Supplementary Information

Oncogenic R248W mutation induced conformational perturbation of p53 core domain and the structural protection by proteomimetic amyloid inhibitor ADH-6

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This supporting information contains two supplementary table (Table S1-S2) and 13 supplementary figures (Figure S1-S13).

Table S1. A summary of the simulation details of the three systems. (WT: wild-type p53C; MT: R248W p53C; MT+ADH-6: R248W p53C with one ADH-6 molecule.)

System	Number of MD runs	Total number of atoms	Box side length (nm)	Simulation time (ns)
WT	3	70237	8.95	1000
MT	3	70230	8.95	1000
MT+ADH-6	8	70250 ~ 70296	8.95	1000

Table S2. Time variation of ADH-6's binding region in eight MD simulations.

Simulation	Regions
MD1	1 (500 – 1000 ns)
MD2	2 (500 – 1000 ns)
MD3	3 (500 – 1000 ns)
MD4	4 (500 – 706 ns) → 5 (706 – 1000 ns)
MD5	1 (500 – 573 ns) → 2 (573 – 701 ns) → 3 (701 – 880 ns) → 2 (880 – 941 ns) → 1 (941 – 1000 ns)
MD6	1 (500 – 1000 ns)
MD7	4 (500 – 1000 ns)
MD8	5 (500 – 1000 ns)

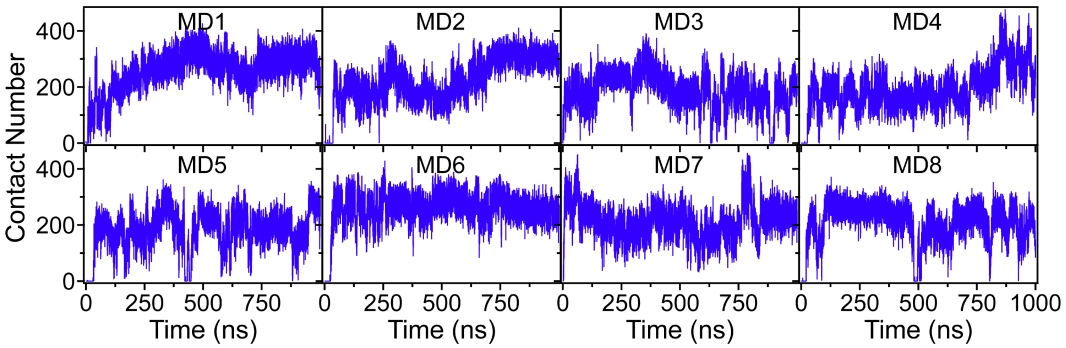

Figure S1. Time variation of the total contact number between ADH-6 molecule and R248W p53C in each of the eight MD runs.

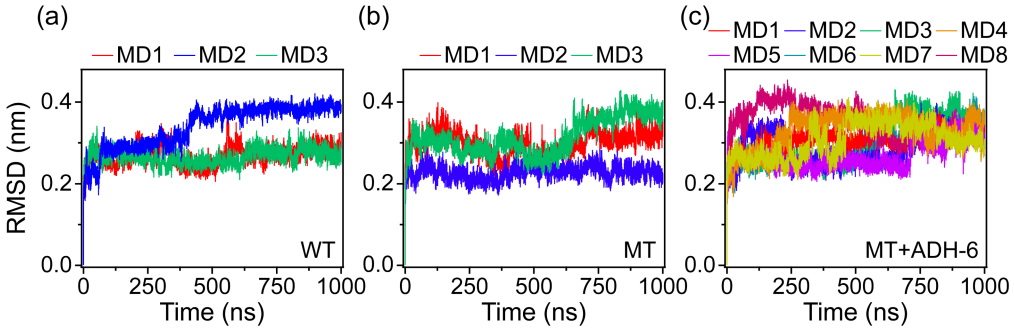

Figure S2. (a-c) Time evolution of main chain root-mean-square deviation (MC-RMSD) values of p53C relative to the initial conformation in each of the three systems: (a) WT, (b) MT, (c) MT+ADH-6.

