Supplementary Table 1. Protein sequence of anti-idiotype antibody variable domains.

>7G1F9_HeavyChain
MEWSRVFIFLLSVTAGVHSQVQLQQSGAELVRPGTSVKVSCKASGYAFTDYLIEWIKQRPGQGLEWIGVNNPGSGETYYNEKFKDKAALTADKSSSTAFMQLSSLT
SEDSAVYFCARRFYYDYADWYFDVWGTGTTVTVSS

>7G1F9_LightChain
MKLPVRLLVLMFWIPASSSDVVMTQTPLSLPVSPGDQASISCRSSQSLVHGNGNTYLHWYLQKPGQSPKLLIYKISDRLSGVPDRFSGSGSGTDFTLNINKVEAED
LGVYFCSQSTHVPFTFGSGTKLEIK

>14H1F6_HeavyChain
MNFGLRMIFLVLTLKGVQCDVNLVESGGDLVMPGGSLILSCAASGFTFSSYTMSWVRQTPEKRLEWVATISSTGDYTYYPDIVKGRFTISRDNAKNTLYLQMSSLK
SEDTAMYYCTRVYYYGSSYWYFDVWGAGTTVTVSS

>14H1F6_LightChain
MDFQVQIFSFLLISASVIVSRGQIVLSQSPAILSASPGEKVTMTCRATSSVSYMYWYQQKPGLSPKPWIYATSKLASGVPPHFSGSGSGTSYSLTISRVEAEDAAT
YYCQQRSSNPLTFGSGTKLELK

>20C6E10_HeavyChain
MEWSRVFIFLLSVTAGVHSQVQLQQSGAELVRPGTSVKVSCKASGYAFIDYLIEWIKQRPGQGLEWIGVINPGSGETNYNEKFKGKATLTADKSSSTAYMQLSSLT
SEDSAVYFCVRRFYYDYADWYFDVWGTGTTVTVSS

>20C6E10_LightChain
MKLPVRLLVLMFWIPASSSDVVMTQIPLSLPVSLGDQASISCRSSQSLVHSNGDAYLHWYLQKPGQSPKLLIYKLSNRFSGVPDRFSGSGSGTDFTLTISRVEAED
LGVYFCSQSTHVPFTFGSGTKLEIK

>24B3D4_HeavyChain
MNFVLSLIFLALILKGVQCEVQLVESGGGLVKPGGSLKLSCTASGFTFSSFAMSWVRQTPEKRLEWVATISSVSTYTYYLDSVKGRYTISRDNAKNTLYLQMNSLG
SSDTAIYYCTRHGDYVLFYYVMDYWGQGTSVTVSS

>24B3D4_LightChain
MEKDTLLLWVLLLWVPGSTGDIVLTQSPASLAVSLGQRATISCRASESVDNSGFSFMNWFQQKPGQPPKLLIYAASNQGSGVPARFSGSGSGTDFSLNIHPMEEDD
TAMYFCQQIKEVPPTFGGGTNLEIK

>24D1C2_HeavyChain
MEWCWVFLFLLSVTAGVHSKVQLQQSGAELVKPGASVKLSCKASGYTFTDYIIHWVKQKSGQGLEWIGWFYPGSGSIKFNEKFKDKATLTADKSSSTVYLELSRLT
SEDSAVYFCARHEPGLWMDYFDYWGQGTTLTVSS

>24D1C2_LightChain
MQIISLLLISVTVIVSNGEIVLTQSPTTMASSPGDKITITCTASSSISSNYLHWYQQKPGFSPKLLIFRTSNLASGVPARFSGSGSGTSYSLTIGTLEAEDVATYF
CQEGSSIPVTFGAGTKLELK

>28H6E11_HeavyChain
MGWSCIIFFLVATATGVHSQVQLQQSGPEVVRPGVSVKISCKGSGYTFTDHAMHWVKQSHAKSLEWIGVFNTYNGDTNYNQKFEDKATMTIDKSSSTAYLELARLT
SEDSAIYYCVRLGLLGFYALDYWGQGTSVTVSS

