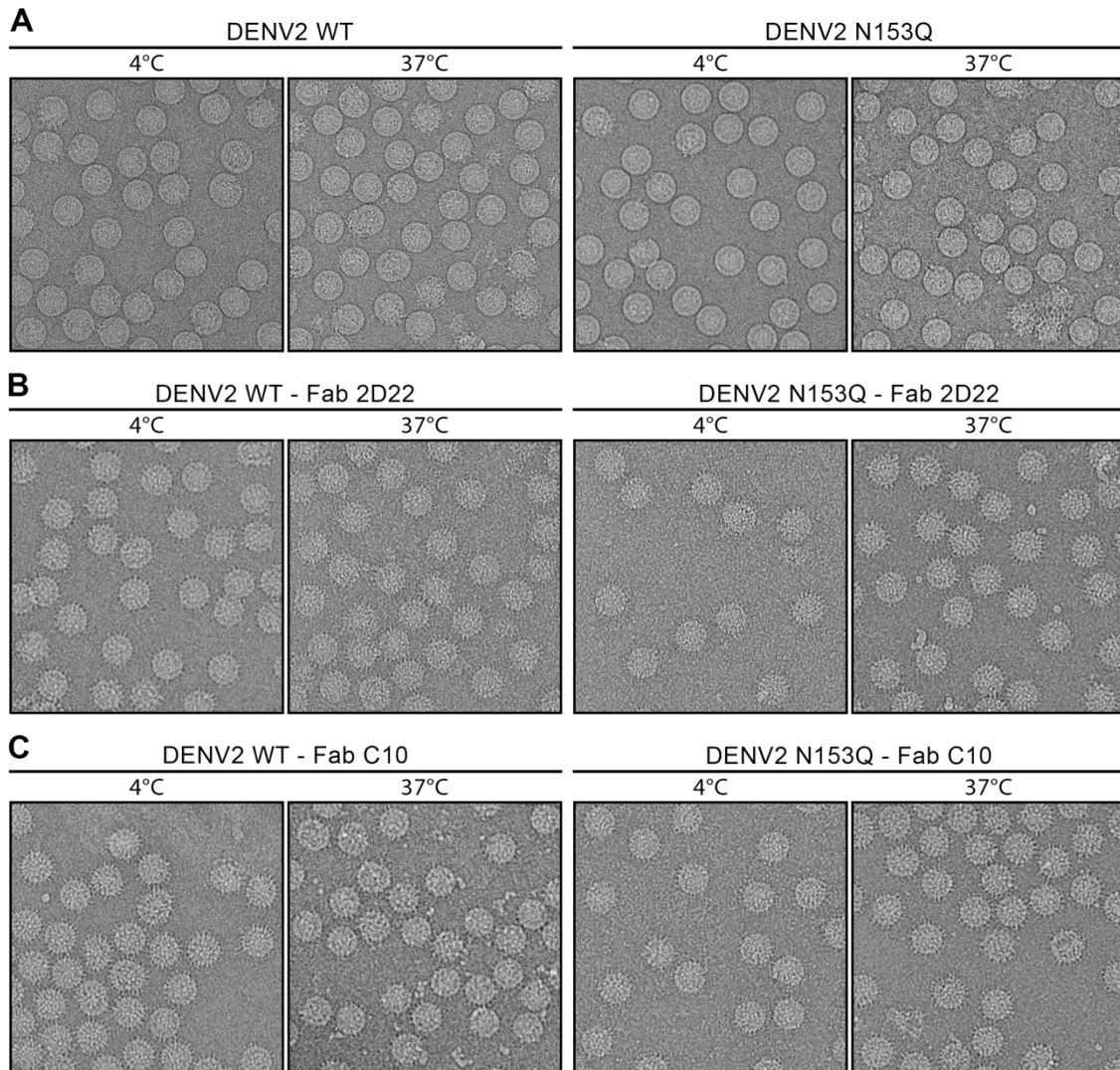


Figure S2. Cryo-electron micrographs of the uncomplexed DENV2 (WT and N153Q mutant) and the virus complexed with Fab 2D22 or C10 at 4 and 37 °C. Both the DENV2 WT and N153Q mutant maintain their morphology at 37°C. Fabs 2D22 and C10 bind to the DENV2 particles at both 4 and 37 °C, resulting in a spiky appearance of the virus particles where the Fabs are bound.

