Supporting Information

Computational Analysis of Hot Spots and Binding Mechanism in the PD-1/PD-L1 Interaction

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Table S1. Result of computational alanine scanning for the PD-1/PD-L1 interaction.

Mutation	$\Delta\Delta E_{vdW}$	$\Delta\Delta E_{ele}$	$\Delta\Delta G_{gb}$	$\Delta\Delta G_{np}$	$\Delta\Delta H$	SD1[a]	$\Delta\Delta IE$	SD2[b]	$\Delta\Delta G$	SD[c]
(A) PD-1										
Q75A	4.14	10.77	-8.48	0.34	6.78	0.27	-1.48	0.28	5.30	0.54
I134A	5.91	-0.29	-0.80	0.12	4.95	0.22	-0.87	0.26	4.09	0.46
I126A	4.53	-0.01	-0.41	-0.08	4.03	0.12	-0.60	0.03	3.42	0.10
E84A	2.03	11.58	-8.62	0.09	5.08	0.14	-2.08	0.18	3.01	0.24
K78A	2.98	4.33	-2.93	0.07	4.46	0.17	-1.58	0.07	2.88	0.21
Y68A	1.80	5.23	-3.74	-0.08	3.22	0.23	-0.84	0.07	2.38	0.27
L128A	3.56	-0.38	-0.67	0.14	2.65	0.10	-0.38	0.03	2.27	0.12
N66A	1.39	3.15	-2.06	-0.06	2.42	0.04	-0.38	0.03	2.04	0.07
K131A	1.69	7.31	-7.43	0.19	1.76	0.08	-0.58	0.06	1.18	0.09
V64A	1.31	-0.20	-0.52	-0.01	0.57	0.07	-0.12	0.02	0.46	0.06
Q133A	1.01	1.74	-2.15	0.10	0.70	0.23	-0.34	0.10	0.36	0.15
T76A	2.03	2.01	-2.41	0.00	1.64	0.27	-1.36	0.09	0.27	0.32
L122A	0.55	-0.12	-0.11	-0.03	0.29	0.07	-0.02	0.01	0.27	0.07
M70A	0.53	-1.16	0.93	0.00	0.30	0.23	-0.11	0.10	0.19	0.13
D77A	0.30	2.51	-2.37	0.03	0.48	0.08	-0.38	0.20	0.09	0.14
S127A	0.03	0.25	-0.26	0.00	0.02	0.01	0.00	0.00	0.01	0.01
N74A	0.42	-1.40	1.02	0.03	0.08	0.05	-0.12	0.02	-0.05	0.03
R139A	0.34	-2.79	2.43	0.03	0.01	0.13	-0.20	0.03	-0.19	0.11
Q88A	0.45	-0.61	0.21	0.12	0.18	0.30	-0.44	0.25	-0.27	0.13
K135A	0.54	10.61	-10.18	0.17	1.14	0.41	-1.77	0.68	-0.63	0.39
S73A	-0.90	2.93	-2.47	0.01	-0.43	0.20	-0.90	0.41	-1.34	0.60