>28H6E11_LightChain
MKLPVRLLVLMFWIPGSSSDVLMTQTPLSLPVSLGDQASISCRSSQSIVHSNGNTYLEWYLQKPGQSPKLLIYKVSNRFSGVPDRFSGSGSGTDFTLKISRVEAED
LGVYYCFQGSHVPLTFGAGTKLELK

>30F3D2_HeavyChain
MEWSRVFIFLLSVTAGVHSQVQLQQSGAELVRPGTSVKVSCKASGYAFTDYLIEWIKQRPGQGLEWIGVNNPGSGETYYNEKFKDKAALTADKSSSTAFMQLSSLT
SEDSAVYFCARRFYYDYADWYFDVWGTGTTVTVSS

>30F3D2_LightChain
MKLPVRLLVLMFWIPASSSDVVMTQTPLSLPVSPGDQASISCRSSQSLVHGNGNTYLHWYLQKPGQSPKLLIYKISDRLSGVPDRFSGSGSGTDFTLNINKVEAED
LGVYFCSQSTHVPFTFGSGTKLEIK

Supplementary Table 2. Protein sequence of L5A7 clones variable domains.

>L5A7.1_HeavyChain
QVQLQQSGPGLVKPSQTLSLTCVISGDSVSSNSAAWDWIRQSPSRGLEWLGRTYYRSKWYSDYAVSVKSRITITPDTSKNQFSLHLNSVTPEDTAVYYCARAGVRI
FGVIVDSLDYWGQGTLVTVSS

>L5A7.2_HeavyChain
QVQLQQSGPGLVKPSQTLSLTCVISGDSVSSNSAAWDWIRQTPSRGLEWLGRTYYRSKWYSDYAVSVKSRITITPDTSKNQFSLRLNSVTPEDTAVYYCARAGVRV
FGVIVDSLDYWGQGTLVTVSS

>L5A7.3_HeavyChain
QVQLQQSGPGLVKPSQTLSLTCVISGDSVSSNTAAWDWIRQSPSRGLEWLGRTYYRSRWYSDYADSVKSRITITPDTSKNQFSLHLNSVTPEDTAVYYCARAGIRI
FGIIVDSLDYWGQGTLVTVSS

>L5A7.4_HeavyChain
QVQLQQSGPRLVKPSQTLSLTCAISGDSVSSTSAAWDWIRQSSSRGLEWLGRTYYRSRWYHDYEESVKSRITINADTSKNQFSLQLASVTPEDTAVYYCARAGIRV
FGIIVDSLDYWGQGSLVTVSS

>L5A7.5_HeavyChain
QVQLQQSGPGLVKPSQTLSLTCGISGDSVSSDAAAWDWIRQSPSRGLEWLGRTFYRSRWHHDYSESVKNRITINADTSKNQFSLQLTSVTPEDTATYYCARAGVRV
FGIIVNSLDYWGQGTLVTVSS

>L5A7.1_LightChain
AIQLTQSPSSLSASVGDRVTITCRASQALNSYLAWYQQKPGKAPKLLIFAASTLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQLSKTFGPGTRVDIE

>L5A7.2_LightChain
AIQLTQSPSSLSASVGDRVTITCRASQGFSSYLAWYQQKPGKAPQLLIYAASTLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSKTFGPGTRVDIE

>L5A7.3_LightChain
AIQLTQSPSSLSASVGDRVTITCRASQGANSYLAWYQQKPGKAPKLLIYAASTLQSGVPSRFSGSGSGTDFSLTISSLQPEDFATYYCQESKTFGPGTRVDIE

>L5A7.4_LightChain
AIQLTQSPSSLSASVGDRVTITCRASQGFNSYLAWYQQKPGKAPELLIYAASTLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSKTFGPGTKVDIK

>L5A7.5_LightChain
AIQLTQSPSSLSASVGDRVTITCRASQATSSYLAWYQQKPGKAPKLLIYAASTLQSGVPSRFSGSGSGTDFTLTITSLQPEDFATYYCQLSKTFGPGTKVEIK

