

Supporting Information

Identification and characterizing the amyloid- β (42) oligomeric conformation and size targeting the receptor LirB2

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Model building and preparation

The LDD receptor (PDB ID: 6BCS)¹, “U”-type (PDB ID: 2BEG)², “S”-type (PDB ID: 7Q4B/ 7Q4M) and “LS”-type³ (PDB ID: 5OQ V) A β 42 fibril are from the RCSB database (<https://www.rcsb.org/>).

*A β O*s: These A β O were selected from different aggregation stages (The definition was based on the β -sheet content between A β 42 peptide chains and the number of A β 42 peptide chains): SP1: A β O species with \sim 10 % β -sheet content (\sim 5 % intermolecular and \sim 5 % intramolecular β -sheet contents), including dimer (*D*), Trimer (*T*), Tetramer (*Te*), Pentamer (*P*), Hexamer (*H*) and Octamer (*O*) from our previous A β 42 models⁴ to mimic various A β O at the initial stage of aggregation. The tertiary structural features observed for these oligomers are supported by the study of Barz et al.⁵ SP2: secondary nucleated A β O species, with \sim 40 % intermolecular β -sheet content and consequently the relatively rigid peptide chains, including dimer (*D_T*), Trimer (*T_T*), Tetramer (*Te_T*) and Pentamer (*F_T*) of A β O in the secondary nucleated stage were built based on the models from A β O conformation reported in the literature^{6, 7}. SP3: initially nucleated A β O species, characterized in between the A β O in the SP1 and SP2, in which four types of tetramers and pentamers with different intermolecular β -sheet contents were constructed, including 0 % intermolecular β -sheet and ca 33% total β -sheet contents (0 %, \sim 33 %), (\sim 12 %, \sim 30.0 %), (\sim 18 %, \sim 18 %), and (\sim 25 %, \sim 25 %). The four kinds of tetramers and pentamers are abbreviated as Te-1/P-1, Te-2/P-2, Te-3/P-3 and Te-4/P-4 in Table S1. Moreover, these A β O species have two “toxicity turns” at residues “22-23” and “38-39”.

A β 42 protofibrils/fibrils chains complement details: Chimera software was used to complement the defective “U”-type (PDB ID: 2BEG)² and “S”-type (PDB ID: 7Q4B/ 7Q4M)⁸ A β 42 fibrils chain, and then performed the simulation annealing for the following model building, as did previously⁹. The initial structure of the A β 42 fibrils of the completed peptide chain was first embedded in the cube box containing TIP3P water model with a margin of 10 Å, and then added sodium ions to keep it neutral. *SA details*: After energy minimization, a periodic algorithm is formulated for each

temperature group from the initial temperature (300 K) to the final temperature (500 K), and the algorithm is repeated throughout the simulation. The number of control temperature points was set to five, with annealing times of 0, 20, 60, 70 and 100 (ps) for each temperature and temperature values of 300 K, 500 K, 500 K, 300 K and 300 K, respectively. After 100 such annealing cycles (10 ns), the “U”-type and “S”-type A β 42 protofibrils with flexible and relaxed ends were obtained.

Protein-Protein Docking Use the “Cluspro 2.0” website,¹⁰ which employed “Fast Fourier Transform” to sample billions of conformations of the receptor and ligand through rigid docking, and ultimately obtained 1000 lowest energy complex structures. The 1000 complex structures were then further analyzed via the root mean square deviation (RMSD) to obtain the 30 most representative complex models. Finally, we used the “Energy Minimization Scoring” module to select three ideal complex structures (Figs.S1-1, S2, S3). In addition, in order to verify Cluspro results, we also used “HDOCK”¹¹ server for protein-protein docking, and the results are shown in the Fig.S1-2. The results of “HDOCK” showed that the I region of LDD receptor was also a suitable binding site for low-MW A β O, and the II/III region was more suitable for the high-MW A β O.

MM/PBSA script specific parameter Frames (0.1 ns for one sample), time scale (last 10 ns), solvation models (continuum model). We utilized an enhanced script for calculating the binding energy, sourced from https://jerkwin.github.io/2021/03/16/gmx_mmpbsa_script_updates_-_shielding_effect_and_the_entropy_contribution/. The script considers not only the ionic strength but also incorporates the Debye characteristic length to calculate ΔE_{cou} , resulting in an exponential decay of the electrostatic interaction.¹²⁻¹⁴

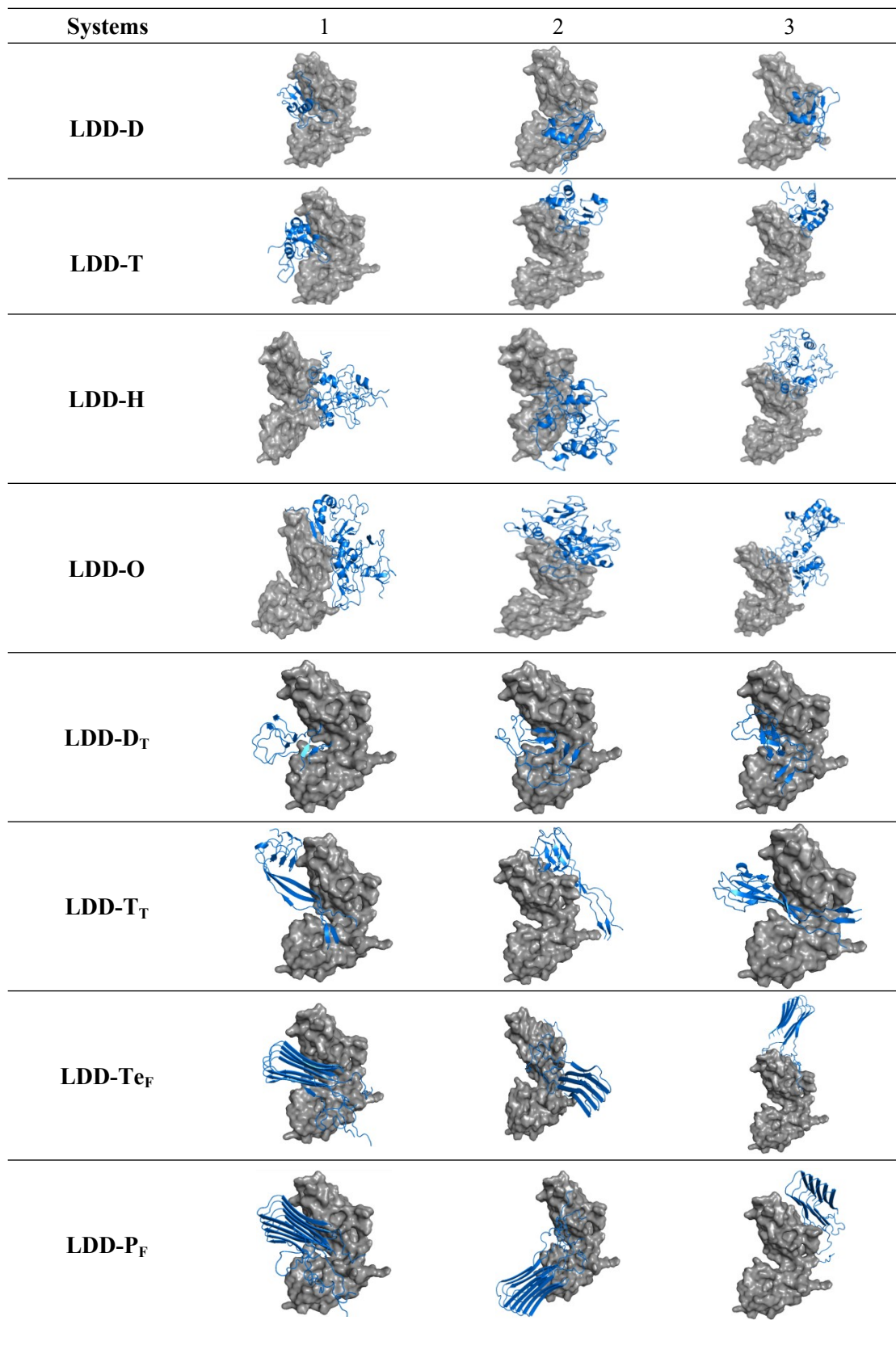

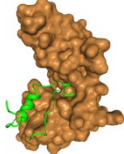










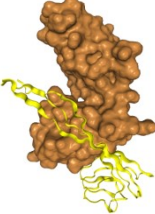
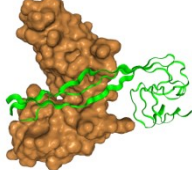
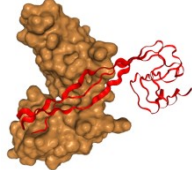

