

Supporting Information

Probing the Interactions of LRP1 Ectodomain Derived Peptides with Fibrillar Tau Protein and its Impact on Cellular Internalization

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Table S1. Thread templates generated from Phyre 2 with 100% confidence level that were modeled to determine the cluster 2 subdomain structure of LRP1.

Number	Template	Confidence%	% i.d.	Template Information
1	cln7dA	100	36	PDB header: lipid transport Chain: A: PDB Molecule: low-density lipoprotein receptor; PDBTitle: extracellular domain of the ldl receptor PDB Entry: PDBe RCSB PDBj
2	c3s94A	100	38	PDB header: signaling protein Chain: A: PDB Molecule: low-density lipoprotein receptor-related protein 6; PDBTitle: crystal structure of lrp6-e1e2 PDB Entry: PDBe RCSB PDBj
3	c3s8vA	100	33	PDB header: signaling protein Chain: A: PDB Molecule: low-density lipoprotein receptor-related protein 6; PDBTitle: crystal structure of lrp6-dkk1 complex PDB Entry: PDBe RCSB PDBj
4	c5b4xD	100	38	PDB header: signaling protein/endocytosis Chain: D: PDB Molecule: low density lipoprotein receptor-related protein 8, PDBTitle: crystal structure of the apoer2 ectodomain in complex with the reelin2 r56 fragment PDB Entry: PDBe RCSB PDBj
5	c3v65D	100	42	PDB header: protein binding Chain: D: PDB Molecule: low-density lipoprotein receptor-related protein 4; PDBTitle: crystal structure of agrin and lrp4 complex PDB Entry: PDBe RCSB PDBj
6	c6fb3A	100	14	PDB header: cell adhesion Chain: A: PDB Molecule: teneurin-2; PDBTitle: teneurin 2 partial extracellular domain PDB Entry: PDBe RCSB PDBj
7	c3v64C	100	44	PDB header: protein binding Chain: C: PDB Molecule: low-density lipoprotein receptor-related protein 4; PDBTitle: crystal structure of agrin and lrp4 PDB Entry: PDBe RCSB PDBj
8	c3m0cC	100	35	PDB header: protein binding Chain: C: PDB Molecule: low-density lipoprotein receptor; PDBTitle: the x-ray crystal structure of pcsk9 in complex with the ldl receptor PDB Entry: PDBe RCSB PDBj
9	c3v65B	100	44	PDB header: protein binding Chain: B: PDB Molecule: low-density lipoprotein receptor-related protein 4;

				PDBTitle: crystal structure of agrin and lrp4 complex PDB Entry: PDBe RCSB PDBj
10	c3p5cL	100	34	PDB header: hydrolase/lipid binding protein Chain: L: PDB Molecule: low density lipoprotein receptor variant; PDBTitle: the structure of the ldlr/pcsk9 complex reveals the receptor in an2 extended conformation PDB Entry: PDBe RCSB PDBj
11	c6fayA	100	13	PDB header: cell adhesion Chain: A: PDB Molecule: odz3 protein; PDBTitle: teneurin3 monomer PDB Entry: PDBe RCSB PDBj
12	c3p5bL	100	35	PDB header: hydrolase/lipid binding protein Chain: L: PDB Molecule: low density lipoprotein receptor variant; PDBTitle: the structure of the ldlr/pcsk9 complex reveals the receptor in an2 extended conformation PDB Entry: PDBe RCSB PDBj
13	c7bamB	99.4	15	PDB header: membrane protein Chain: B: PDB Molecule: teneurin-4; PDBTitle: human teneurin4 wt c2 PDB Entry: PDBe RCSB PDBj
14	C3soqA	100	40	PDB header: protein binding/antagonist Chain: A: PDB Molecule: low-density lipoprotein receptor-related protein 6; PDBTitle: the structure of the first ywtd beta propeller domain of lrp6 in2 complex with a dkk1 peptide PDB Entry: PDBe RCSB PDBj
15	clijqA	100	36	PDB header: lipid transport Chain: A: PDB Molecule: low-density lipoprotein receptor; PDBTitle: crystal structure of the ldl receptor ywtd-egf domain pair PDB Entry: PDBe RCSB PDBj
16	dlijqal	100	35	Fold: 6-bladed beta-propeller Superfamily: YWTD domain Family: YWTD domain PDB entry: PDBe RCSB PDBj
17	dlnpea	100	35	Fold: 6-bladed beta-propeller Superfamily: YWTD domain Family: YWTD domain PDB entry: PDBe RCSB PDBj
18	c4a2lD	96.7	11	PDB header: transcription Chain: D: PDB Molecule: two-component system sensor histidine kinase/response; PDBTitle: structure of the periplasmic domain of the heparin and heparan2 sulphate sensing hybrid two component system bt4663 in apo and3 ligand bound forms PDB Entry: PDBe RCSB PDBj
19	c7djlC	99.9	20	PDB header: plant protein Chain: C: PDB Molecule: protein suppressor of quenching 1, chloroplastic; PDBTitle: structure of four truncated and mutated forms of quenching protein PDB Entry: PDBe RCSB PDBj
20	c5a1vK	97.7	14	PDB header: transport protein Chain: K: PDB Molecule: coatomer subunit alpha; PDBTitle: the structure of the copi coat linkage i PDB Entry: PDBe RCSB PDBj