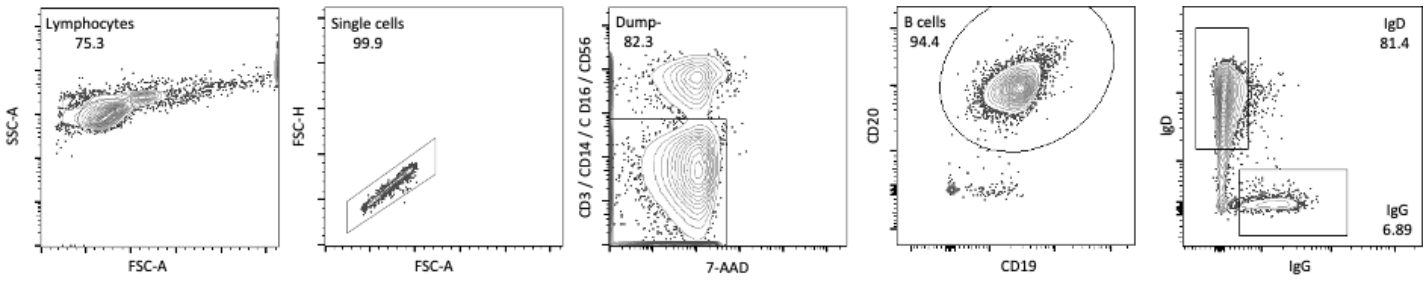
Supplementary Table 3. Data collection statistics related to Supplementary Figure 1.

	L5A7 Fab
PDB ID	8VVB
Data collection	
Space group	$P2_12_12_1$
Cell constants	
a, b, c (Å)	65.760, 109.190, 140.570
a, b , g (°)	90, 90, 90
Resolution (Å)	50 – 1.73 (1.78 – 1.73)
R_{merge} (%)	8.6 (85.3)
I / sI	18.7 (0.8)
$CC_{1/2}$	0.999 (0.836)
Completeness (%)	94.2 (98.1)
Redundancy	11.9 (11.1)
Refinement	
Resolution (Å)	48 – 1.78
No. reflections	94,910 (6,197)
R_{work} / R_{free} (%)	17.38 / 20.92
No. atoms	
Protein	7722
Ligand/ion	0
Water	1193
B-factors	
Protein	23.09
Ligand/ion	N/A
Water	34.57
R.m.s. deviations	
Bond lengths (Å)	0.005
Bond angles (°)	0.845

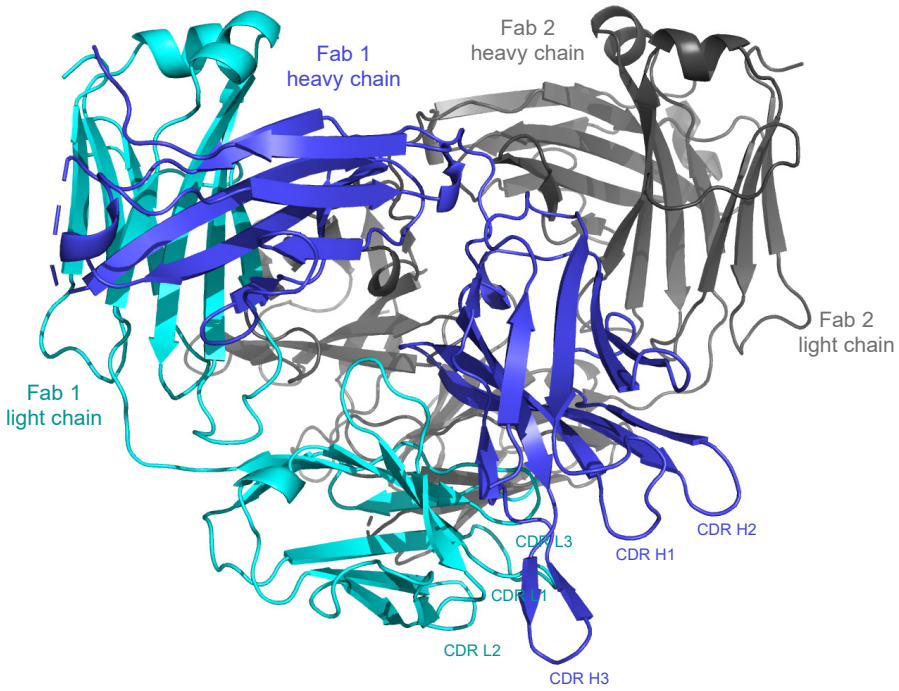
*Values in parentheses are for the highest-resolution shell

Supplementary Table 4. Cryo-EM structure statistics related to Figures 5 and 6.