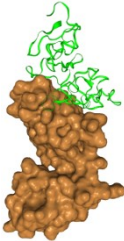
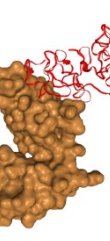
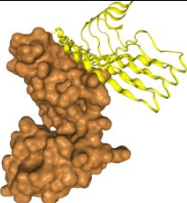
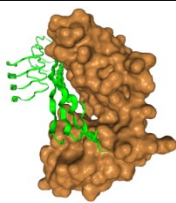
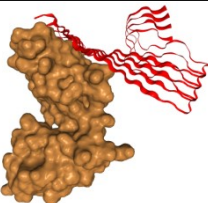


Fig. S1-1 The initial top3 models for each AβO(SP1, SP2, SP4) -LDD interaction ranked by "ClusPro" website.

Systems	1	2	3
LDD-M			
LDD-D			
LDD-D _T			
LDD-T			
LDD-T _T			
LDD-Te			
LDD-Te _T			

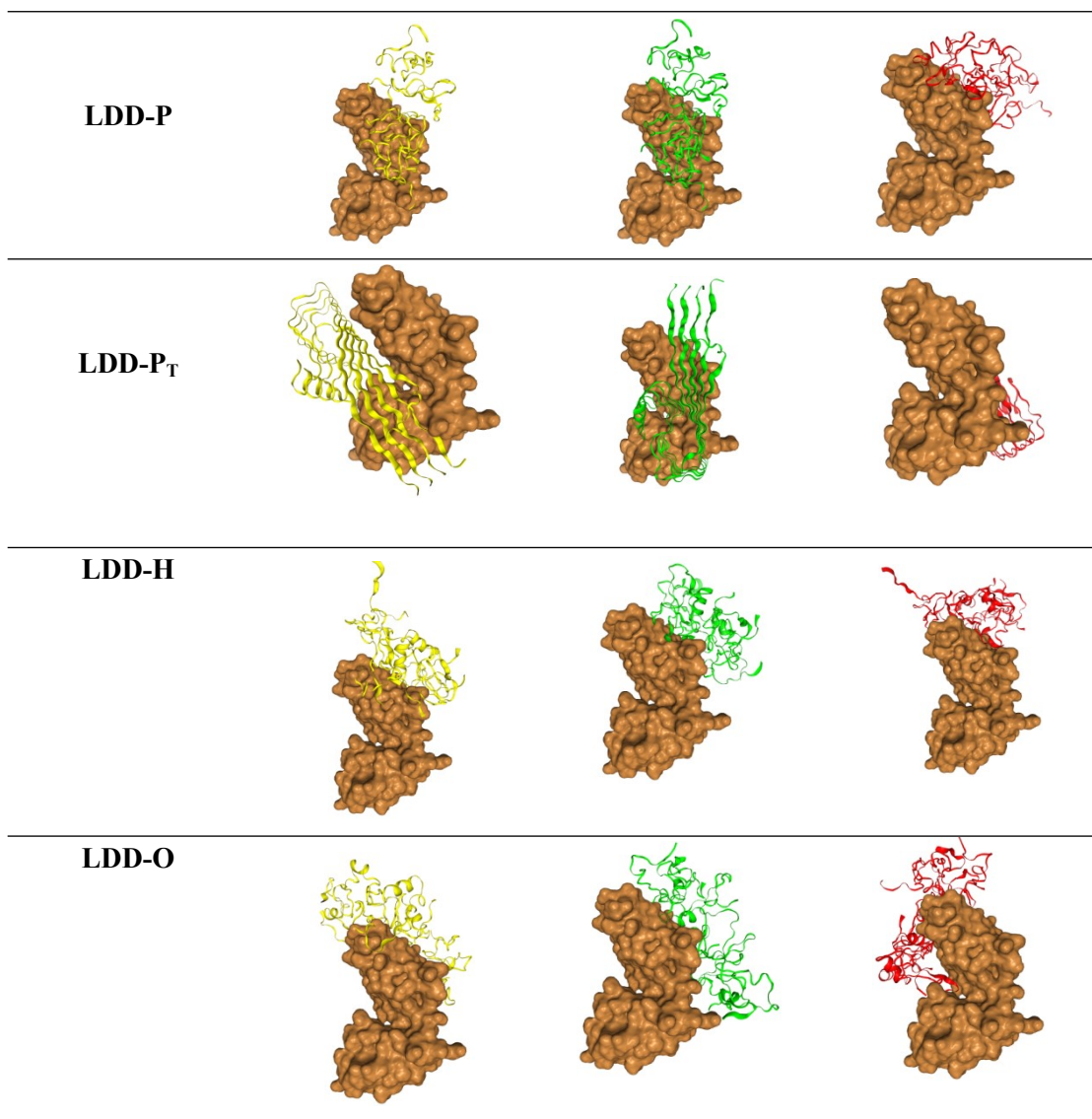
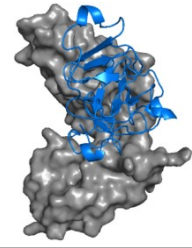
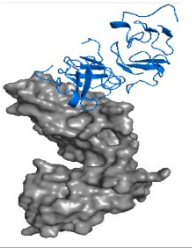
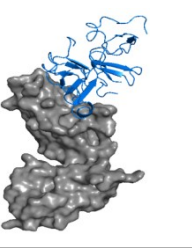
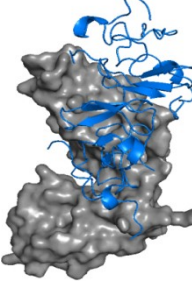
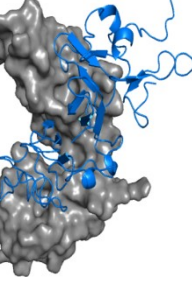
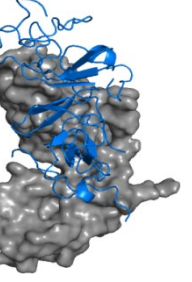
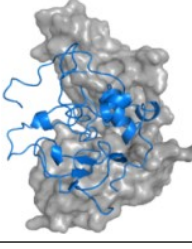
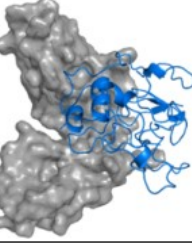
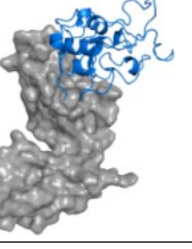
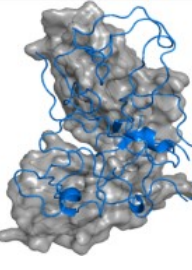
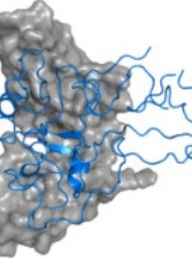
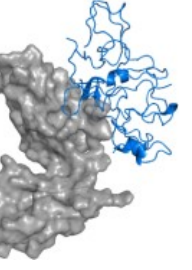
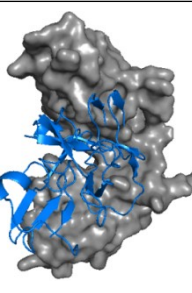
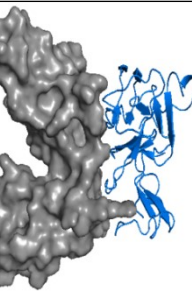
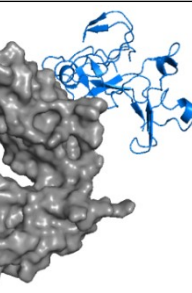
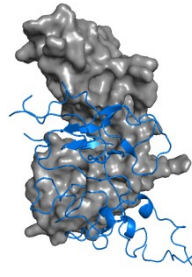
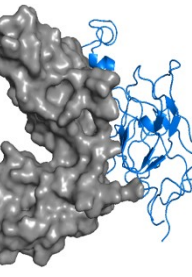
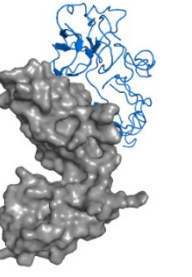


Fig. S1-2 The initial top3 models for each AβO-LDD interaction ranked by “HDOCK” website.