E136A	-1.19	10.94	-8.66	0.16	1.25	0.10	-2.95	0.23	-1.70	0.24
(B) PD-L1										
Y123A	7.14	3.96	-3.98	0.49	7.60	0.50	-1.69	0.11	5.92	0.46
Y56A	5.24	0.50	-0.68	0.04	5.10	0.28	-0.52	0.04	4.59	0.27
R125A	4.64	-2.21	1.50	0.55	4.48	0.38	-1.39	0.10	3.09	0.41
M115A	3.93	-0.96	-0.03	0.06	2.99	0.12	-0.47	0.04	2.52	0.10
R113A	2.59	0.48	0.62	0.30	3.99	0.72	-1.84	0.10	2.15	0.65
Q66A	2.25	3.16	-2.92	0.04	2.53	0.03	-0.43	0.04	2.11	0.04
I54A	1.88	-0.08	-0.38	0.13	1.55	0.05	-0.14	0.00	1.41	0.04
K124A	3.02	3.21	-3.56	0.34	3.01	0.11	-1.78	0.52	1.23	0.59
E58A	0.87	10.12	-9.66	0.05	1.38	0.13	-0.61	0.16	0.77	0.11
V76A	1.43	-0.25	-0.51	0.06	0.72	0.09	-0.15	0.00	0.57	0.10
F19A	0.46	-0.28	0.38	0.00	0.56	0.01	0.01	0.05	0.57	0.06
T20A	0.75	-0.37	0.15	0.05	0.59	0.04	-0.05	0.01	0.54	0.03
V23A	0.63	-0.09	0.02	-0.01	0.55	0.12	-0.03	0.01	0.53	0.13
D122A	0.32	9.34	-7.65	0.01	2.01	0.08	-1.49	0.13	0.53	0.17
D73A	0.13	6.39	-6.02	0.00	0.50	0.01	-0.16	0.02	0.34	0.03
I126A	0.20	-0.01	0.12	0.00	0.32	0.01	0.00	0.00	0.32	0.01
N63A	0.87	-0.63	0.12	0.10	0.47	0.07	-0.16	0.03	0.31	0.05
S117A	0.50	-0.08	-0.12	0.02	0.32	0.04	-0.04	0.00	0.28	0.04
V68A	0.46	-0.03	-0.18	0.03	0.29	0.04	-0.01	0.00	0.27	0.03
D26A	-0.50	9.05	-7.89	0.13	0.79	0.16	-1.80	0.46	-1.01	0.51

[a]Standard deviation of ΔΔH.

[b]Standard deviation of ΔΔIE.

[c]Standard deviation of ΔΔG.