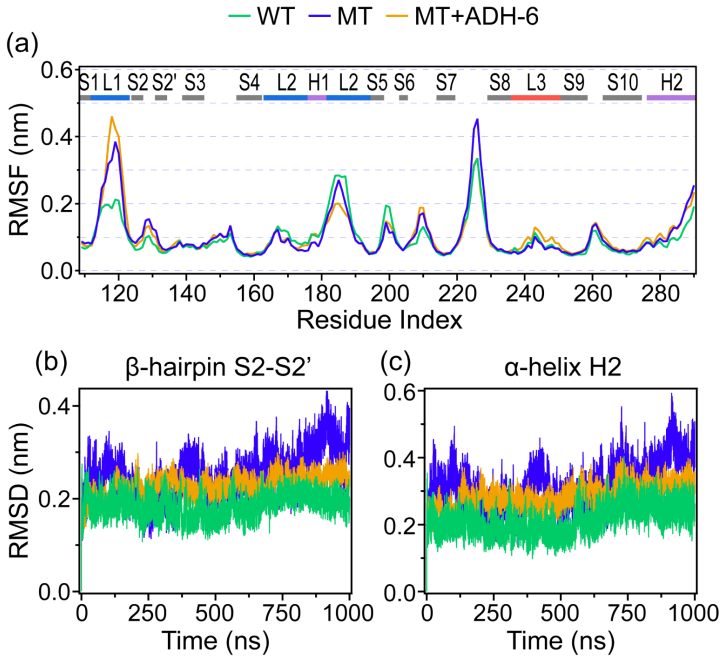

Figure S3. (a) Residue-based MC root-mean-square fluctuation (MC-RMSF) of p53C in the three systems. (b-c) Time evolution of MC-RMSD values of (b) the β-hairpin S2-S2' and (c) the α-helix H2 averaged over all MD runs for each of the three systems.

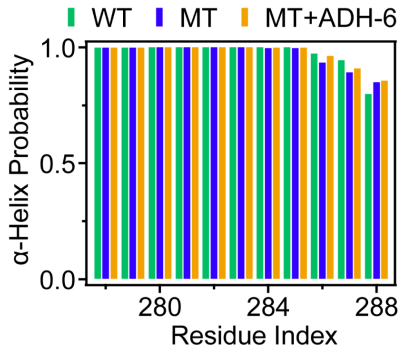

Figure S4. α-helix probability of each residue in helix H2.

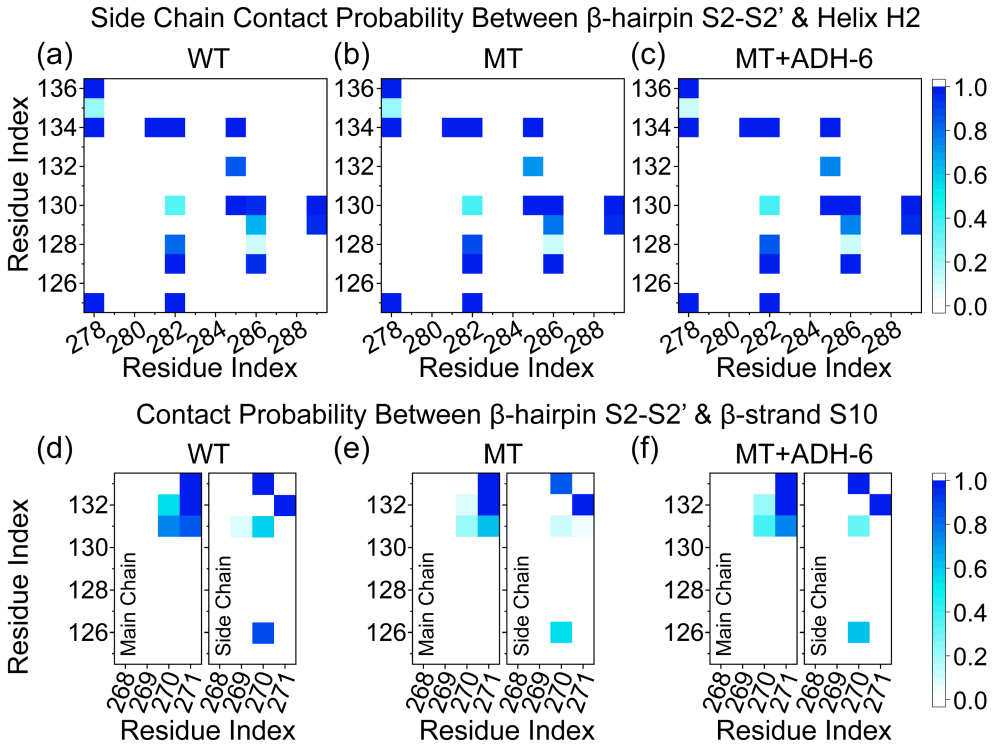

Figure S5. (a-c) Contact probabilities between the side chain atoms of β-hairpin S2-S2' (residues 125-136) and helix H2 (residues 278-289): (a) WT, (b) MT, (c) MT+ADH-6. (d-f) Contact probabilities between the main chain or side chain atoms of residues from β-hairpin S2-S2' and β-strand S10: (d) WT, (e) MT, (f) MT+ADH-6.