Systems	1	2	3
LDD-Te-1			
LDD-P-1			
LDD-Te			
LDD-P			
LDD-Te-2			
LDD-P-2			

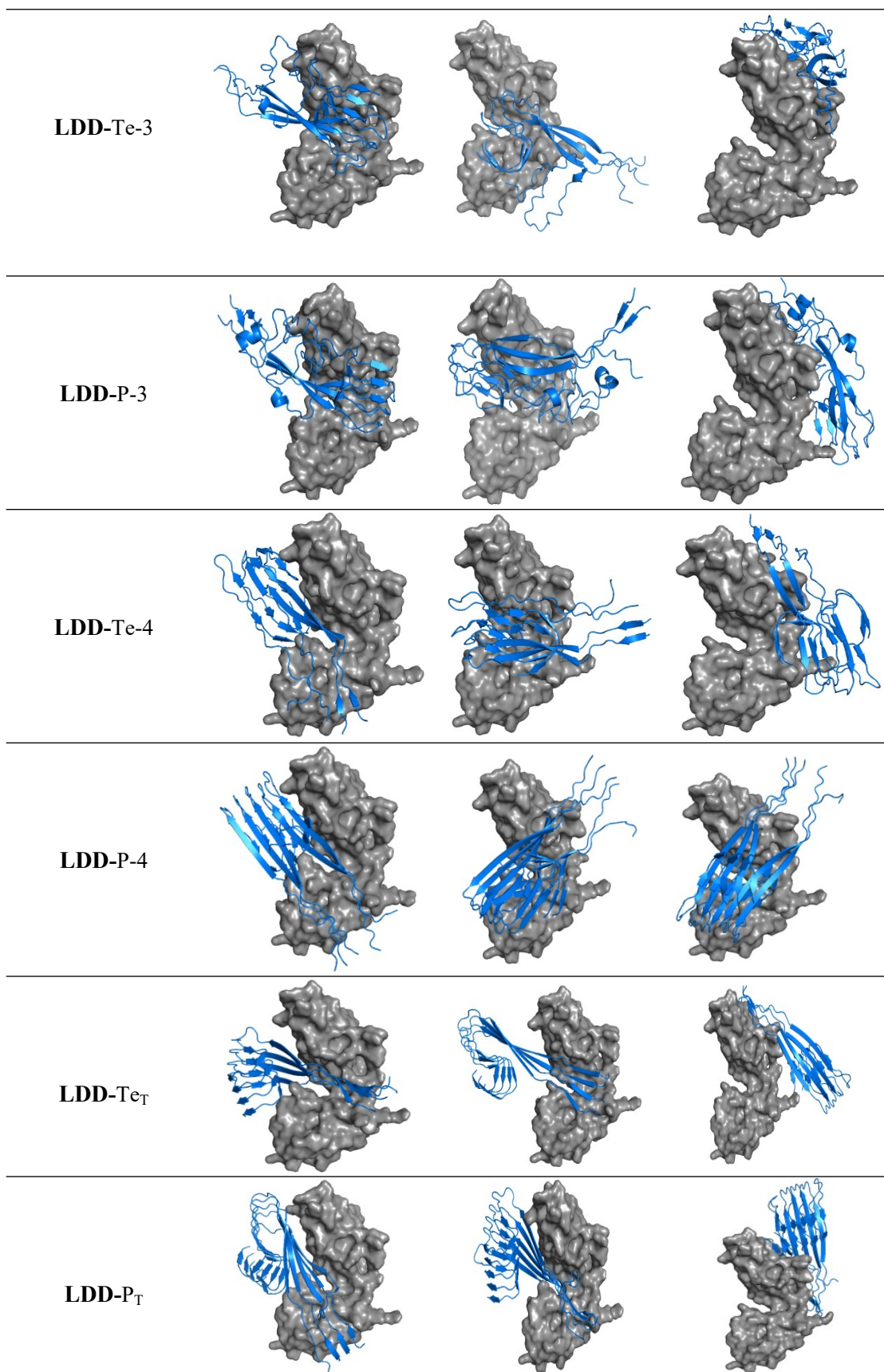
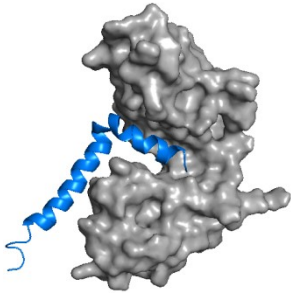
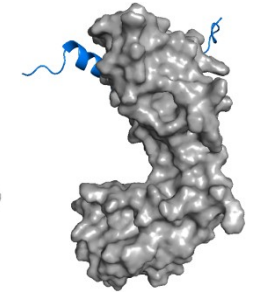
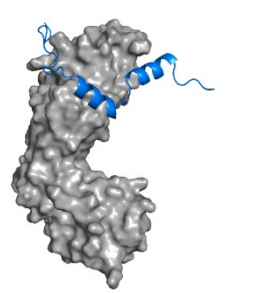
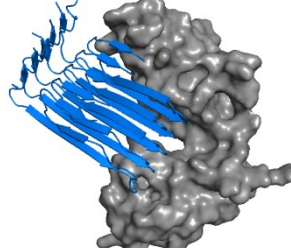
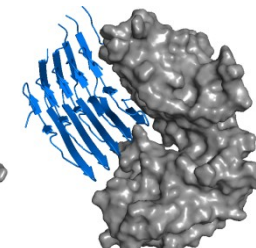
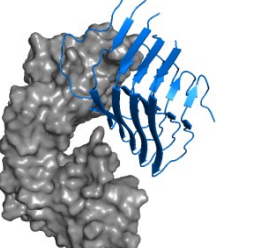
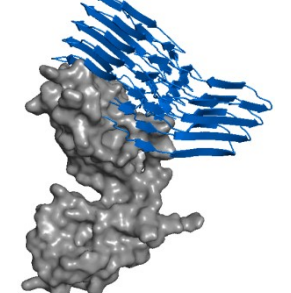
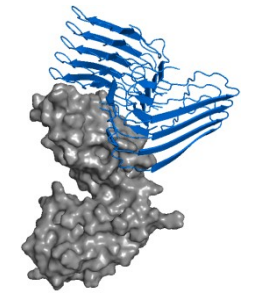
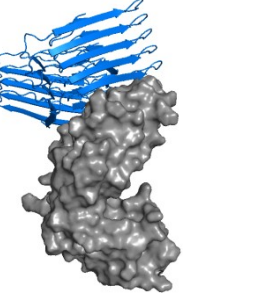
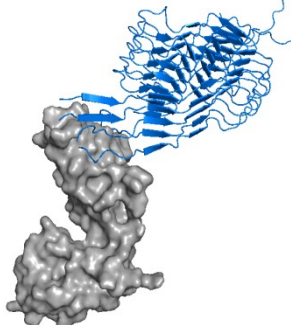
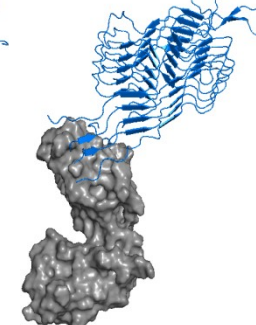
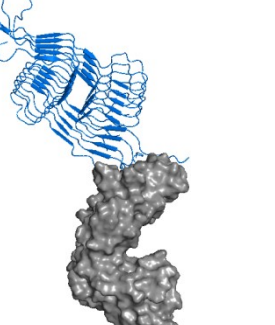
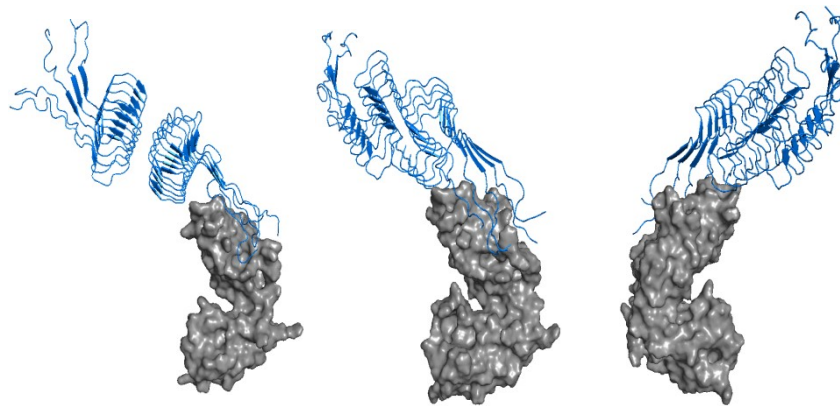