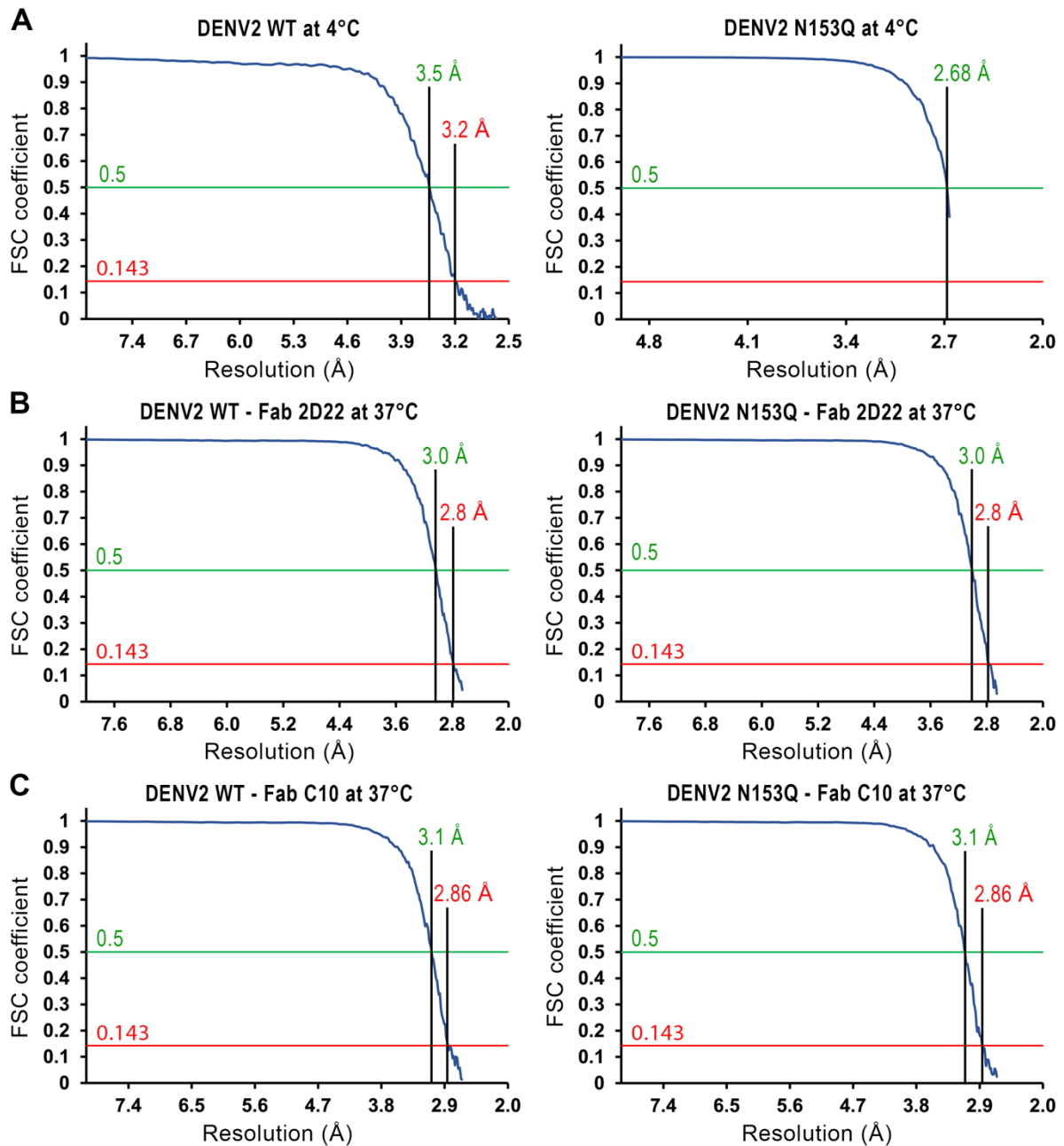
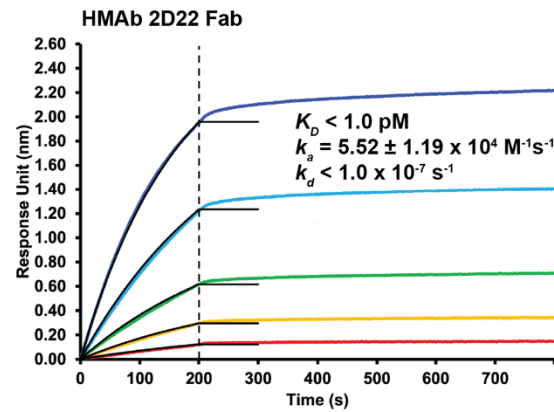
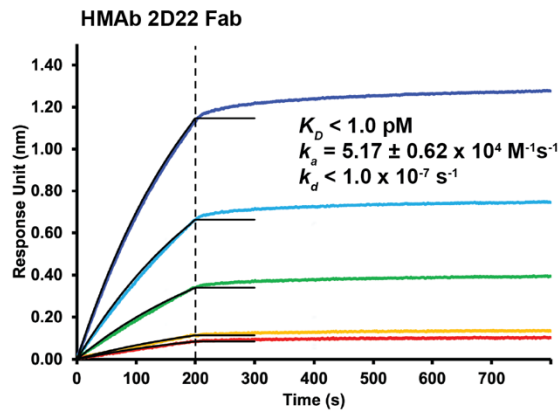
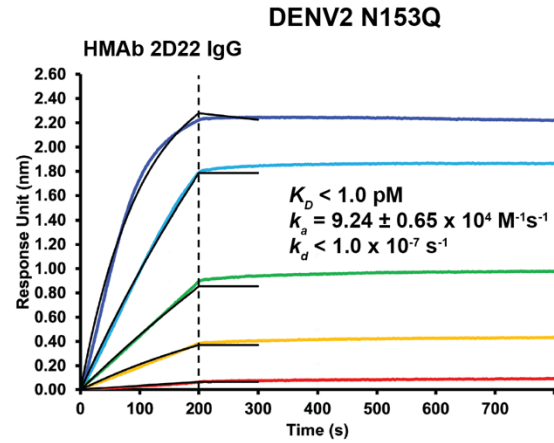
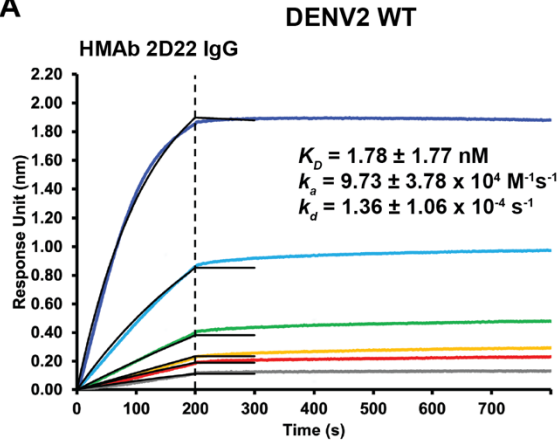
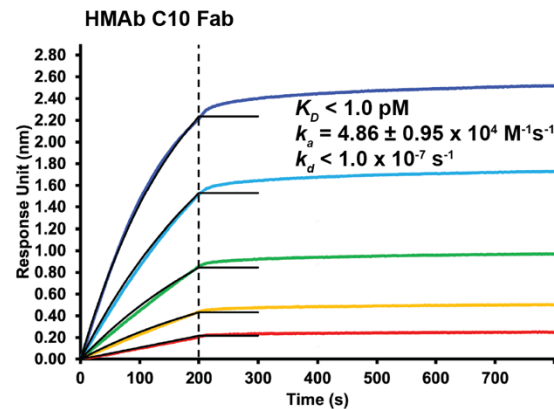
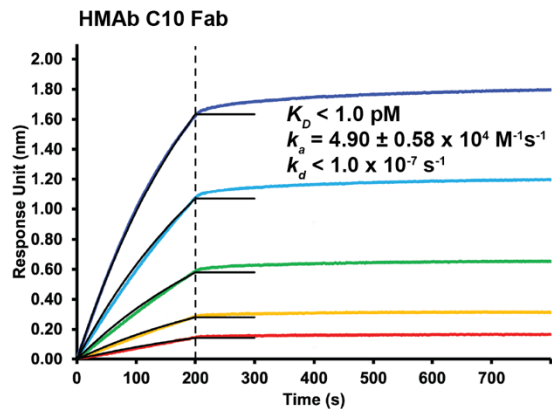
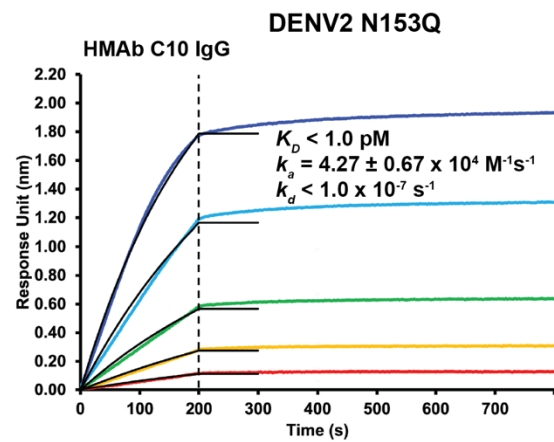
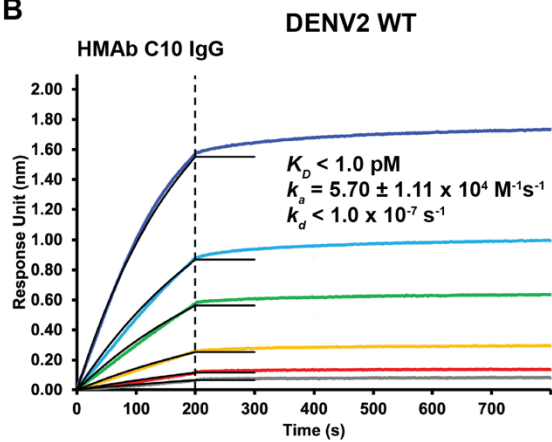


Figure S3. Resolution assessment of the cryoEM density maps by Fourier Shell Correlation (FSC). The FSC curves for all cryoEM maps are displayed. The FSC curve is calculated by comparing two independently reconstructed maps, each derived from a half-dataset, at the final refinement iteration step. The resolutions at the 0.143 and 0.5 FSC cut-off values are indicated.

A**B**

100 nM 50 nM 25 nM 12.5 nM 6.25 nM 3.125 nM

Figure S4. HMABs 2D22 and C10 bind to DENV2 WT and N153Q with higher affinity at 37 °C. (A-B) HMABs 2D22 and C10, in both IgG and Fab forms, bound DENV2 WT and N153Q with high affinity at 37 °C. The binding affinities of both antibodies were higher at 37 °C than to at 30 °C (**Figs. 3D and 3E**). The binding affinity at 37 °C was measured by biolayer interferometry. The experiment was repeated three times for each antibody-virus combination, and a representative sensorgram is shown.