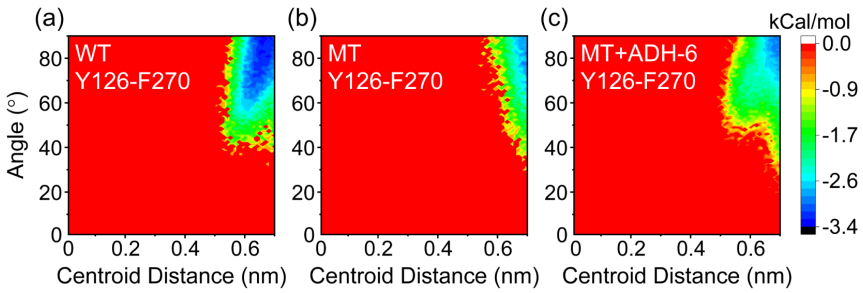

Figure S6. (a-c) PMFs (potential of the mean force) as a function of the centroid distance of two rings and the angle of the two rings, with one ring from Y126 (in β-hairpin S2-S2') and the other ring from F270 (in β-strand S10): (a) WT, (b) MT, (c) MT+ADH-6.

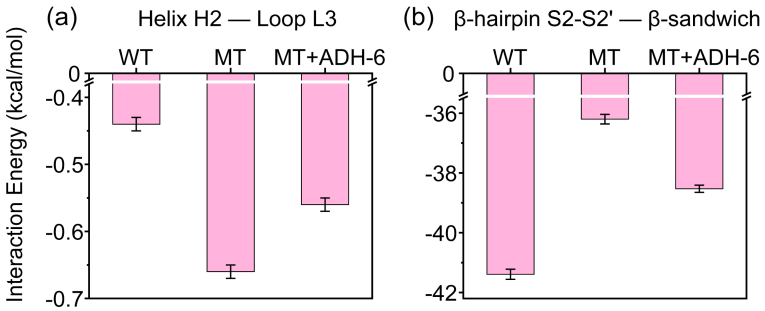

Figure S7. Interaction Energies between (a) helix H2 and loop L3, and between (b) β-hairpin S2-S2' and β-sandwich.