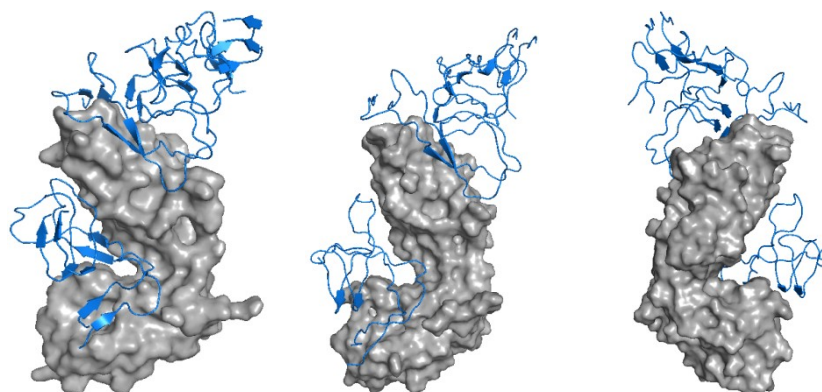
Fig. S2 The initial top3 models for each model of tetramer (Te)/pentamer (P) (SP1, SP2, SP3) bound LDD receptor, ranked by “ClusPro” website.

Systems	Front view of initiating structure	Front view of equilibrium structure	$\mathbb{S} 180^\circ$	Back view of equilibrium structure
LDD-M				
LDD-F50qv-1				
LDD-F50qv-2				
LDD-F7q4b				

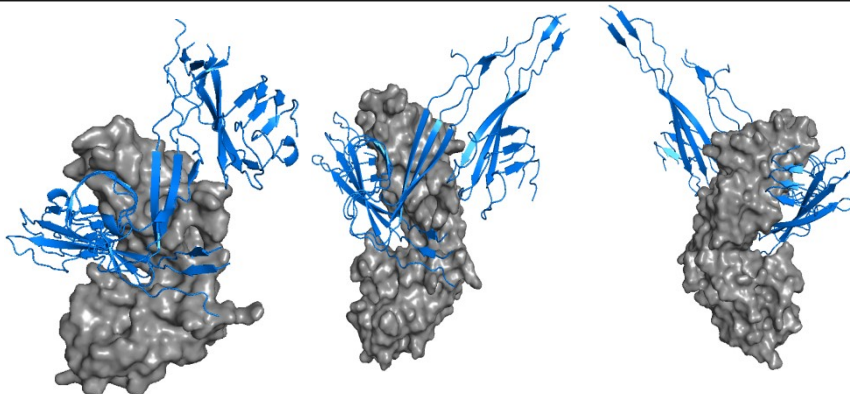
LDD-F7q4m



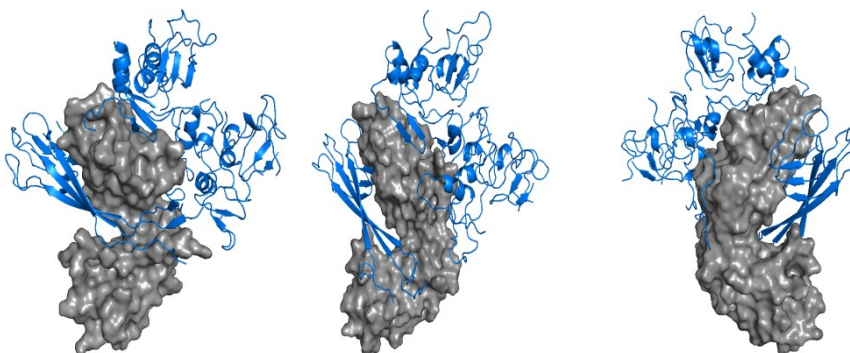
LDD-D_TD_TD_T



LDD-T_TT_TT_T



LDD-T_T-O



LDD-Te_T-O

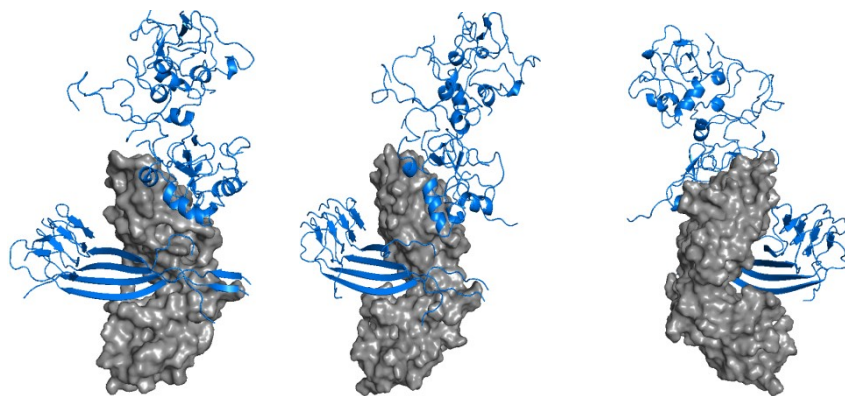


Fig. S3 Conformations of LDD-A β O (SP1, SP2, SP4) complexes at initial (2nd column) and equilibrium (3rd-4th columns) states.