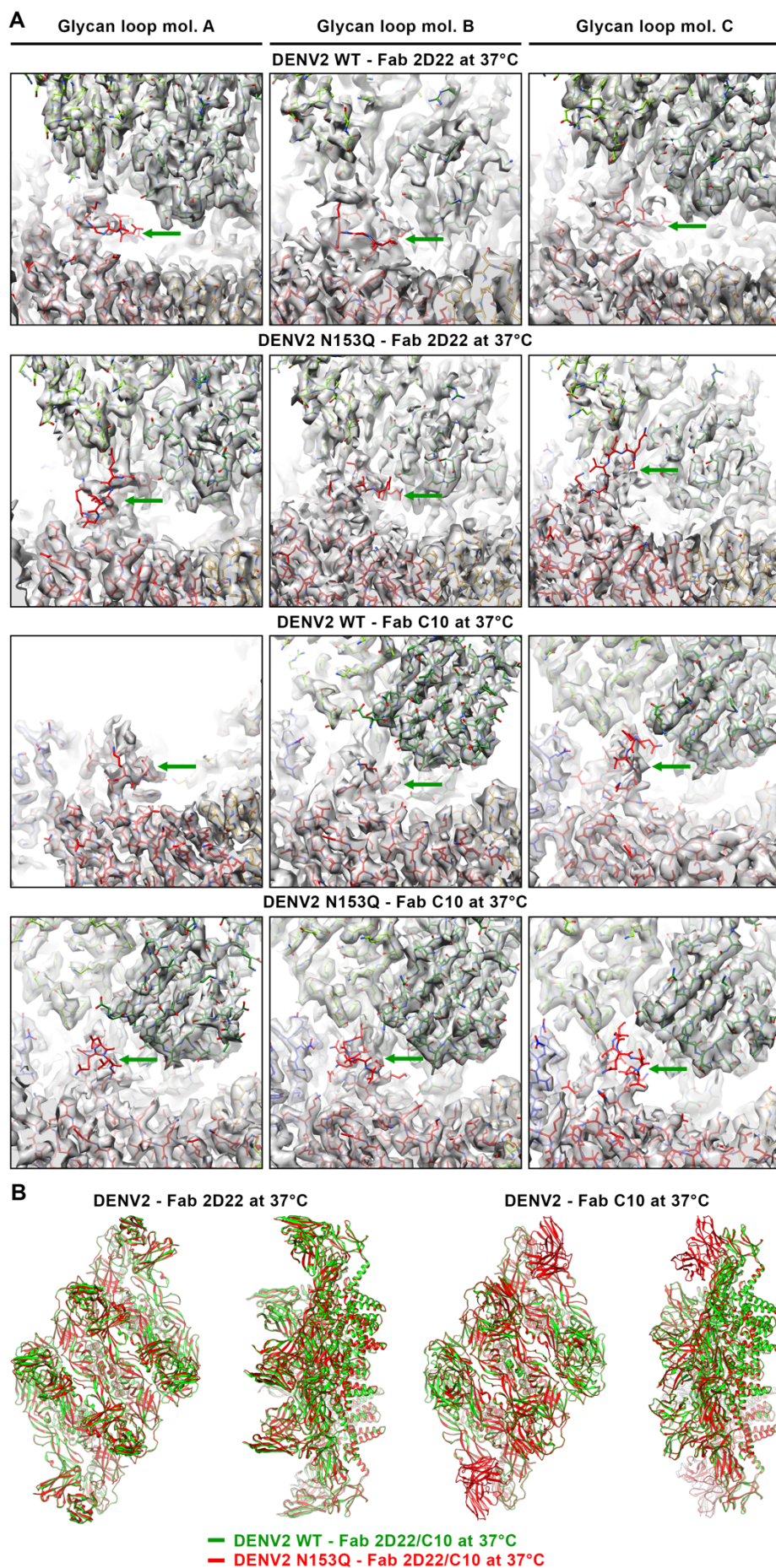


Figure S5. Fabs 2D22 and C10 binding to the E protein disrupted the glycan loop structure. (A) The glycan loop densities became poor when Fab 2D22 or C10 were bound to the DENV2 WT and the N153Q mutant. The coordinate models of the glycan loops (residues 140-160) could not be properly fitted into the densities. Only the glycan loop on E protein molecule A of the DENV2 WT in complex with Fab C10 showed well-defined densities. This is because Fab C10 are likely poorly bound to this site. CryoEM maps are shown as a transparent grey surface, while the E protein and Fab 2D22 and C10 are depicted in stick representation. The E protein DI, DII, and DIII are colored in red, yellow, and blue, respectively, while the heavy and light chains of Fabs 2D22 and C10 are in dark and light green, respectively. The glycan loops on E protein molecules A, B, and C of each virus complex are pointed out with green arrows. (B) Superposition of the Fab 2D22 complexed DENV2 WT and N153Q structures and the respective viruses complexed with Fab C10. The superimposed structures of Fabs 2D22 and C10 complexes showed that both Fabs bound to the E protein of the wild type virus and the N153Q mutant in the same binding conformation. There are minimal structural differences between the E proteins of the DENV2 WT and those of the N153Q mutant.

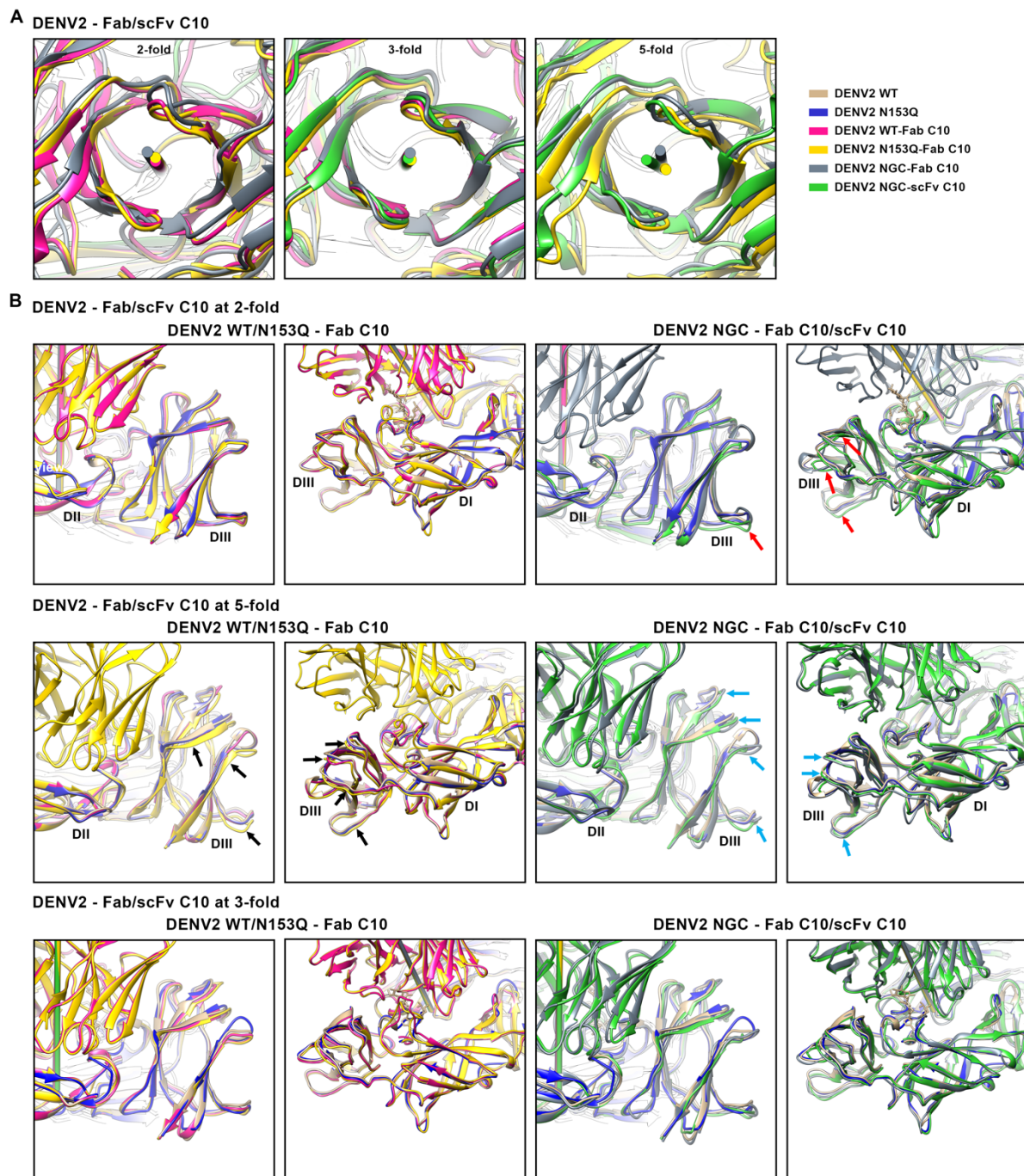


Figure S6. Conformational changes in the E protein upon binding of Fab C10. (A) The binding axes of Fab C10/scFv C10 on DENV2 WT, N153Q, and DENV2 NGC are similar when Fab C10 binds to epitopes near the 2-fold and 3-fold vertices. However, slight variations are observed when Fab C10 binds near the 5-fold vertices. (B) [Top, left] Superimposition of E proteins at the 2-fold vertices of DENV2 WT/N153Q, with and without Fab C10, showed that the binding of Fab C10 to the E protein near the 2-fold vertices of DENV2 WT or N153Q

