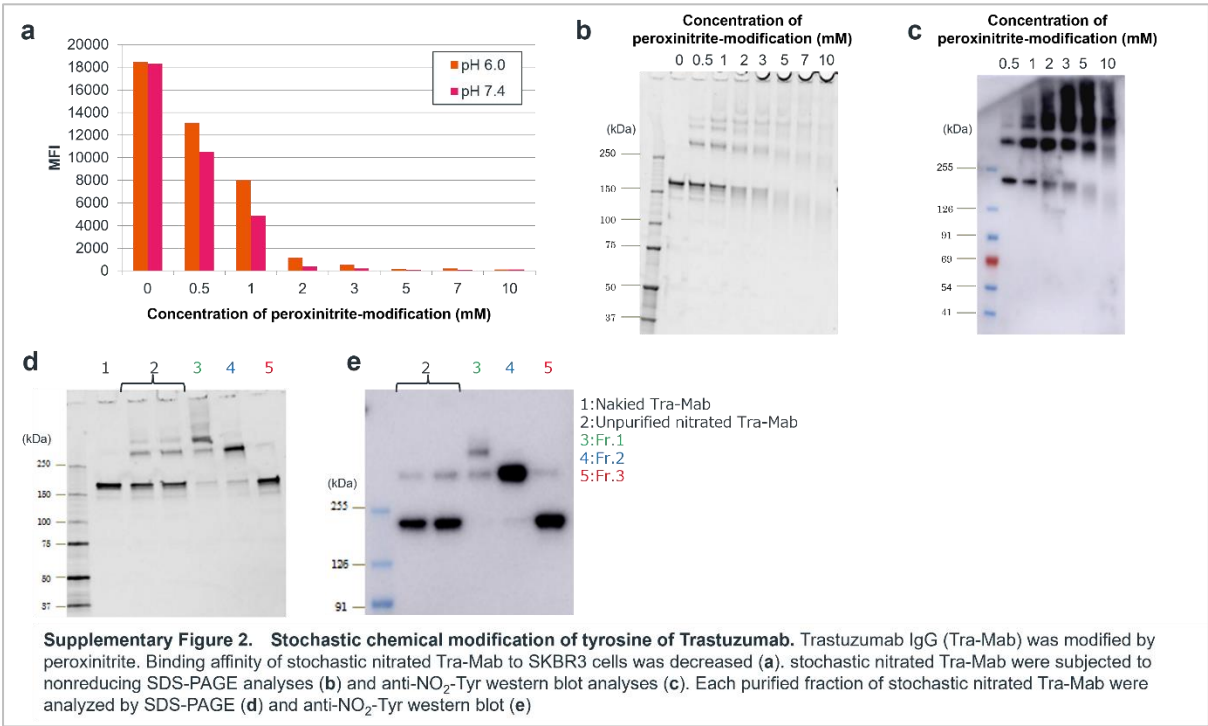
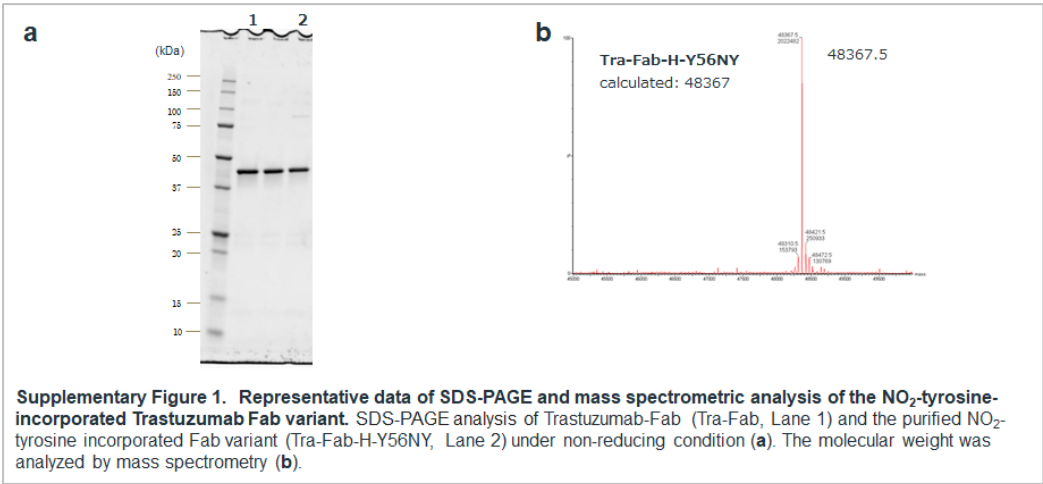


SUPPLEMENTARY FIGURES AND TABLES



Supplementary Table 1. List of antibody residues showing pH-dependency through 3-nitro-L-tyrosine substitution, and interaction pairs in antibody-antigen interface.