Systems	1	2	3
LDD-D			
LDD-T			
LDD-H			
LDD-O			
LDD-D_T			

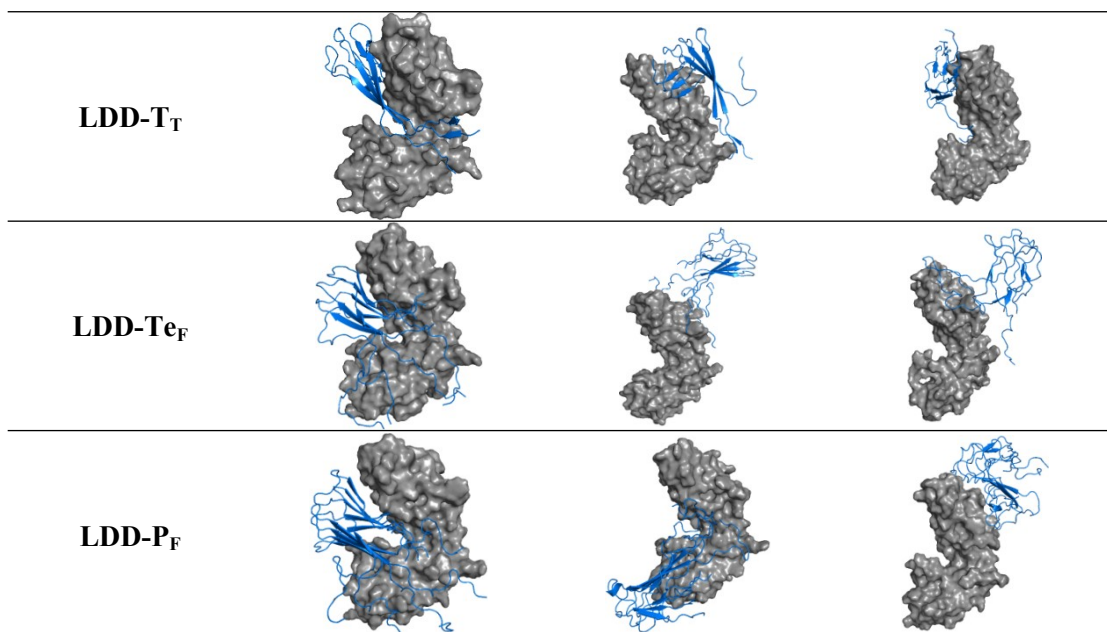
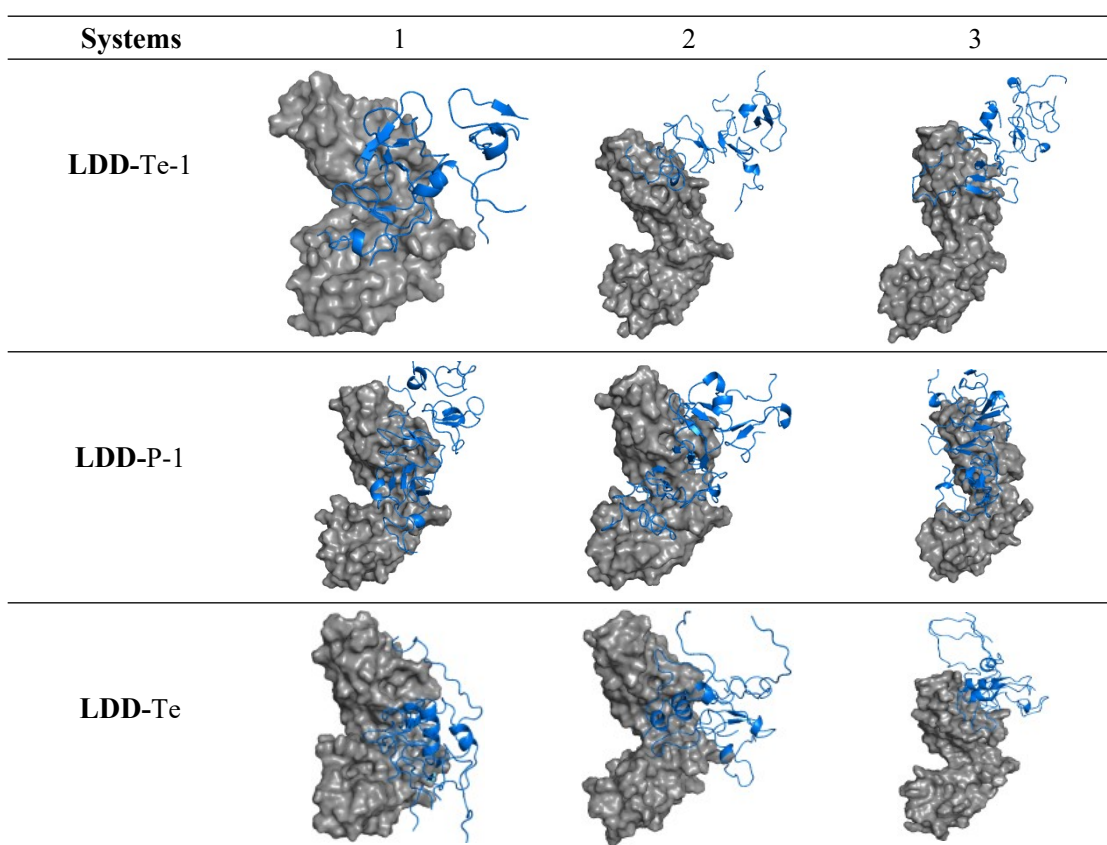
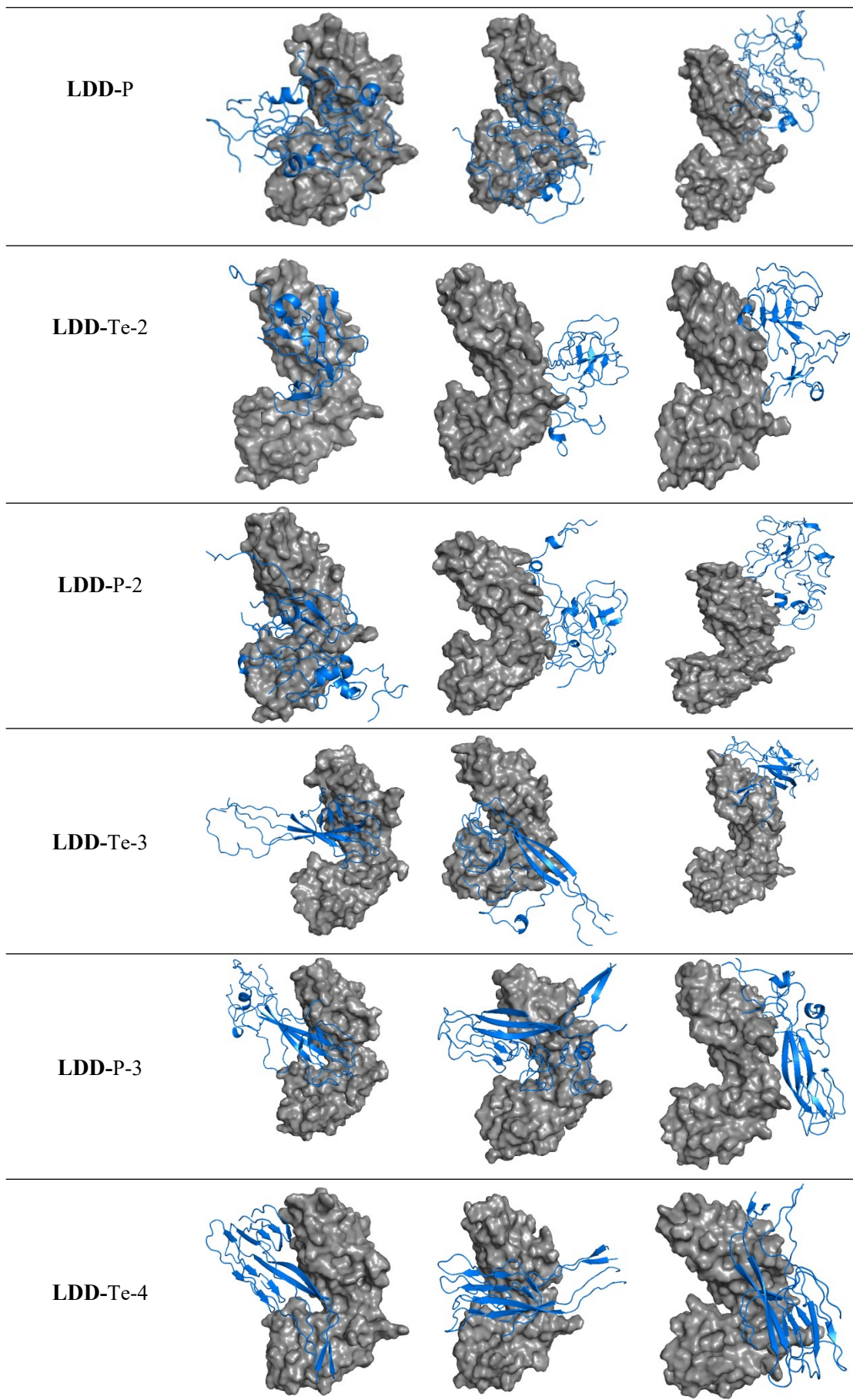


Fig. S4 Top 3 conformations of each LDD-A β O complexes (SP1, SP2, SP4) at equilibrium states.