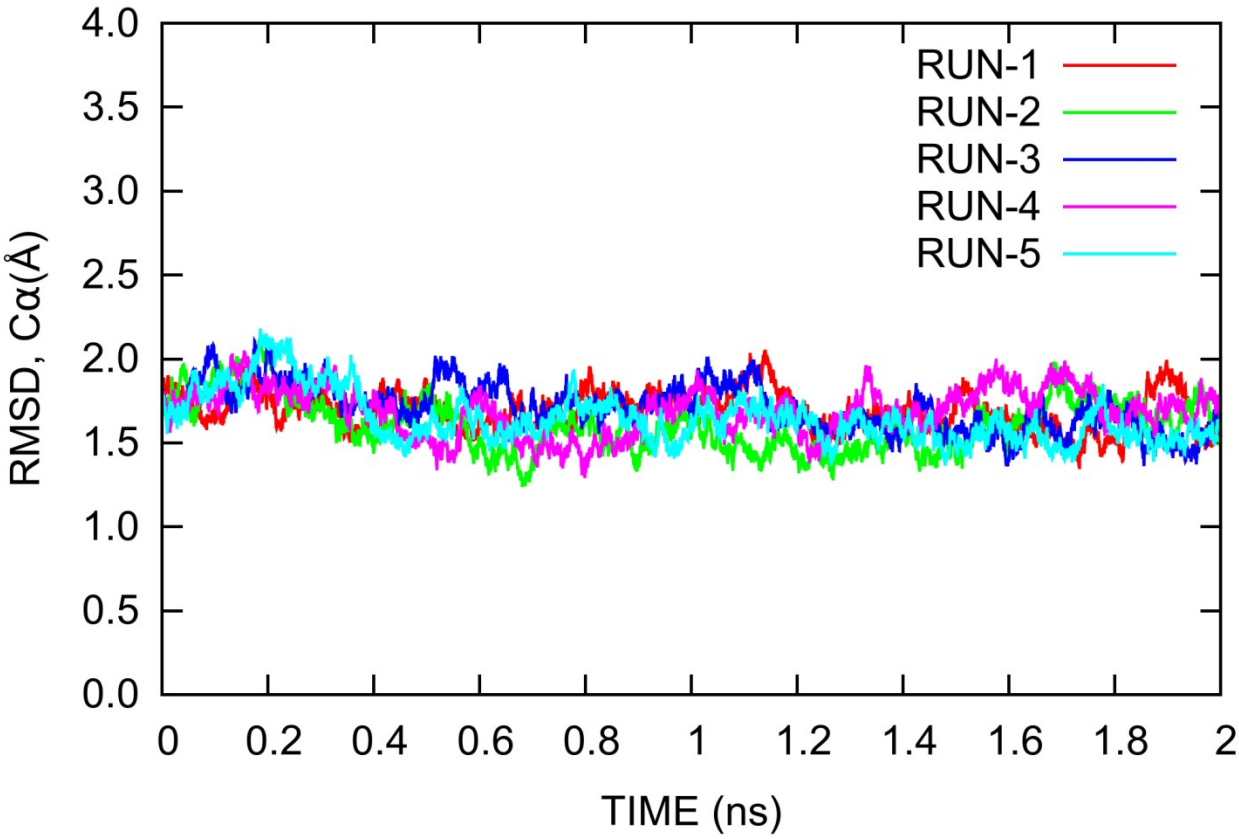

Figure S1. RMSDs of the C_α atoms of the PD-1/PD-L1 complex of the 5 production runs relative to the initial crystal structure in the final 2 ns..