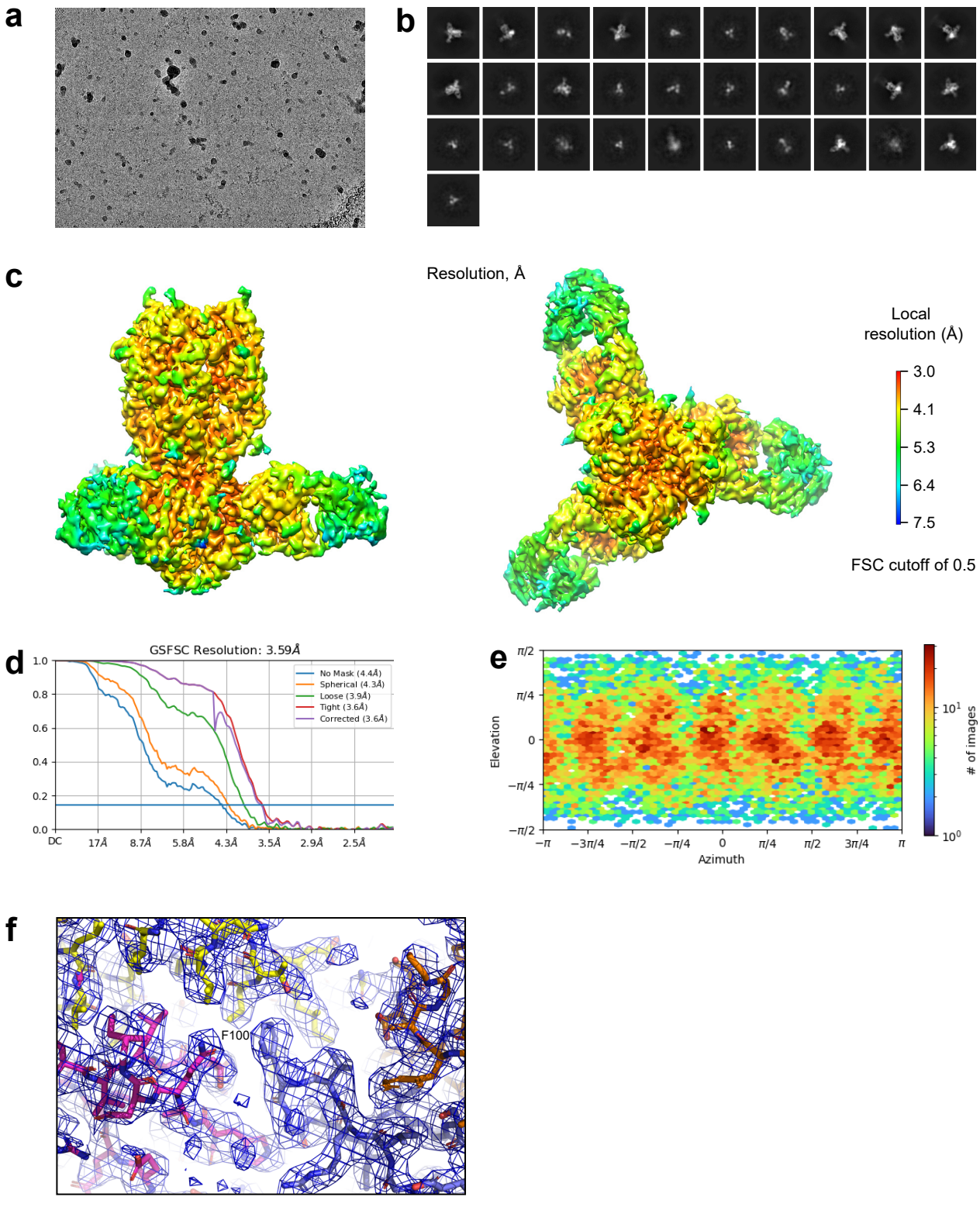
	L5A7 Fab bound to INDO05 HA (EMD-43529) (PDB 8VUE)	**L5A7 Fab bound to 28H6E11 Fab** (EMD-43545) (PDB 8VUZ)
Data collection and processing		
Magnification	105,000	105,000
Voltage (kV)	300	300
Electron exposure (e–/Å^2)	64	40
Defocus range (μm)	-0.7 to -2.0	-0.7 to -2.0
Pixel size (Å)	1.083	0.83
Symmetry imposed	C3	C1
Initial particle images (no.)	201,079	4,203,652
Final particle images (no.)	20,728	215,254
Map resolution (Å)	3.59	3.88
FSC threshold	0.143	0.143
Refinement		
Model resolution (Å)	3.6	3.95
FSC threshold	0.143	0.143
Model composition		
Protein residues	2724	870
Ligands	3	0
B factors (Å^2)		
Protein	69.0	52.1
Ligand	65.43	N/A
R.m.s. deviations		
Bond lengths (Å)	0.004	0.004
Bond angles (°)	0.616	0.712
Validation		
MolProbity score	1.86	2.12
Clashscore	10.27	14.49
Poor rotamers (%)	0.42	0.53
Ramachandran plot		
Favored (%)	95.30	92.81
Allowed (%)	4.70	6.96
Disallowed (%)	0.0	0.23