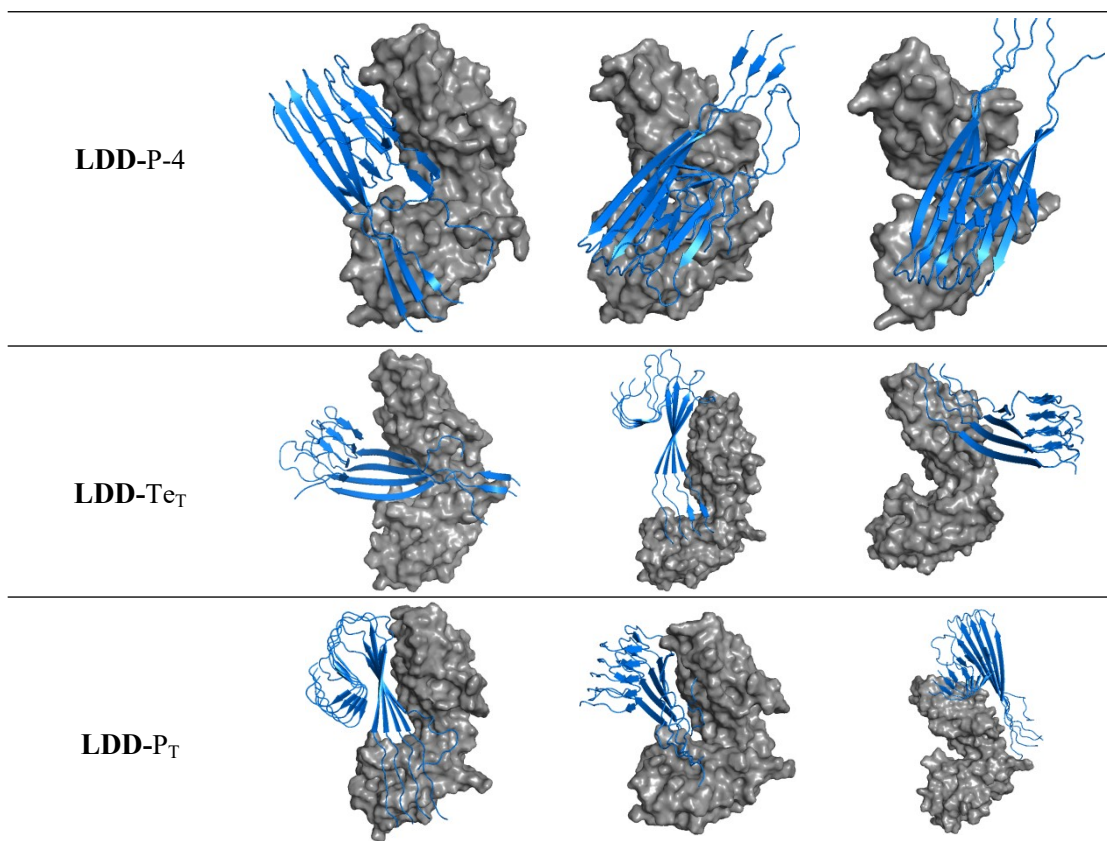


Fig. S5 Top 3 conformations for each model of tetramer (Te)/pentamer (P) (SP1, SP2, SP3) bound LDD receptor complexes at equilibrium states.

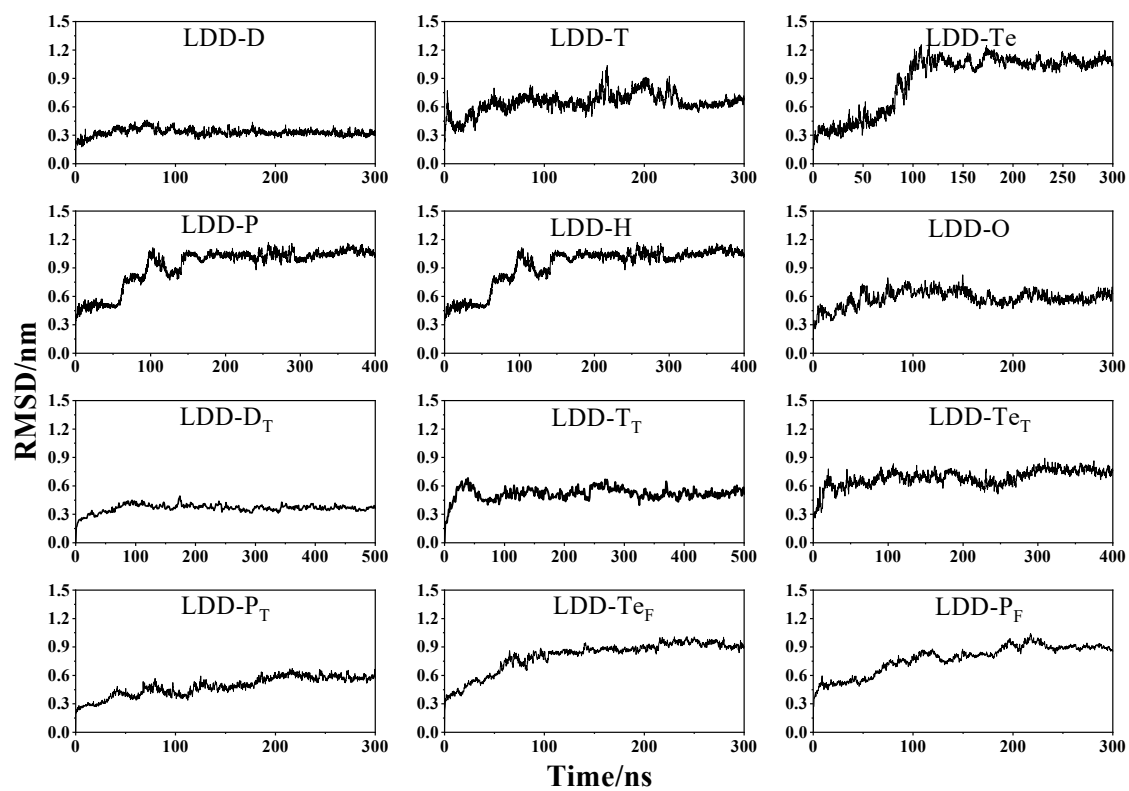


Fig. S6 The RMSD of the complex formed by A β O and LDD.

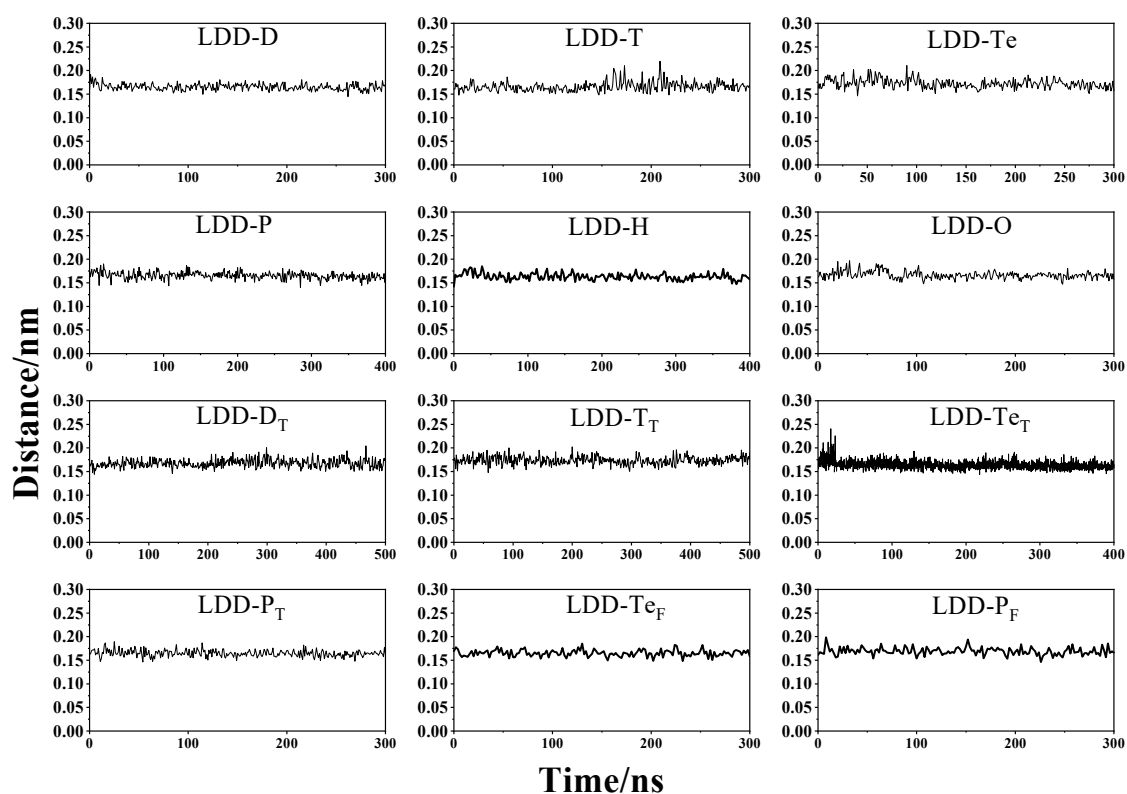


Fig. S7 Microprocesses of minimum distance between A β O and the LDD "initial Docking site" during the equilibrium simulation.