100 did not cause any conformational changes in the E proteins. [**Top, right**] The structure of the
101 DENV2 NGC – Fab C10 complex (PDB ID: 7V3H) shows that Fab C10 can bind to the E
102 protein at the 2-fold vertices, although with low occupancy (**Fig. 5C**)¹. However, in the similar
103 structure of the scFv C10 complexed with DENV2 NGC (referred to as NGC-2 here, as it is a
104 substrain with some mutations compared to the DENV2 NGC mentioned earlier, **Fig. S8**; PDB
105 ID: 7CTH), no Fab binding at this location was observed². Superimposition of the E proteins,
106 with and without Fab C10, indicates possible local structural differences at DIII in DENV2
107 NGC-2 (indicated by red arrows) that affect the Fab C10 binding. For reference, the respective
108 E proteins of uncomplexed DENV2 WT and N153Q, where Fab C10 binds to this epitope, are
109 shown. [**Middle, left**] Superimposition of E proteins at the 5-fold vertices of DENV2
110 WT/N153Q, with and without Fab C10, revealed that the binding of Fab C10 caused
111 conformational changes to the E proteins, particularly in the DIII region (indicated by black
112 arrows). These conformational changes are not observed in the E protein of the DENV2 WT –
113 Fab C10 complex where Fab C10 did not bind to the E protein. [**Middle, right**] The structures
114 of DENV2 NGC – Fab C10 and DENV2 NGC2 – scFv C10 complexes showed Fab/scFv C10
115 binding to the E protein at 5-fold. The superimposition of the E proteins of these complexes at
116 the 5-fold vertices with those of uncomplexed DENV2 WT and N153Q showed differences at
117 DIII region (indicated by blue arrows), similar to what is observed in DENV2 N153Q – Fab
118 C10 complex. [**Bottom, left**] Superimposition of E proteins at the 3-fold vertices of DENV2
119 WT/N153Q, with and without Fab C10, showed that the binding of Fab C10 to the E protein
120 near the 3-fold vertices of DENV2 WT or N153Q did not cause any conformational changes
121 in the E proteins. [**Bottom, right**] Similarly, the superimposed structures of the DENV2 NGC
122 in complex with Fab C10 or scFv C10 at the 3-fold vertices show that the Fab/scFv C10 binding
123 does not cause conformational changes when compared to the respective E proteins of
124 uncomplexed DENV2 WT and N153Q. The E protein-Fab complexes, from Fab that binds to

epitope near the 2-, 3-, or 5-fold vertices, were aligned separately in the same way as described in **Fig. 6**.