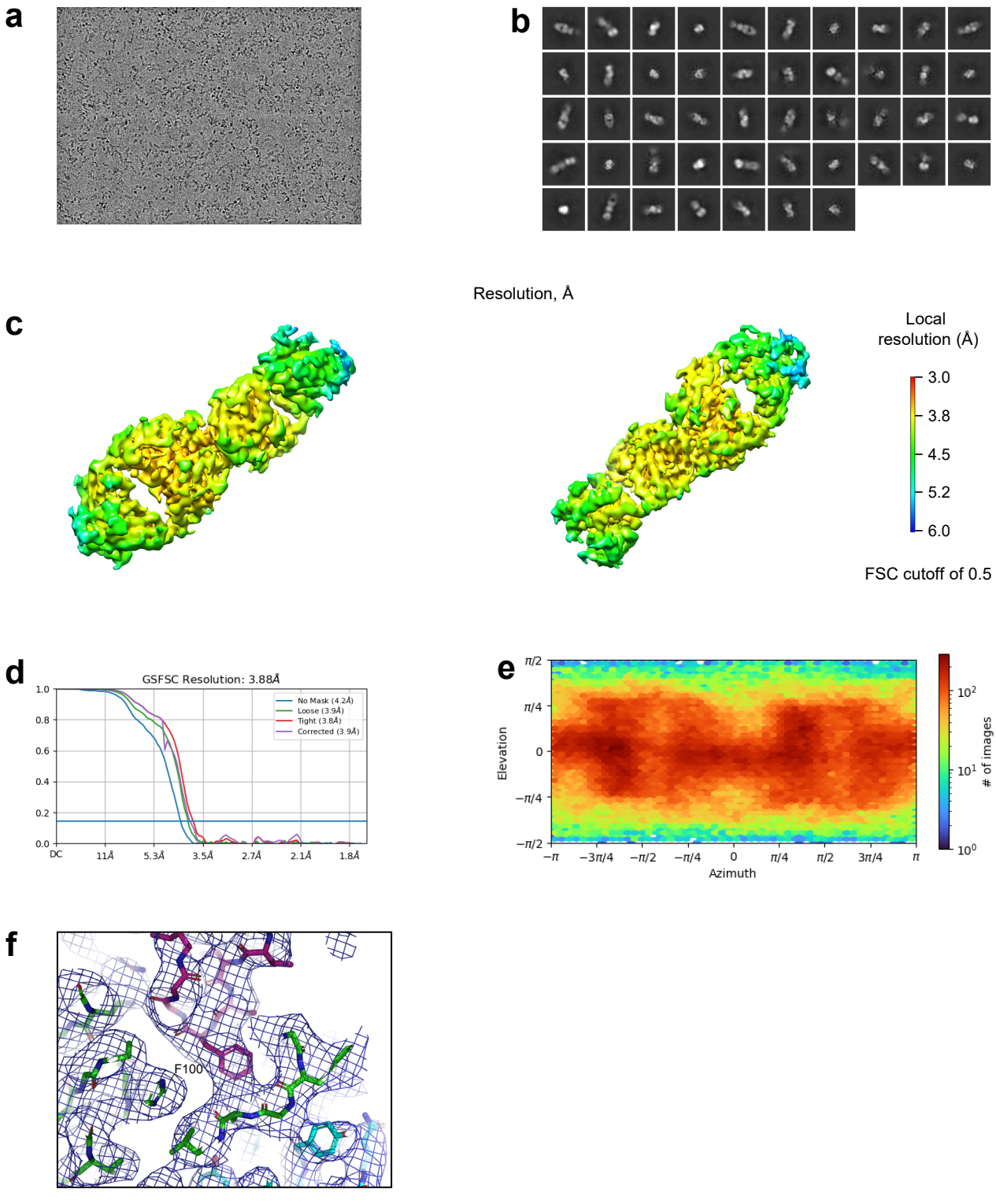
Supplementary Figure 1. Flow cytometry gating strategy. Gating scheme followed to identify naïve and memory B cells.