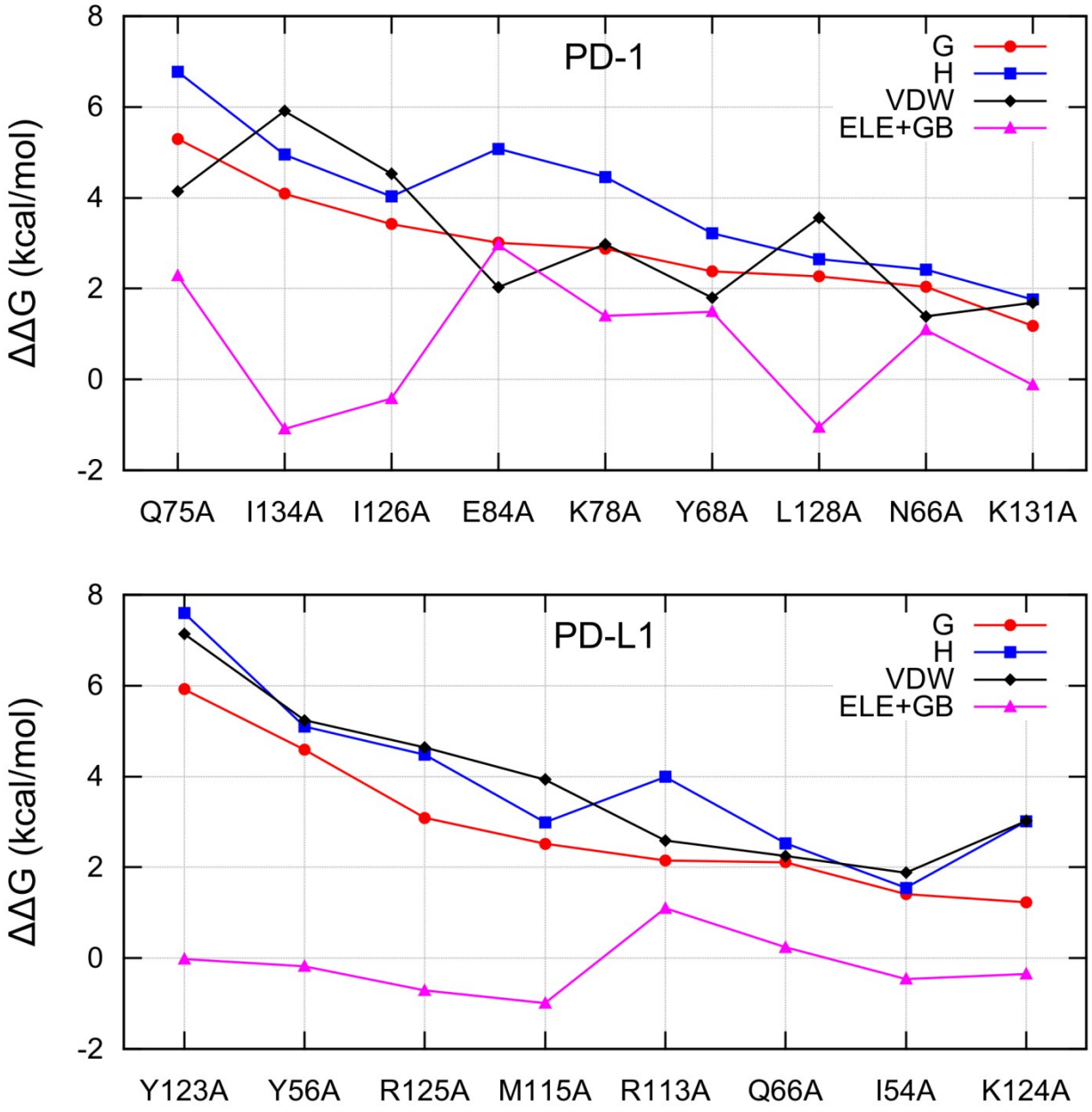

Figure S2. Energy components of the hot and warm spots predicted by the computational alanine scanning. For each hot spot, ΔΔG (red), ΔΔH (blue), $\Delta\Delta E_{vdw}$ (black) and $\Delta\Delta E_{ele}+\Delta\Delta G_{gb}$ (pink) are displayed.

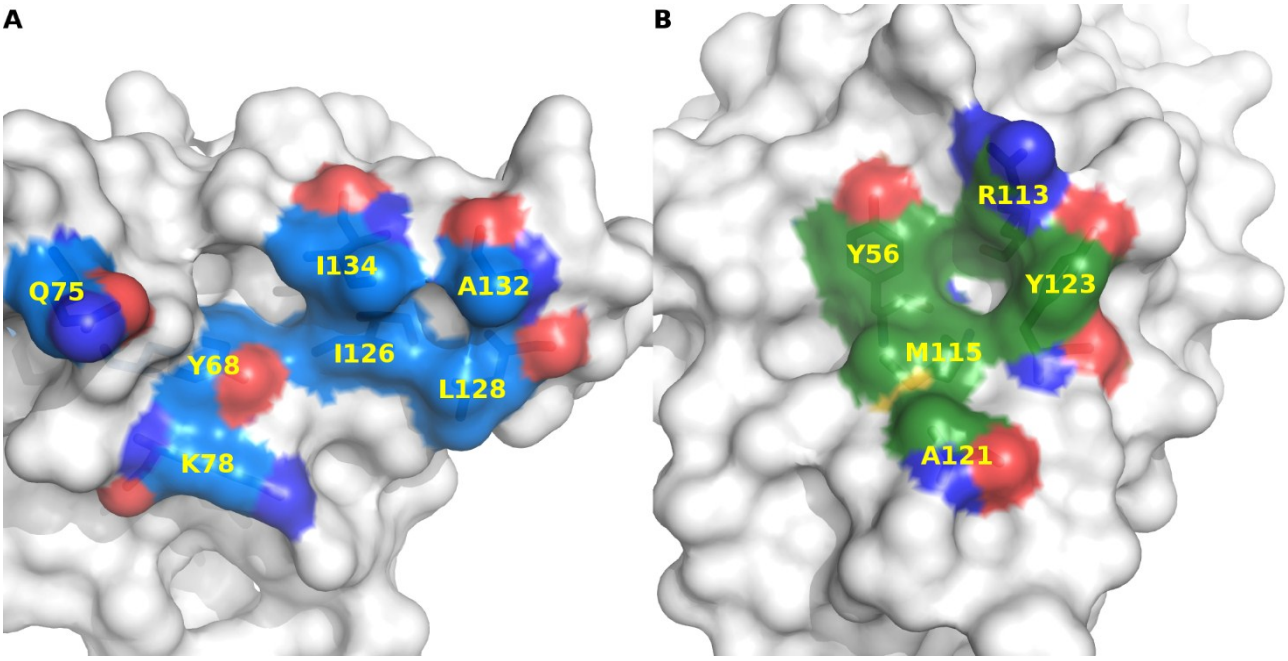

Figure S3. Hot spots (colored surface and labeled in yellow colors) in PD-1 (A) and PD-L1 (B) predicted by over 50% of the methods as listed in Table 4