a									
Type	Antibody	Residue	CDR	Antigen	Residue	Energy[kcal/mol]	Distance[Å]	BB	Freq
D	2-1N8Z.B	Tyr33	H1	3-1N8Z.C	His542	0.00	7.65--	2	
D	2-1N8Z.B	Tyr33	H1	3-1N8Z.C	Glu558	-0.15	6.46**	34	
D	2-1N8Z.B	Tyr33	H1	3-1N8Z.C	Ala559	0.00	7.25-*	6	
D	2-1N8Z.B	Tyr33	H1	3-1N8Z.C	Asp560	0.00	7.22-*	22	
D	2-1N8Z.B	Tyr33	H1	3-1N8Z.C	Pro572	0.00	7.54--	11	
D	2-1N8Z.B	Tyr33	H1	3-1N8Z.C	Phe573	-3.27	5.86**	56	
D	2-1N8Z.B	Tyr56	H2	3-1N8Z.C	Tyr532	0.00	6.93--	20	
D	2-1N8Z.B	Tyr56	H2	3-1N8Z.C	Leu539	0.00	7.55-*	75	
D	2-1N8Z.B	Tyr56	H2	3-1N8Z.C	Pro540	0.00	7.17-*	13	
D	2-1N8Z.B	Tyr56	H2	3-1N8Z.C	His542	0.00	7.72-*	9	
D	2-1N8Z.B	Tyr56	H2	3-1N8Z.C	Gly556	0.00	7.48-b	12	
D	2-1N8Z.B	Tyr56	H2	3-1N8Z.C	Pro557	1.55	5.56**	64	
D	2-1N8Z.B	Tyr56	H2	3-1N8Z.C	Glu558	-2.56	5.82**	85	
D	2-1N8Z.B	Tyr56	H2	3-1N8Z.C	Ala559	0.00	7.36-b	3	
D	2-1N8Z.B	Tyr56	H2	3-1N8Z.C	Asp560	0.00	7.59--	2	
D	2-1N8Z.B	Tyr56	H2	3-1N8Z.C	Gln561	0.00	7.42*-	19	
D	1-1N8Z.A	His91	L3	3-1N8Z.C	Asp560	0.00	7.62-b	2	
D	1-1N8Z.A	His91	L3	3-1N8Z.C	Lys569	0.00	7.65-b	3	
D	1-1N8Z.A	His91	L3	3-1N8Z.C	Asp570	0.00	7.12**	28	
DH	1-1N8Z.A	His91	L3	3-1N8Z.C	Pro571	-2.50	5.80**	68	
D	1-1N8Z.A	His91	L3	3-1N8Z.C	Pro572	-0.23	5.82**	60	
D	1-1N8Z.A	His91	L3	3-1N8Z.C	Phe573	0.00	7.39**	16	
D	1-1N8Z.A	His91	L3	3-1N8Z.C	Lys593	0.00	7.20--	4	
D	1-1N8Z.A	His91	L3	3-1N8Z.C	Cys601	0.00	7.60-b	1	
D	2-1N8Z.B	Trp95	H3	3-1N8Z.C	Glu558	0.00	7.35--	15	
D	2-1N8Z.B	Trp95	H3	3-1N8Z.C	Asp560	0.00	7.05--	1	
D	2-1N8Z.B	Trp95	H3	3-1N8Z.C	Asp570	0.00	7.67-b	1	
D	2-1N8Z.B	Trp95	H3	3-1N8Z.C	Pro571	0.00	7.07-b	15	
D	2-1N8Z.B	Trp95	H3	3-1N8Z.C	Pro572	-1.84	6.29-*	44	
D	2-1N8Z.B	Trp95	H3	3-1N8Z.C	Phe573	-1.69	6.54**	50	
d									
Type	Antibody	Residue	CDR	Antigen	Residue	Energy[kcal/mol]	Distance[Å]	BB	Freq
D	2-3PP4.L	Tyr32	L1	3-3PP4.P	Pro169	0.00	7.47-b	6	
D	2-3PP4.L	Tyr32	L1	3-3PP4.P	Ala170	0.03	5.94-*	36	