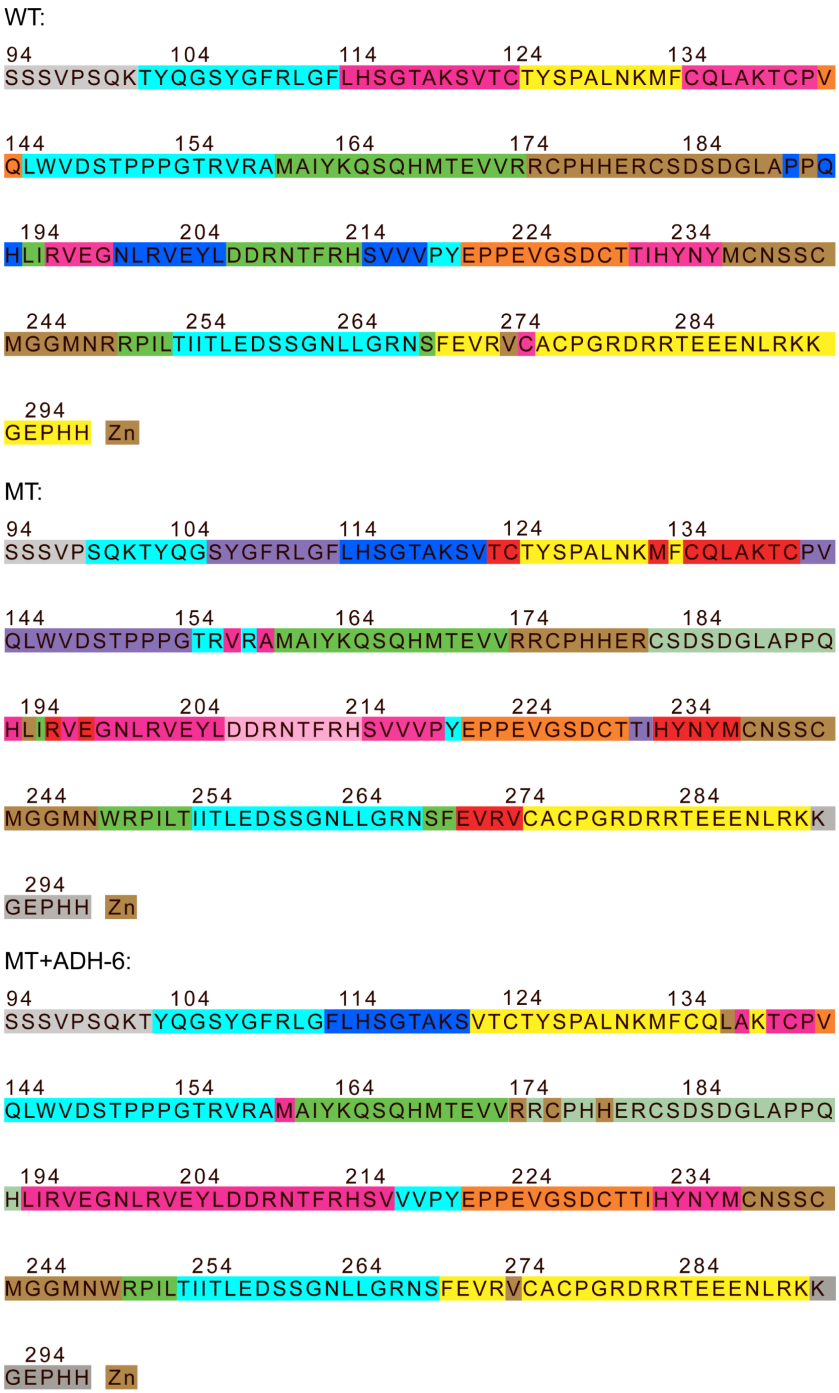

Figure S8. The amino acid sequences of p53C in three systems, in which residues sharing the same color belonging to the same community. The color assignments for the communities are consistent with those in Figure 6.

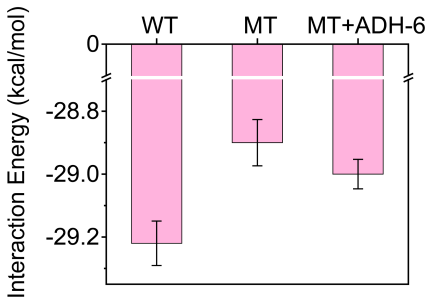

Figure S9. Total interaction energy between the neighboring regions involved in the allosteric pathway, namely residues R248/W248-R249 in L3, APR S9 (residues 251-257), APR S10 (residues 268-271), residues P142-V143 in S3, and residues I232-H233 in S8.