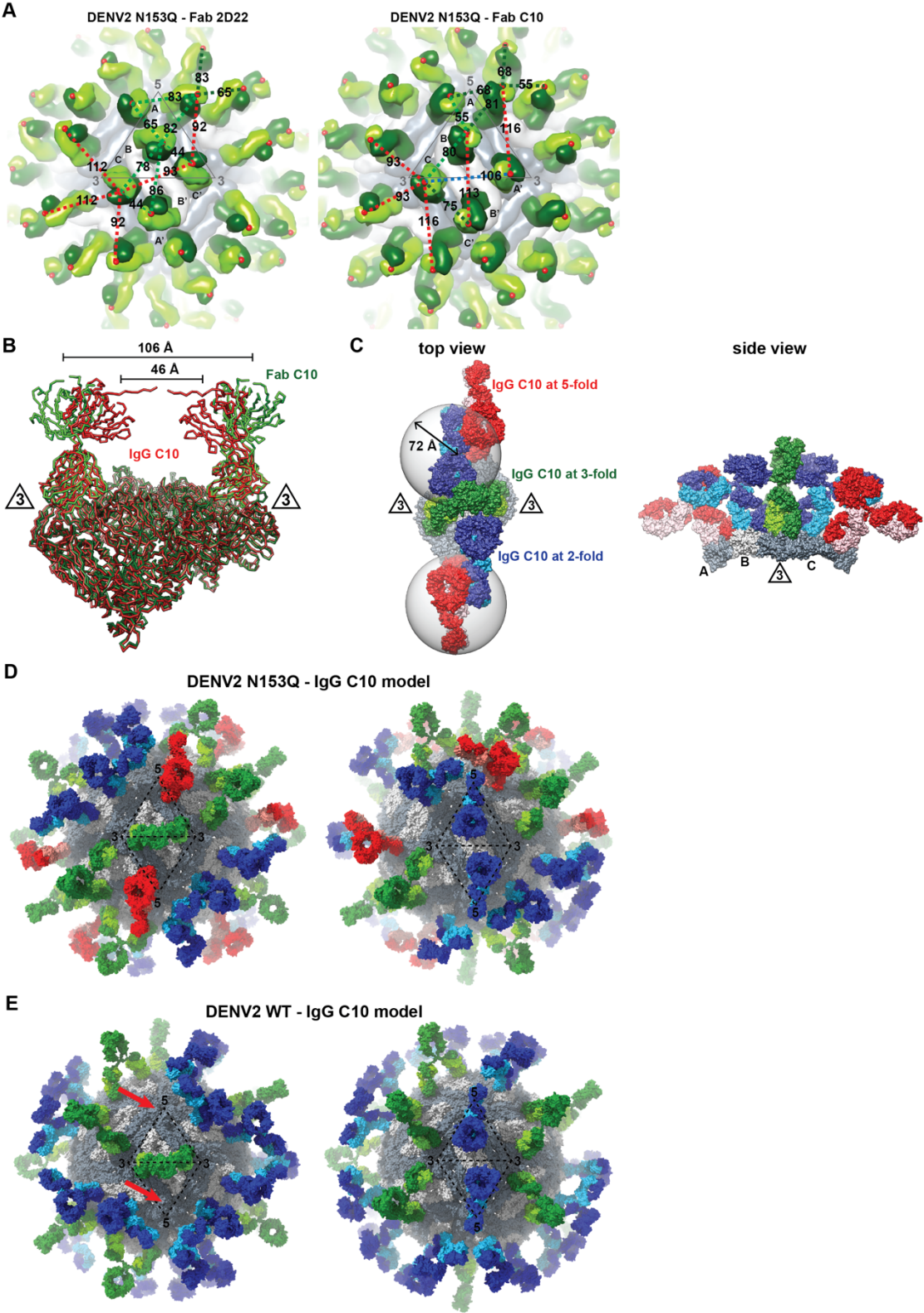


Figure S7. Model of IgG C10 binding to DENV2 WT and the N153Q mutant. (A) Fab-to-Fab distances in the DENV2 N153Q–Fab 2D22 and DENV2 N153Q–Fab C10 complexes. The maximum Fab-to-Fab span of an IgG is estimated to be $\sim 87 \text{ \AA}$ ³. Distances shorter than $87 \text{ \AA}$ are indicated by green dashed lines, whereas distances greater than $87 \text{ \AA}$ are indicated by red dashed lines. The Fab-to-Fab distance between Fabs located near the 3-fold vertices is shown in blue. **(B)** Comparison of Fab and F(ab')₂ binding to the epitope near the 3-fold vertices. Cryo-EM analysis of DENV2 NGC in complex with F(ab')₂ C10 showed simultaneous engagement of both Fabs with two epitopes near the 3-fold vertices within an E-protein raft¹. Binding of both Fabs to these epitopes brings their constant regions into closer proximity through bending at the C_HCL–V_HVL hinge. **(C)** Simultaneous binding of three IgGs C10 to epitopes near the 2-, 3-, and 5-fold vertices within an icosahedral unit is unlikely because of steric hindrance. Cryo-EM analysis of the DENV2 NGC–F(ab')₂ complex suggested that when IgG C10 binds to epitopes near the 2- or 5-fold vertices, only one Fab can engage, whereas the second Fab cannot access a nearby epitope¹. Binding of IgG C10 to an epitope near a 2-fold vertex would clash with IgG molecules bound near the 3- or 5-fold vertices, whereas simultaneous binding of two IgGs C10 to epitopes near the 3- and 5-fold vertices is feasible. The potential space occupied by the second Fab arm and Fc region is indicated by a circle of the indicated radius. IgG C10 molecules bound near the 2-, 3-, and 5-fold vertices are colored blue, green, and red, respectively. Heavy and light chains are shown in dark and light shades of the corresponding color. **(D)** Model of IgG C10 binding to DENV2 N153Q. IgG C10 can bind epitopes near the 2-, 3-, and 5-fold vertices. When IgG C10 binds epitopes near the 3-fold vertices within an E-protein raft (demarcated by dashed lines), additional IgG C10 molecules can bind epitopes near the 5-fold vertices (left panel). When an IgG C10 binds an epitope near a 2-fold vertex, other IgG molecules can bind only the equivalent epitope within the same raft (right panel). **(E)** Model of IgG C10 binding to DENV2 WT. IgG C10 can bind only epitopes

154 near the 2- and 3-fold vertices. Consequently, when IgG C10 simultaneously occupies both
155 epitopes near the 3-fold vertices within a raft (demarcated by a dashed line), some regions of
156 the viral surface remain unoccupied by IgG antibody (indicated by red arrows, left panel).
157 Binding of IgG C10 to epitopes near the 2-fold vertices is similar to that observed in the
158 DENV2 N153Q–IgG C10 model shown above (right panel).

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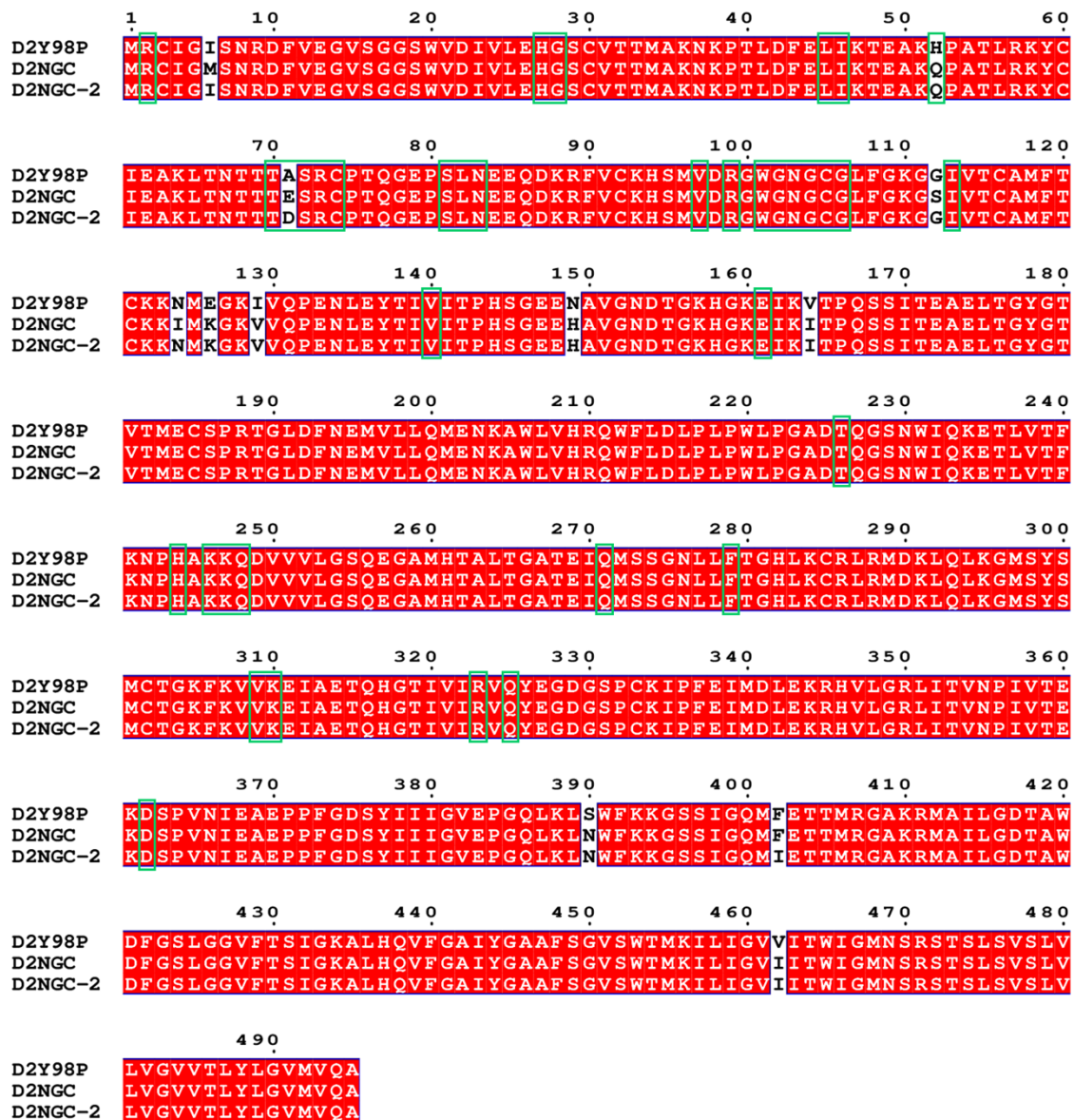
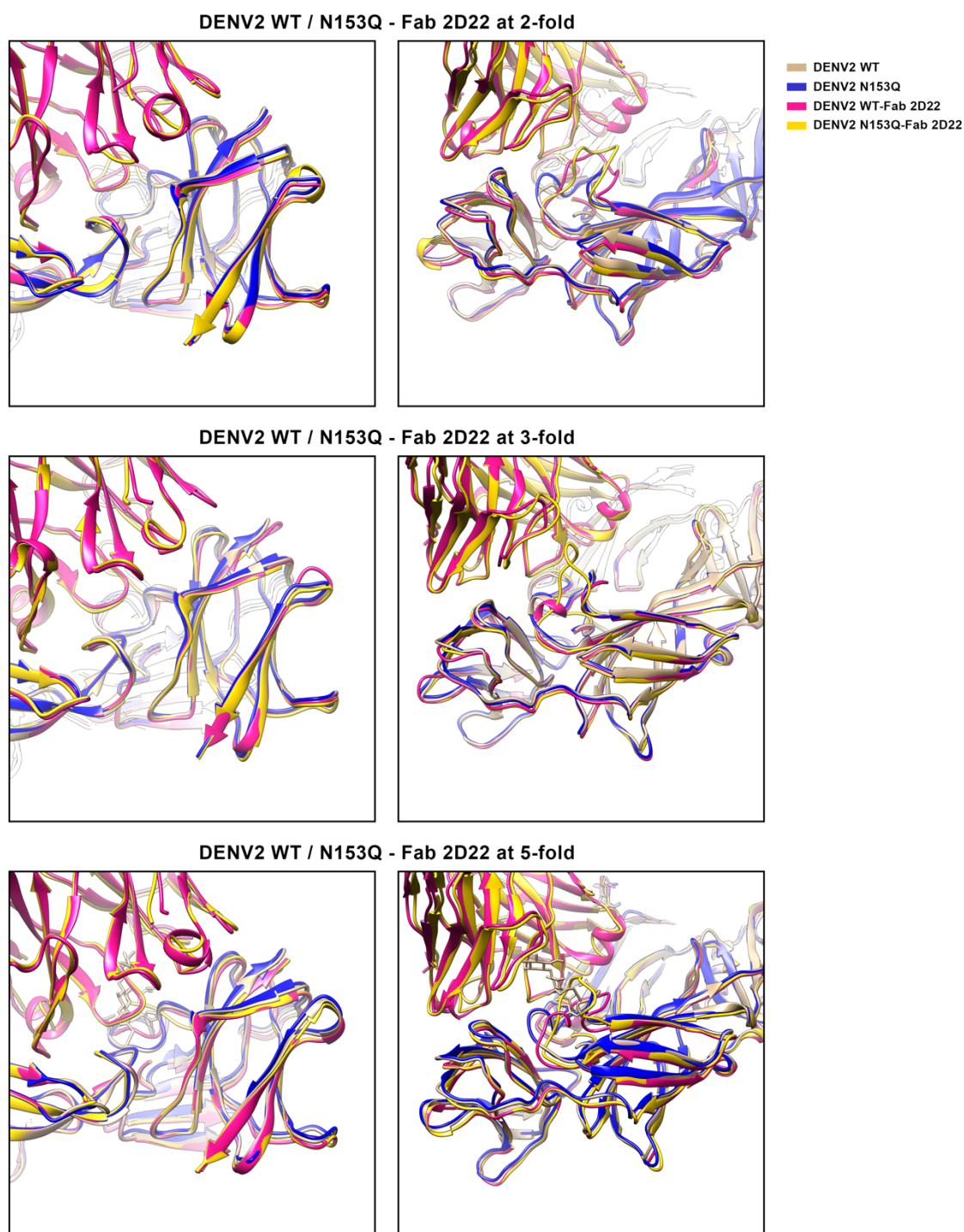