D	2-3PP4.L	Tyr32	L1	3-3PP4.P	Asn171	-0.11	5.98**	75	
D	2-3PP4.L	Tyr32	L1	3-3PP4.P	Pro172	0.00	7.46-*	11	
D	2-3PP4.L	Tyr32	L1	3-3PP4.P	Ser173	0.00	7.10-*	14	
D	2-3PP4.L	Tyr32	L1	3-3PP4.P	Glu174	0.00	7.14-*	23	
D	1-3PP4.H	Phe97	H3	3-3PP4.P	Pro169	0.00	7.64--	2	
D	1-3PP4.H	Phe97	H3	3-3PP4.P	Asn171	0.00	7.58-*	3	
D	1-3PP4.H	Phe97	H3	3-3PP4.P	Pro172	0.00	7.09-b	9	
D	1-3PP4.H	Phe97	H3	3-3PP4.P	Ser173	-0.75	6.32**	52	
D	1-3PP4.H	Phe97	H3	3-3PP4.P	Glu174	-3.41	5.75**	95	
D	1-3PP4.H	Phe97	H3	3-3PP4.P	Lys175	-1.17	5.98**	37	
D	1-3PP4.H	Phe97	H3	3-3PP4.P	Asn176	-1.69	5.87**	48	
D	1-3PP4.H	Phe97	H3	3-3PP4.P	Ser177	-3.87	5.42**	61	
D	1-3PP4.H	Phe97	H3	3-3PP4.P	Pro178	-0.87	6.19**	61	
D	1-3PP4.H	Phe97	H3	3-3PP4.P	Ser179	0.00	7.28**	24	
D	1-3PP4.H	Phe97	H3	3-3PP4.P	DTH180	0.00	7.81-b	4	
D	1-3PP4.H	Phe97	H3	3-3PP4.P	Gln181	0.00	7.42--	10	
D	2-3PP4.L	Tyr96	L3	3-3PP4.P	Asn171	0.03	6.74-*	28	
D	2-3PP4.L	Tyr96	L3	3-3PP4.P	Pro172	0.28	6.08**	54	
D	2-3PP4.L	Tyr96	L3	3-3PP4.P	Ser173	0.23	5.88-*	36	
D	2-3PP4.L	Tyr96	L3	3-3PP4.P	Glu174	0.00	7.14-b	6	
D	2-3PP4.L	Tyr96	L3	3-3PP4.P	Lys175	0.00	7.33-*	3	
b									
Type	Antibody	Residue	CDR	Antigen	Residue	Energy[kcal/mol]	Distance[Å]	BB	Freq
D	1-3WLW.L	Tyr91	L3	3-3WLW.B	His171	0.01	6.96-*	51	
D	1-3WLW.L	Tyr91	L3	3-3WLW.B	Pro172	3.01	5.40**	62	
DH	1-3WLW.L	Tyr91	L3	3-3WLW.B	Cys173	-3.50	5.92-*	38	
D	1-3WLW.L	Tyr91	L3	3-3WLW.B	Ser174	-0.10	6.28-*	37	
D	1-3WLW.L	Tyr91	L3	3-3WLW.B	Pro175	0.64	5.89**	54	
D	1-3WLW.L	Tyr91	L3	3-3WLW.B	Met176	0.00	7.20-b	5	
D	1-3WLW.L	Tyr91	L3	3-3WLW.B	Cys177	0.00	7.80-b	3	
D	1-3WLW.L	Tyr91	L3	3-3WLW.B	Ser180	0.00	6.89-*	9	
D	1-3WLW.L	Tyr91	L3	3-3WLW.B	Glu185	0.00	7.41-b	4	
c									
Type	Antibody	Residue	CDR	Antigen	Residue	Energy[kcal/mol]	Distance[Å]	BB	Freq
D	2-2OSL.H	Tyr97	H3	3-2OSL.P	Asn171	0.00	7.68-b	7	
e									
Type	Antibody	Residue	CDR	Antigen	Residue	Energy[kcal/mol]	Distance[Å]	BB	Freq