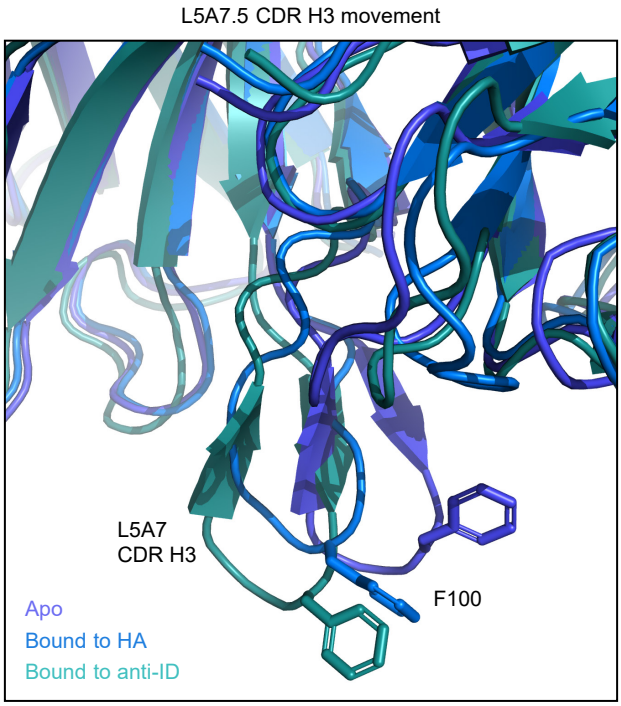
Supplementary Figure 2. Asymmetric unit of L5A7.5 Fab solved to 1.8Å. One paired heavy chain (blue) and light chain (cyan) are colored.



Supplementary Figure 3. Cryo-EM validation of L5A7.5-INDO05 HA complex. (**a**) Representative micrograph. (**b**) Representative 2D class averages. (**c**) The local resolution map. (**d**) The gold-standard Fourier shell correlation after non-uniform refinement. (**e**) Heatmap showing the orientations of all particles used in the non-uniform refinement. (**f**) Electron density for selected parts of the protein after focused refinement contorted at 3.0 σ in PyMOL.



Supplementary Figure 4. Cryo-EM validation of L5A7.5-28H6E11 complex. (**a**) Representative micrograph. (**b**) Representative 2D class averages. (**c**) The local resolution map. (**d**) The gold-standard Fourier shell correlation after non-uniform refinement. (**e**) Heatmap showing the orientations of all particles used in the non-uniform refinement. (**f**) Electron density for selected parts of the protein after focused refinement contorted at 3.0 σ in PyMOL.



Supplementary Figure 5. L5A7.5 CDR H3 movement. View of the CDR H3 region of L5A7.5 from the apo crystal structure and the cryo-EM structures bound to HA and the anti-idiotype antibody.