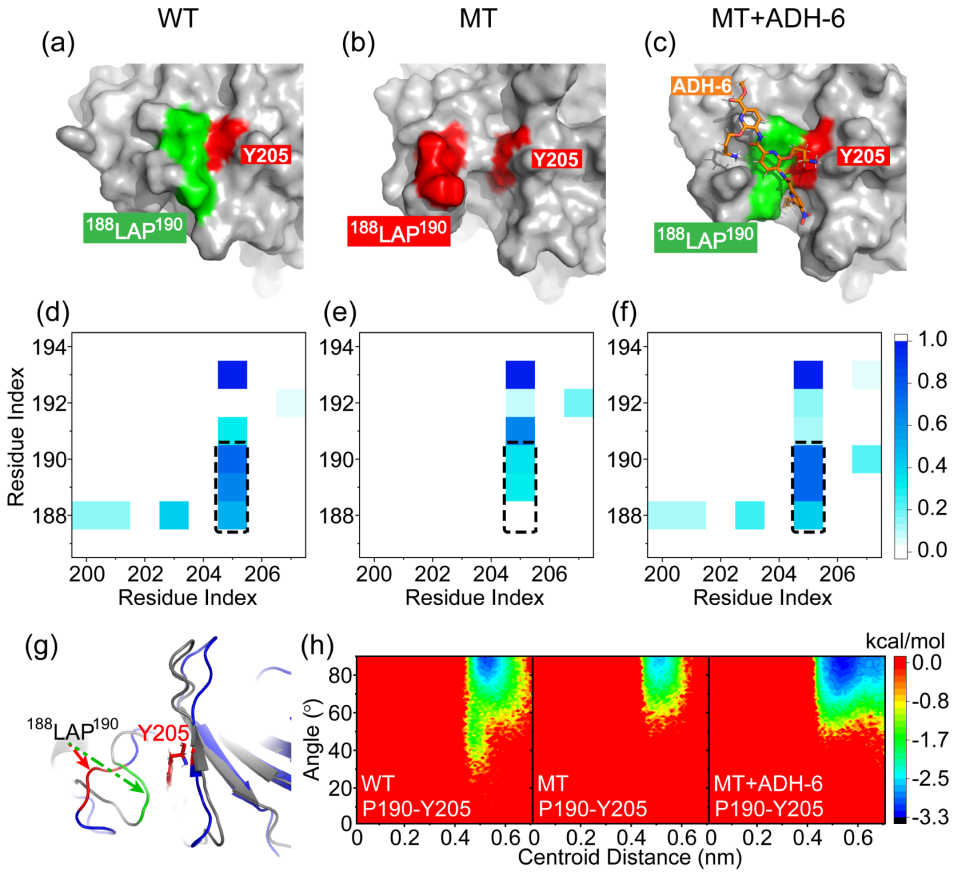

Figure S10. (a-c) Representative snapshots showing the cluster 2 region of R248W p53C with residues ^{188}LAP^{190} in the C-terminus of L2 and Y205 in S6 highlighted: (a) WT, (b) MT, (c) MT+ADH-6. (d-f) Contact probabilities of pairwise residues in the C-terminus of L2 and in/near β-strand S6 (residues 204-205): (d) WT, (e) MT, (f)

MT+ADH-6. (g) Representative snapshot showing the cluster 2 region in R248W p53C (blue) and WT p53C (grey) with residues ^{188}LAP^{190} in the C-terminus of L2 highlighted in red and green respectively. (h) PMFs as a function of the centroid distance of two rings and the angle of the two rings, with one ring from P190 (in L2) and the other ring from Y205 (in S6) in the three systems.

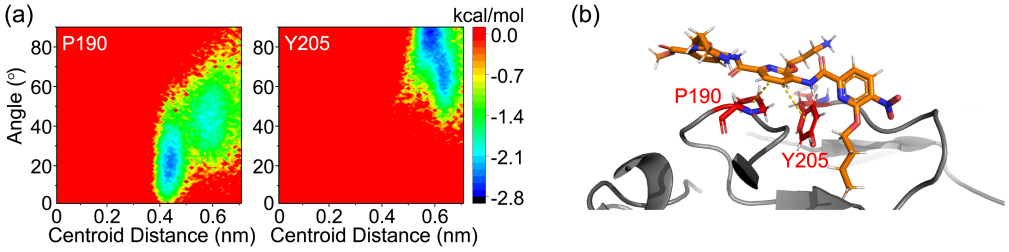

Figure S11. (a) PMF of π−π stacking as a function of the centroid distance and the angle of the two rings, with one ring from ADH-6 and the other ring from P190 or Y205 in R248W p53C. (b) The snapshot showing these π−π stacking interactions with ADH-6 colored in orange and residues P190 and Y205 colored in red.

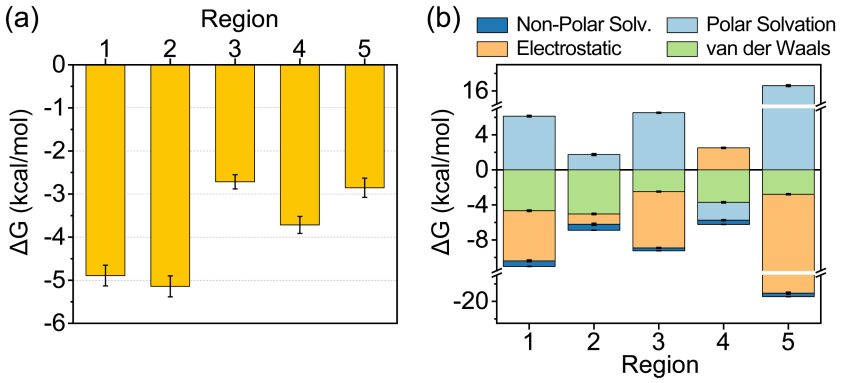

Figure S12. (a) Total binding free energy contributions of each of the five regions and (b) their decompositions into each energy component.

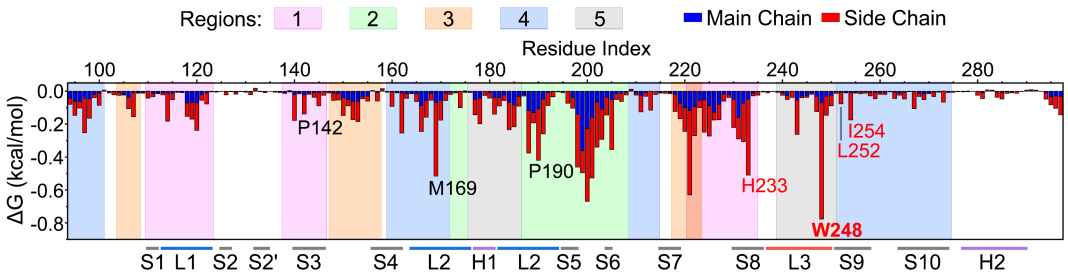

Figure S13. Main-chain and side-chain binding free energy contributions of each residue in p53C.