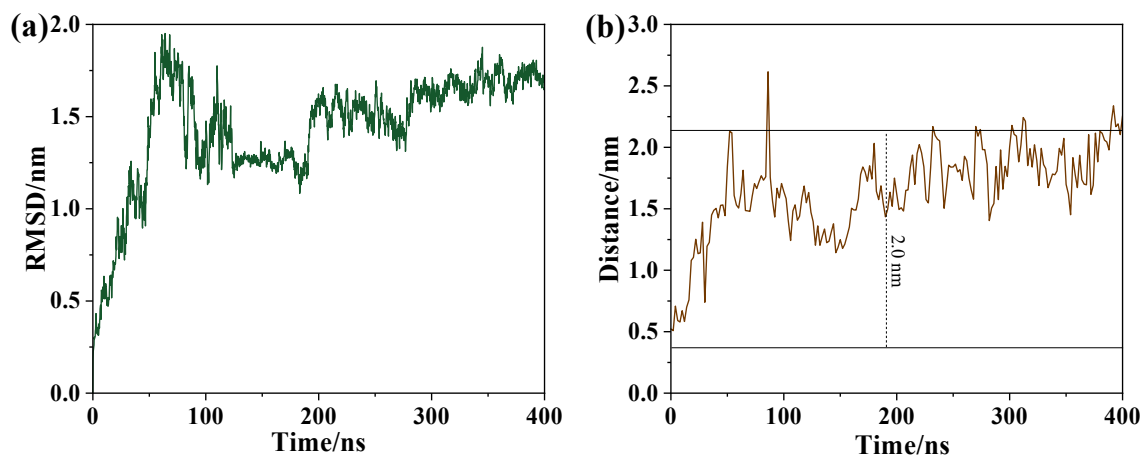


Fig. S8 The RMSD of the complex formed by A β 42 monomer and LDD(a), and microprocesses of minimum distance between A β 42 monomer and the LDD "initial Docking site" during the equilibrium simulation(b).

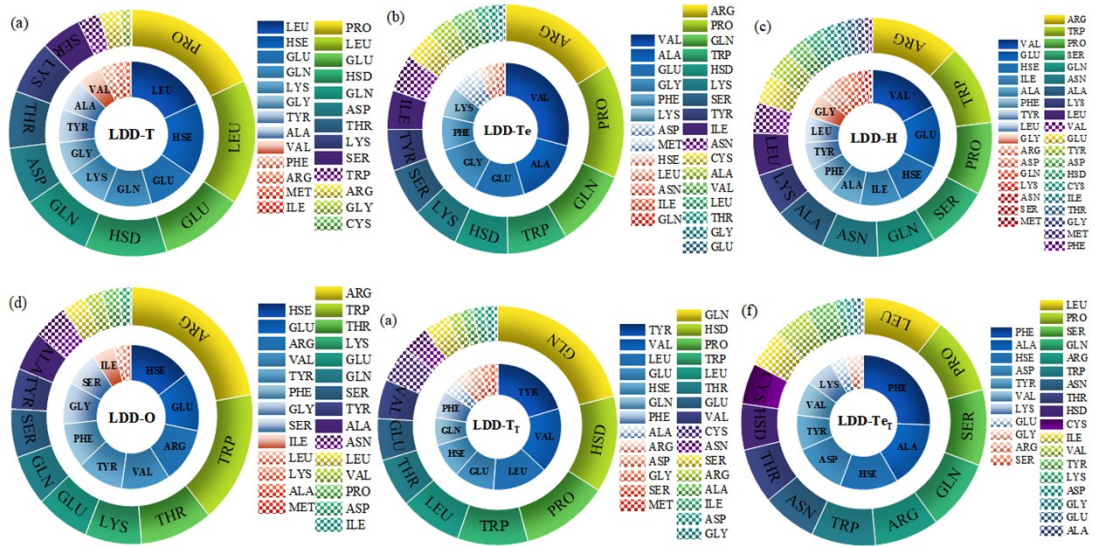


Fig. S9 The probability of residues contributing to the contact interface of $A\beta O$ (inner torus)-LDD (outer torus) complexes. The residues with less ($< \sim 5\%$) contact contributions are represented by mosaic. The residues on the contact interface are highlighted in light color, embedding in the deep-blue surface. $A\beta O$ species involved in complexes (a-f) are T , Te , H , O , T_T and Te_T , respectively.

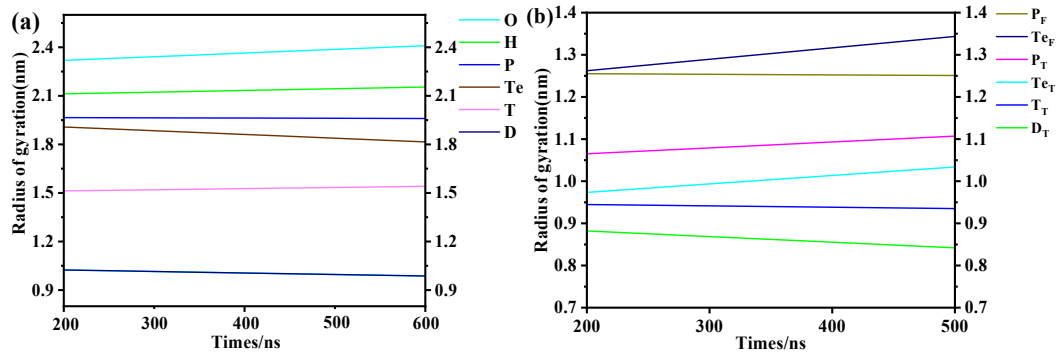


Fig. S10-1 The variation of the gyration radius of $A\beta 42$ oligomers in the $A\beta O$ -LDD complex with time after linear fitting.

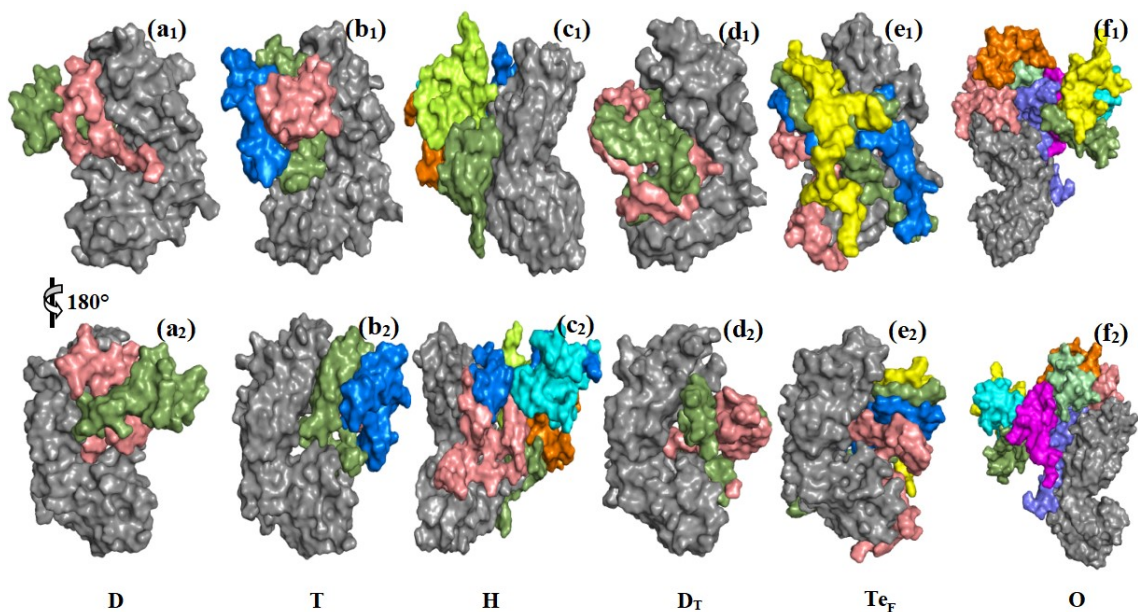


Fig. S10-2 3D contact map of LDD and Aβ42 oligomers. Gray is LDD, green, yellow and blue are Aβ42 oligomers/fibril peptide chain; (a₁₋₂), (d₁₋₂) and (e₁₋₂) represent LDD-*D*, *T*, *D_T* and *Te_F* bound to LDD I binding region, respectively; (b₁₋₂) represents LDD-*H* bound to LDD II binding region; (c₁₋₂) represents LDD-*O* bound in the LDD III binding region.