D	2-5GRJ.L	Tyr32	L1	3-5GRJ.A	Met59	-0.65	6.51-*	36	
DH	2-5GRJ.L	Tyr32	L1	3-5GRJ.A	Glu60	-2.89	5.80**	72	
D	2-5GRJ.L	Tyr32	L1	3-5GRJ.A	Asp61	3.43	5.41**	88	
D	2-5GRJ.L	Tyr32	L1	3-5GRJ.A	Lys62	-0.19	6.04-*	58	
D	2-5GRJ.L	Tyr32	L1	3-5GRJ.A	His78	0.00	7.37--	15	
D	2-5GRJ.L	Tyr32	L1	3-5GRJ.A	Tyr81	0.00	7.67--	2	
D	2-5GRJ.L	Tyr32	L1	3-5GRJ.A	Gln107	0.00	7.30-*	5	
D	2-5GRJ.L	Tyr32	L1	3-5GRJ.A	Ala109	0.00	7.06-b	1	
D	2-5GRJ.L	Tyr32	L1	3-5GRJ.A	Gly110	0.00	7.78-b	1	
D	2-5GRJ.L	Tyr32	L1	3-5GRJ.A	Val111	0.00	7.83-b	2	
D	1-5GRJ.H	Tyr52	H2	3-5GRJ.A	Ile54	0.00	7.67*-	4	
D	1-5GRJ.H	Tyr52	H2	3-5GRJ.A	Val55	0.00	7.75-b	3	
D	1-5GRJ.H	Tyr52	H2	3-5GRJ.A	Tyr56	0.78	6.03**	103	
D	1-5GRJ.H	Tyr52	H2	3-5GRJ.A	Trp57	0.00	7.68-b	4	
DH	1-5GRJ.H	Tyr52	H2	3-5GRJ.A	Glu58	-5.61	5.81**	39	
D	1-5GRJ.H	Tyr52	H2	3-5GRJ.A	Glu60	0.00	7.19-b	1	
D	1-5GRJ.H	Tyr52	H2	3-5GRJ.A	Asn63	0.00	7.52-*	13	
D	1-5GRJ.H	Tyr52	H2	3-5GRJ.A	Ile65	0.00	7.76-b	2	
D	1-5GRJ.H	Tyr52	H2	3-5GRJ.A	Gln66	0.00	7.38*-	22	
D	1-5GRJ.H	Tyr52	H2	3-5GRJ.A	Arg113	-0.10	6.36--	32	
D	1-5GRJ.H	Tyr52	H2	3-5GRJ.A	Met115	-1.99	5.97**	39	
D	1-5GRJ.H	Tyr52	H2	3-5GRJ.A	Ser117	0.00	7.89--	1	
D	1-5GRJ.H	Tyr52	H2	3-5GRJ.A	Tyr123	0.00	7.76--	6	
D	1-5GRJ.H	Phe58	H2	3-5GRJ.A	Glu58	0.00	7.35--	8	
D	1-5GRJ.H	Phe58	H2	3-5GRJ.A	Arg113	-1.50	5.93--	34	
D	1-5GRJ.H	Phe58	H2	3-5GRJ.A	Met115	-0.57	6.58--	18	
D	1-5GRJ.H	Phe58	H2	3-5GRJ.A	Tyr123	-0.94	6.02**	55	
D	1-5GRJ.H	Phe58	H2	3-5GRJ.A	Arg125	0.00	7.12--	2	
D	2-5GRJ.L	Tyr91	L3	3-5GRJ.A	Glu58	0.00	7.40-*	11	
D	2-5GRJ.L	Tyr91	L3	3-5GRJ.A	Met59	0.00	6.99-*	26	
D	2-5GRJ.L	Tyr91	L3	3-5GRJ.A	Glu60	-0.68	5.59**	74	
D	2-5GRJ.L	Tyr91	L3	3-5GRJ.A	Asp61	0.49	5.67**	87	
D	2-5GRJ.L	Tyr91	L3	3-5GRJ.A	Lys62	0.00	7.19-b	14	
D	2-5GRJ.L	Tyr91	L3	3-5GRJ.A	Val111	0.00	6.95-*	17	
D	2-5GRJ.L	Tyr91	L3	3-5GRJ.A	Tyr112	0.00	7.76-b	4	
D	2-5GRJ.L	Tyr91	L3	3-5GRJ.A	Arg113	0.00	7.25-*	16	