Figure S8. Sequence alignment of the E protein from DENV2 D2Y98P, DENV2 NGC and DENV2 NGC-2. DENV2 NGC is the strain used in the structure of the DENV2 NGC – Fab C10 complex, with PDB ID: 7V3H ¹. Whereas, DENV2 NGC-2 is the strain used in the structure of the DENV2 NGC – scFv C10 complex with PDB ID: 7CTH ².



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171 **Figure S9. The binding of Fab 2D22 to DENV2 WT and N153Q mutant does not induce**
 172 **conformational changes in the E protein.** Superposition of E proteins at the 2-, 3-, and 5-fold
 173 vertices of DENV2 WT and N153Q mutant, with and without Fab 2D22, showed that the
 174 binding of Fab 2D22 to the E protein did not cause significant conformational changes in the

175 E proteins. The E protein-Fab complexes, from Fabs that bind to epitopes near the 2-, 3-, or 5-
176 fold vertices, were aligned separately in the same way as described in **Fig. 6**.

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Table S1: Cryo-EM data collection, refinement and validation statistics of DENV2 WT and N153Q

	DENV2 Y98P-PP1 at 4 °C (EMD-38884, PDB 8Y3J)	DENV2 Y98P-PP1 N153Q at 4 °C (EMD-38881, PDB 8Y3G)
Data collection and processing		
Microscope	FEI Titan Krios	FEI Titan Krios
Voltage (kV)	300	300
Camera	Gatan K3	Gatan K3
Pixel size (Å)	1.345	1.345
Magnification	64,000	64,000
Number of micrographs	1,980	8,533
Dose rate e ⁻ /Å ² .s ⁻¹	5.27	5.78
Frames per movie	18	25
Total electron exposure (e ⁻ /Å ²)	23.75	25
Defocus range (µm)	-0.4 to -5.2	-0.4 to -5.1
Symmetry imposed	Icosahedral	Icosahedral
Initial particle images (no.)	212,371	640,232
Final particle images (no.)	14,421	173,676
Map-sharpening B-factor (Å ²)	-100	-94
Map Resolution (Å)	3.2	2.7
FSC threshold	0.143	0.143
Model refinement		
Initial model used (PDB code)	4UIF	4UIF
Model resolution at 0.5 FSC threshold (Å)	3.2	2.7
Model composition		
Non-hydrogen atoms	14,910	14,829
Protein residues	1,710	1,710
Ligand	9	3
Global CC (CC volume)	0.81	0.78
Local CC (CC mask)	0.87	0.87
B factors (Å ²)		
Protein	31.31	14.75
Ligand	66.82	30.43
R.M.S.D. deviations		
Bond lengths (Å)	0.005	0.003
Bond angles (°)	0.527	0.497
Validation		
MolProbity score	2.05	2.27
Clashscore	25.49	25.25
Rotamers outliers (%)	0.00	0.00
Ramachandran plot		
Favored (%)	97.17	94.46
Allowed (%)	2.83	5.54
Disallowed (%)	0.00	0.00
CaBLAM outliers (%)	2.14	4.09

Table S2: Cryo-EM data collection, refinement and validation statistics of DENV2 WT and N153Q complexes

	DENV2 Y98P-PP1 - Fab 2D22 at 37 °C (EMD-38885, PDB 8Y3K)	DENV2 Y98P-PP1 N153Q - Fab 2D22 at 37 °C (EMD-38882, PDB 8Y3H)	DENV2 Y98P-PP1 - Fab C10 at 37 °C (EMD-38886, PDB 8Y3L)	DENV2 Y98P-PP1 N153Q - Fab C10 at 37 °C (EMD-38883, PDB 8Y3I)
Data collection and processing				
Microscope	FEI Titan Krios	FEI Titan Krios	FEI Titan Krios	FEI Titan Krios
Voltage (kV)	300	300	300	300
Camera	Gatan K3	Gatan K3	Gatan K3	Gatan K3
Pixel size (Å)	1.345	1.345	1.345	1.345
Magnification	64,000	64,000	64,000	64,000
Number of micrographs	4,778	4,919	5,921	4,439
Dose rate e ⁻ /Å ² .s ⁻¹	5.40	5.15	5.42	5.19
Frames per movie	19	18	18	18
Total electron exposure (e ⁻ /Å ²)	25.69	23.22	24.43	23.37
Defocus range (µm)	-0.5 to -4.4	-0.5 to -5.0	-0.5 to -3.7	-0.5 to -4.7
Symmetry imposed	Icosahedral	Icosahedral	Icosahedral	Icosahedral
Initial particle images (no.)	281,127	272,647	337,394	242,187
Final particle images (no.)	123,807	149,073	64,522	102,447
Map-sharpening B-factor (Å ²)	-107	-106	-104	-119
Map Resolution (Å)	2.8	2.8	2.9	2.9
FSC threshold	0.143	0.143	0.143	0.143
Model refinement				
Initial model used (PDB code)	4UIF	4UIF	4UIF, 5H37	4UIF, 5H37
Model resolution at 0.5 FSC threshold (Å)	2.8	2.9	2.9	2.9
Model composition				
Non-hydrogen atoms	20,042	20,049	18,471	20,283
Protein residues	2,403	2,403	2,182	2,419
Ligand	3	3	4	3
Global CC (CC volume)	0.74	0.74	0.76	0.74
Local CC (CC mask)	0.83	0.83	0.81	0.82
B factors (Å²)				
Protein	11.20	15.76	195.60	17.91
Ligand	20.79	21.59	29.02	32.25
R.M.S.D. deviations				
Bond lengths (Å)	0.005	0.003	0.004	0.004
Bond angles (°)	0.542	0.487	0.499	0.623
Validation				
MolProbity score	2.20	2.27	2.22	2.27
Clashscore	27.23	30.36	27.76	32.36
Rotamers outliers (%)	0.10	0	0	0.00
Ramachandran plot				
Favored (%)	95.96	95.59	95.79	96.03
Allowed (%)	4.04	4.41	4.16	3.97
Disallowed (%)	0.00	0.00	0.05	0.00
CaBLAM outliers	2.85	3.23	2.52	2.19