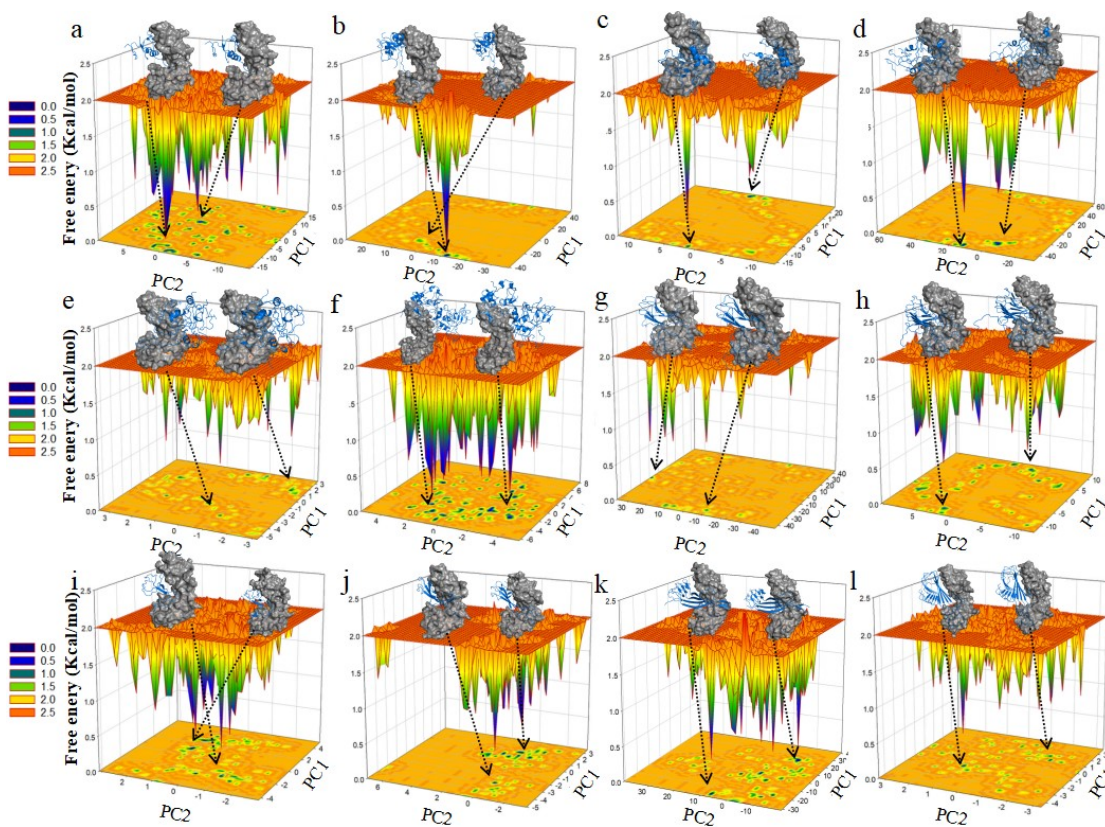


Fig. S11 3D/2D free energy landscapes of the LDD – AβO complexes, the PC1 and PC2 are the

two largest eigenvectors. a-f represents LDD - A β 42 D/T/Te/P/H/O respectively, g-h represents LDD - A β 42 Te_F/P_F respectively, and i-l represents D_T/T_T/Te_T/P_T respectively. On each figure, the model with the lowest energy is depicted on the left, while the model with the next lowest energy is shown on the right.

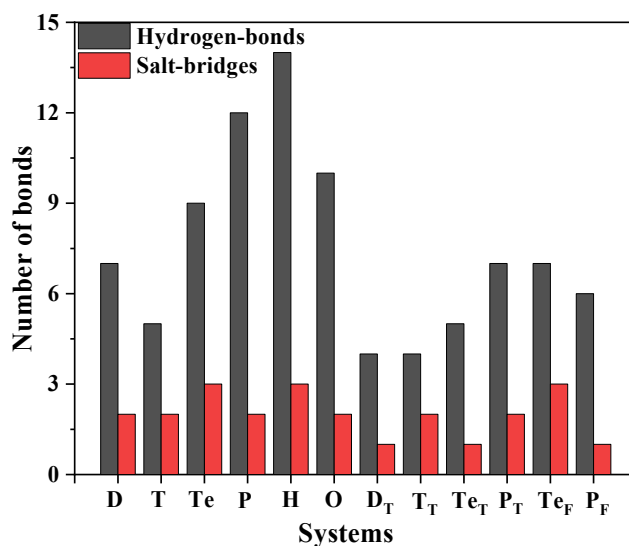


Fig. S12 Number of hydrogen-bond and salt-bridge in total A β O-LDD.

Table S1-1. The β -sheet content (%) of A β O at four characteristic subphases.

Systems	SPs	Intramolecular β -sheet (%)	Intermolecular β -sheet (%)	Total β -sheet (%)	Regions of A β O binding
LDD-D	SP(1)	10.3	6.4	16.7	Region I
LDD-T	SP(1)	8.1	8.6	16.7	Region I
LDD-H	SP(1)	7.0	6.1	13.1	Region II
LDD-O	SP(1)	0.4	7.6	8.0	Region III
LDD-D _T	SP(2)	4.0	36.2	40.2	Region I
LDD-T _T	SP(2)	0	42.3	42.3	Region I
LDD-Te _F	SP(4)	0	45.8	45.8	Region I
LDD-P _F	SP(4)	0	46.2	46.2	Region I
LDD-F5oqv1	SP(4)	0	83.3	83.3	Region I
LDD-F5oqv-2	SP(4)	0	88.6	88.6	Region III
LDD-F7q4b	SP(4)	0	74.7	74.7	Region III
LDD-F7q4m	SP(4)	0	75.8	75.8	Region III

Table S1-2. The β -sheet content (%) of all the constructed tetramers (Te) and pentamers (P) at the SP3.

Systems	Intramolecular β -sheet (%)	Intermolecular β -sheet (%)	Total β -sheet (%)	Regions of A β O binding
LDD-Te-1	33.3	0	33.3	Region II
LDD-P-1	32.1	0	32.1	Region II
LDD-Te	6.0	5.8	11.4	Region II
LDD-P	5.4	6.0	13.3	Region II
LDD-Te-2	17.8	11.9	29.7	Region II
LDD-P-2	17.1	11.4	28.5	Region II
LDD-Te-3	0	18.5	18.5	Region I
LDD-P-3	0	18.0	18.0	Region I
LDD-Te-4	0	24.4	24.4	Region I
LDD-P-4	0	27.6	27.6	Region I
LDD-Te _T	0	38.1	38.1	Region I
LDD-P _T	0	36.2	36.2	Region I

Table S2. The binding energy (kcal/mol) / dissociation constant(mol/L) between the LDD receptor and A β fibril.

Systems	ΔG_{PB}	ΔG_{SA}	ΔE_{COU}	ΔE_{VDW}	$-T\Delta S$	ΔG_{bind}	$\Delta G_{bindfit}$	K_d	Regions
LDD-F5oqv-1	221.9	-12.9	-167.2	-81.9	15.8	-24.3	-12.9	3.4×10^{-10}	I
LDD-F5oqv-2	170.3	-8.7	-184.9	-42.3	36.7	-28.9	-8.2	9.6×10^{-7}	III
LDD-F7q4b	269.3	-11.8	-212.2	-74.6	26.6	-2.7	-10.4	2.3×10^{-8}	III
LDD-F7q4m	202.1	-13.8	-148.4	-78.2	33.9	-4.4	-10.4	2.3×10^{-8}	III

Table S3. Relative difference between the first and second lowest free energies (kcal·mol⁻¹) of the LDD-A β O complexes.

Complexes	LDD-D	LDD-T	LDD-Te	LDD-P	LDD-H	LDD-O	LDD-Te _F	LDD-P _F	LDD-D _T	LDD-T _T	LDD-Te _T	LDD-P _T
Relative difference	0.50	0.95	0.74	0.25	0.40	0.09	0.02	0.13	0.29	0.46	0.30	0.45

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