D	2-5GRJ.L	Tyr91	L3	3-5GRJ.A	Arg125	0.00	6.82--	10	

(a) Trastuzumab-Fab-HER2 interface(PDB ID: 1N8Z) (b) anti-HER2 antibody-Fab-HER2 interface(PDB ID: 3WLW) (c) Rituximab-Fab-CD20 interface (PDB ID: 2OSL) (d) Obinutuzumab-Fab-CD20 interface (PDB ID: 3PP4) (e) avelumab-Fab-PD-L1 interface(PDB ID: 5GRJ)

- Type describes the type of interaction, such as D (distance), and H (hydrogen bond).
- CDR represents complementarity determining region, and corresponding loop definition is noted in the column.
- Energy describes the interaction energy between antibody and antigen.
- Distance describes the average of inter-atomic distances between antibody and antigen.
- BB describes the backbone and side chain used in each interaction pair. The symbol "-", "b", and "*" represent side chain, backbone, and both respectively.
- Freq indicates the frequency of interactions found in each interaction pair.
- Acidic residues in antigen are highlighted.

Supplementary Table 2. List of mutants showing pH-dependency.

Name	Recognized Antigen	CDR	Original Res.	Incorporated Res.	MOA Type
Tra-Fab-H-Y33NY	HER2	H1	Y	NY	B
Tra-Fab-H-Y33CN	HER2	H1	Y	CN	B
Tra-Fab-H-Y33FBr	HER2	H1	Y	Fbr	B
Tra-Fab-H-Y56NY	HER2	H2	Y	NY	B
Tra-Fab-H-Y56FBr	HER2	H2	Y	FBr	B
Tra-Fab-L-H91NY	HER2	L3	H	NY	AB
Tra-Fab-H-W95NY	HER2	H3	W	NY	B
3w1w-Fab-L-Y91NY	HER2	L3	Y	NY	AB
3w1w-Mab-L-Y91CN	HER2	L3	Y	CN	AB
2OSL-Fab-H-Y97NY	CD20	H3	Y	NY	C
2OSL-Fab-L-Y32NY	CD20	L2	Y	NY	C
3PP4-Fab-L-Y32NY	CD20	L1	Y	NY	B
3PP4-Fab-L-Y96NY	CD20	L3	Y	NY	C
3PP4-Fab-H-F97NY	CD20	H3	F	NY	B
5GRJ-Fab-L-Y32NY	PD-L1	L1	Y	NY	AB
5GRJ-Fab-H-Y52NY	PD-L1	H2	Y	NY	AB
5GRJ-Fab-H-F58NY	PD-L1	H2	F	NY	B
5GRJ-Fab-L-Y91NY	PD-L1	L3	Y	NY	B

MOA Type described the type of mechanisms of the pH-dependency, such as A (controlling hydrogen bond of Tyr), B ("intermolecular" electrostatic repulsion), and C ("intramolecular" electrostatic repulsion).