208 **Table S3. Interacting residues between DENV2 WT and Fab 2D22 at 37°C (Fab 2D22**
209 **binds to an epitope located near the 5-fold vertices)**

No.	Fab 2D22 chain H	mol. A	mol. C'	mol. A*	mol. B*	Fab 2D22 chain L	mol. A	mol. C'	mol. A*	mol. B*
1	S17				D329	S26			S298	
2	N30		K247						Y299	
3	I52		N103			S30	K307			
4	I54		T70				Q325			
5			K247			S31			S298	
6			T70				V309			
7			A71			Y33	R323			
8			S72				P364			
9	F55		V97			N52	D362			
10			R99			N53	E360			
11			N103				D362			
12			K246			K67	D362			
13	G56		T70			D94			Q293	
14			S72				V309			
15	G57		S72						E174	
16				E174					G177	
17	Q62			T180		S95			Y178	
18					K305				G179	
19	G66				G385				Q293	
20	R67				K305					
21	V68				P384					
22	T69				P384					
23	A72		T69							
24			N67							
25	D73		T68							
26			T68							
27			T70							
28	R74		K247							
29			Q248							
30			D249							
31			T66							
32	S75		N67							
33			T68							
34	S84				K305					
35			G102							
36	Q101		N103							
37			G104							
38	S102		W101							
39			G102							
40			W101							
41			G104							
42	I103		C105							
43			G106							
44		K310								
45		W101								
46	F104	K310								
47		R323								

Table S4. Interacting residues between DENV2 WT and Fab 2D22 at 37°C (Fab 2D22 binds to an epitope located near the 2-fold vertices)

No.	Fab 2D22 chain H	mol. B	mol. B'	mol. A	Fab 2D22 chain L	mol. B	mol. B'	mol. A
1	N30		K247		S26	K307		
2	I52		N103		G30	K307		
3	P53		T70			Q325		
4	I54		T70		S31	K307		
5			I113			V309		
6	F55		T70		Y33	R323		
7			A71			P364		
8			S72		N52	D362		
9			V97		N53	E360		
10			R99			D362		
11			N103		K67	D362		
12			I113		D94	V309		
13			K246					
14	G56		T70					
15			A71					
16			S72					
17	G57		A71					
18			S72					
19	A72		T68					
20			T69					
21			T70					
22	D73		N67					
23			T68					
24			T69					
25			glycan					
26	R74		T68					
27			T70					
28			T115					
29			K247					
30			Q248					
31	S75		T66					
32			N67					
33			T68					
34	Y80		glycan					
35	Q101		G102					
36			N103					
37			G104					
38	S102		W101					
39			G102					
40	I103		W101					
41			G104					
42			C105					
43	F104		W101					
44		K310						
45		R323						

Table S5. Interacting residues between DENV2 WT and Fab 2D22 at 37°C (Fab 2D22 binds to an epitope located near the 3-fold vertices)

No.	Fab 2D22 chain H	mol. C	mol. A'	mol. B	Fab 2D22 chain L	mol. C	mol. A'	mol. B
1	N30		K247		G30	K307		
2	I52		N103			V309		
3			N103			Q325		
4	I54		T70		S31	V309		
5			K247		Y33	R323		
6	F55		T70			P364		
7			A71		N52	D362		
8			S72		N53	D362		
9			V97		K67	Q325		
10			R99			D362		
11			N103		G69	K307		
12			I113		D94	V309		
13			K246		S95			H52
14	G56		T70					
15			A71					
16			S72					
17	G57		A71					
18			S72					
19	A72		T68					
20			T69					
21			T70					
22	D73		N67					
23			T68					
24			glycan					
25	R74		T68					
26			T70					
27			T115					
28			K247					
29			Q248					
30			D249					
31	S75		T66					
32			N67					
33			T68					
34	T76		glycan					
35	Q101		G102					
36			N103					
37			G104					
38	S102		W101					
39			G102					
40	I103		W101					
41			G104					
42			C105					
43		K310						
44	F104		W101					
45		K310						
46		R323						

Table S6. Interacting residues between DENV2 WT and Fab C10 at 37°C (Fab C10 binds to an epitope located near to 2-fold vertices)

No.	Fab C10 chain H	mol. B	mol. B'	mol. A	Fab C10 chain L	mol. B	mol. B'	mol. A	
1	Q65		glycan		G31		C74		
2	D103	R2			F32		S72		
3		I46					R73		
4		E161					C74		
5	Y104	H27					R99		
6		G28					G104		
7		L45					C105		
8		I46			N33		G104		
9		Q271					C105		
10		F279					G106		
11			H244		N33	K310			
12	D106		K247		Y34		G102		
13	W108		T70				N103		
14			I113				G104		
15			K247		D52	R323			
16			Q248		S55	R323			
17	F109		S72		R56	D362			
18			R99		S62	D362			
19			N103		S69			H52	
20	L112		W101		G70			H52	
21			G102		S95		T70		
22								A71	
23								S72	
24								T70	

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Table S8. Interacting residues between DENV2 N153Q and Fab 2D22 at 37°C (Fab 2D22 binds to an epitope located near to 5-fold vertices)

No.	Fab 2D22 chain H	mol. A	mol. C'	mol. A*	mol. B*	Fab 2D22 chain L	mol. A	mol. C'	mol. A*	mol. B*
1	S17				D329				S298	
2	N30		K247			S26			Y299	
3			R99				K307			
4	I52		N103			G30	K307			
5	P53		T70				Q325			
6			T70						S298	
7	I54		K247			S31	V309			
8			T70				Q325			
9			A71			Y33	R323			
10			S72				P364			
11			V97			N52	D362			
12			R99			N53	E360			
13			N103			K67	Q325			
14			I113				D362			
15			K246			S68	D362			
16			T70						Q293	
17	G56		S72			D94	V309			
18	G57		S72						G177	
19	Q62			E174		S95			G179	
20					K305				Q293	
21	G66				P384					
22	T69				P384					
23	A72		T68							
24			N67							
25	D73		T68							
26			T68							
27			T70							
28			K247							
29			Q248							
30			D249							
31			T66							
32			N67							
33			T68							
34	S84				K305					
35			W101							
36			G102							
37			N103							
38			G104							
39			W101							
40			G102							
41			W101							
42			G104							
43			C105							
44			G106							
45		K310								
46		M1								
47			W101							
48		K310								
49		R323								

Table S9. Interacting residues between DENV2 N153Q and Fab 2D22 at 37°C (Fab 2D22 binds to an epitope located near to 2-fold vertices)

No.	Fab 2D22 chain H	mol. B	mol. B'	mol. A	Fab 2D22 chain L	mol. B	mol. B'	mol. A
1	N30		K247		G30	K307		
2	I52		N103			Q325		
3			G104		S31	K307		
4	P53		T70			V309		
5	I54		T70			Q325		
6			I113		Y33	R323		
7			K247			P364		
8	F55		T70		R51	E360		
9			A71		N52	D362		
10			S72		N53	E360		
11			V97			D362		
12			R99		K67	D362		
13			N103		G69	K307		
14			K246		D94	V309		
15	G56		T70					
16			A71					
17			S72					
18	G57		A71					
19			S72					
20	T69		N83					
21	A72		T68					
22			T69					
23	D73		N67					
24			T68					
25			glycan					
26	R74		T68					
27			T70					
28			T115					
29			K247					
30			Q248					
31			D249					
32	S75		T66					
33			N67					
34			T68					
35	Q101		G102					
36			N103					
37			G104					
38	S102		W101					
39			G102					
40			G104					
41	I103		W101					
42			G104					
43			C105					
44			G106					
45	F104		W101					
46		K310						
47		R323						

Table S10. Interacting residues between DENV2 N153Q and Fab 2D22 at 37°C (Fab 2D22 binds to an epitope located near to 3-fold vertices)

No.	Fab 2D22 chain H	mol. C	mol. A'	mol. B	Fab 2D22 chain L	mol. C	mol. A'	mol. B
1	N30		K247		G30	K307		
2	I52		N103			V309		
3	I54		T70			Q325		
4			K247		S31	K307		
5	F55		T70			V309		
6			A71		Y33	R323		
7			S72			P364		
8			V97		N52	D362		
9			R99		K67	D362		
10			N103		S68	D362		
11			I113					
12			K246					
13	G56		T70					
14			A71					
15			S72					
16	G57		A71					
17			S72					
18	A72		T69					
19	D73		N67					
20			T68					
21			glycan					
22	R74		T68					
23			T70					
24			T115					
25			K247					
26			Q248					
27			D249					
28	S75		T66					
29			N67					
30			T68					
31	T76		glycan					
32	Q101		G102					
33			N103					
34			G104					
35	S102	M1						
36			W101					
37			G102					
38	I103		W101					
39			G104					
40			C105					
41			G106					
42		K310						
43	F104	M1						
44			W101					
45		K310						
46		R323						

Table S11. Interacting residues between DENV2 N153Q and Fab C10 at 37°C (Fab C10 binds to an epitope located near to 5-fold vertices)

No.	Fab C10 chain H	mol. A	mol. C'	mol. A*	mol. B*	Fab C10 chain L	mol. A	mol. C'	mol. A*	mol. B*
1	Q65		glycan			S26			K291	
2		R2				G30			K291	
3	D103	I46						C74		
4		E161				G31		C105		
5		E44						S72		
6	Y104	I46				F32		C74		
7			K246					R99		
8		F279						G104		
9	D106		K247					G104		
10	Y107		K247			N33		C105		
11			T70					G106		
12			I113					G102		
13	W108		K246			Y34		N103		
14			K247					G104		
15			Q248			S55	R323			
16			S72			R56	Q325			
17			V97				D362			
18	F109		R99			S62	D362			
19			N103			K68			Q293	
20			K246						T176	
21	L112		W101			S69			G179	
22									Q293	
23									G179	
24									T180	
25						G70			K291	
26									Q293	
27									E172	
28						N71			T180	
29									K291	
30								T70		
31						S95		A71		
32								S72		
33						R96		T70		

Table S12. Interacting residues between DENV2 N153Q and Fab C10 at 37°C (Fab C10 binds to an epitope located near to 2-fold vertices)

No.	Fab C10 chain H	mol. B	mol. B'	mol. A	Fab C10 chain L	mol. B	mol. B'	mol. A
1	K59		T70		G31		C74	
2	D103	R2			F32		S72	
3		I46					C74	
4	Y104	H27					R99	
5			H244				G104	
6			K246				C105	
7		F279				G104		
8	D106		K247		N33		C105	
9	W108		T70				G106	
10			I113			K310		
11			K246		Y34		N103	
12		K247				G104		
13	F109		Q248		D52	K310		
14			S72				R323	
15			R99		T54	V309		
16			N103		S55	R323		
17	L112		W101		R56	D362		
18			G102		S62	D362		
19			G104		S69			H52
20					G70			H52
21					S95		T70	
22							A71	
23							S72	
24					R96		T70	
25							S81	
26							L82	
27							N83	
28								

Table S13. Interacting residues between DENV2 N153Q and Fab C10 at 37°C (Fab C10 binds to an epitope located near to 3-fold vertices)

No.	Fab C10 chain H	mol. C	mol. A'	mol. B	Fab C10 chain L	mol. C	mol. A'	mol. B	
1	D102		K246		S26		R73		
2	D103	R2			G31		C74		
3		E44			F32		S72		
4		I46					C74		
5	Y104	H27					R99		
6		E44					G104		
7		I46					C105		
8			K246		N33		G104		
9		F279					C105		
10	D106		K246				G106		
11			K247			K310			
12	W108		T70		Y34		N103		
13			V97				G104		
14			I113		D52	K310			
15			K246				R323		
16			K247			T54	V309		
17	F109		S72		S55	R323			
18			R99		R56	Q325			
19			N103				D362		
20	L112		W101		S62	D362			
21			G102		S69			H52	
22			G104		G70			H52	
23					S95		T70		
24							A71		
25							S72		
26					R96		T70		
27							S81		
28							L82		
29							N83		
30								D225	
31								T226	

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Table S14. Number of interactions on the E protein – Fab interface.

DENV2-Fab complexes	Epitope location	No. of interactions			Interface area (Å ²)
		Fab chain H	Fab chain L	E proteins	
DENV2 WT - Fab 2D22 at 37 °C	5f	38 / 9	10 / 9	48 / 18 (66)	994 / 444 (1438)
	2f	45 / 0	12 / 0	57 / 0 (57)	1082 / 77 (1159)
	3f	46 / 0	12 / 1	58 / 1 (59)	1048 / 104 (1152)
DENV2 N153Q - Fab 2D22 at 37 °C	5f	43 / 6	13 / 7	56 / 13 (69)	1028 / 399 (1427)
	2f	47 / 0	14 / 0	61 / 0 (61)	1081 / 56 (1137)
	3f	46 / 0	10 / 0	56 / 0 (56)	1030 / 54 (1084)
DENV2 WT - Fab C10 at 37 °C	5f	NA	NA	NA	NA
	2f	21 / 0	22 / 2	43 / 2 (45)	1067 / 116 (1183)
	3f	19 / 0	29 / 3	48 / 3 (51)	1151 / 170 (1321)
DENV2 N153Q - Fab C10 at 37 °C	5f	21 / 0	20 / 13	41 / 13 (54)	1106 / 173 (1279)
	2f	19 / 0	25 / 3	44 / 3 (47)	1060 / 291 (1351)
	3f	22 / 0	27 / 4	49 / 4 (53)	1079 / 169 (1248)
DENV2 NGC - Fab C10 (PDB ID: 7V3H)	5f	21 / 0	24 / 11	45 / 11 (56)	1135 / 299 (1434)
	2f	23 / 0	21 / 3	44 / 3 (47)	1108 / 134 (1242)
	3f	20 / 0	26 / 2	46 / 2 (48)	1131 / 124 (1255)
DENV2 NGC - scFv C10 (PDB ID: 7CTH)	5f	16 / 0	13 / 21	29 / 21 (50)	1036 / 292 (1328)
	2f	NA	NA	NA	NA
	3f	15 / 0	23 / 1	38 / 1 (39)	1066 / 113 (1179)

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330 The number of interactions and interface areas for interactions between Fab molecules and the
 331 E protein dimer or the adjacent E protein are separated by a forward slash (“/”). The total
 332 number of interactions and interface areas are shown in parentheses.

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References

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- 341 1 Lim, X. X. *et al.* Human antibody C10 neutralizes by diminishing Zika but enhancing
 342 dengue virus dynamics. *Cell* **184**, 6067-6080 e6013 (2021).
 343 <https://doi.org/10.1016/j.cell.2021.11.009>
- 344 2 Sharma, A. *et al.* The epitope arrangement on flavivirus particles contributes to Mab
 345 C10's extraordinary neutralization breadth across Zika and dengue viruses. *Cell* **184**,
 346 6052-6066 e6018 (2021). <https://doi.org/10.1016/j.cell.2021.11.010>
- 347 3 Fibriansah, G. *et al.* Ultrapotent human antibodies lock E protein dimers central
 348 region of diverse DENV3 morphological variants. *Nature communications* **16**, 9182
 349 (2025). <https://doi.org/10.1038/s41467-025-64210-7>

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