Table S2. Top template Threads obtained from I-TASSER studies to determine the secondary structures of the 23-amino acid sequence of Cluster II domain and the fourteen designed peptides.

1. Sequence: SKAWVCDGDND CEDNSDEENCES (23-amino acid sequence) derived from Cluster II domain of LRP1.

IDEN is the percentage sequence identity in the structurally aligned region.

Rank	PDB Hit	I den1	I den2	Cov.	Norm. Z-Score	Sec. Struc. Seq CCCSSCCCCCCCCCHHHCCC SKAWVCDGDND CEDNSDEENCES
1	1n7dA	0.50	0.39	0.78	0.38	-----CDREYDCKDMSDEVGCVN
2	7qbdD	0.57	0.52	0.91	2.16	PLTWRCDRDLDCSDGSDEEEC--
3	3t5oA	0.48	0.61	1.00	1.41	ARKLECNGENDCGDN SDERDCGR
4	4zrpC	0.48	0.48	1.00	3.92	PLTWRCDGHPDCPDSSDELGCGT
5	3t5oA	0.52	0.61	0.91	1.56	-RKLECNGENDCGDN SDERDCG-
6	1cr8A	0.57	0.56	1.00	0.70	PLRWRCGDGTD C MDS SDEKSC EG
7	3a7qB	0.52	0.48	0.91	2.27	PSVWRCDEDDCLDH SDEDDC--
8	7jpnH	0.09	0.22	1.00	0.39	ASKGAAAEIREQGDGAED EEWDD
9	1ajjA	0.59	0.56	0.96	2.97	HSSWRC DGGPDCKDKSDEENCA-
10	1cr8A	0.57	0.56	1.00	0.55	PLRWRCGDGTD C MDS SDEKSC EG

2. Sequence: SKAWVCDGDN (TauRP1-1)

Rank	PDB Hit	I den1	I den2	Cov.	Norm. Z-Score	Sec. Struc. Seq CCCSSCCCC SKAWVCDGDN
1	4zrpC	0.44	0.40	0.90	2.07	-LTWRCDRDL
2	1pvjA	0.50	0.60	0.80	1.06	-HAFVIDGA-
3	3a7qB	0.40	0.40	1.00	1.24	PSVWRCDEDD
4	6qxfK	0.40	0.40	1.00	3.59	EERLVFLGDN
5	1ajjA	0.40	0.50	1.00	2.01	HSSWRC DGGP
6	3bb7A	0.50	0.70	0.80	1.05	-HAFVIDGY-
7	1ajjA	0.40	0.50	1.00	1.22	HSSWRC DGGP
8	5hkpC	0.30	0.30	1.00	2.44	SPRGCADGRD
9	2fyIB	0.50	0.50	1.00	1.90	NINWRC DNDN
10	1lupA	0.40	0.30	1.00	1.21	QKMWTCDEER

3. Sequence: KAWVCDGDND (Tau RP1-2)

Rank	PDB Hit	I den1	I den2	Cov.	Norm. Z-Score	Sec. Struc. Seq CCSSCCCCC KAWVCDGDND
1	7nyc	0.60	0.60	1.00	1.01	KSLVCNGDSD
2	4zrpC	0.50	0.50	1.00	2.46	LTWRCDRDL
3	1pviA	0.44	0.40	0.90	1.03	HAFVIDGAD-
4	3a7qB	0.50	0.50	1.00	1.51	SVWRCDEDDD
5	6qxfK	0.40	0.40	1.00	3.33	ERLVFLGDNY
6	1ajjA	0.50	0.50	1.00	2.39	SSWRC DGGPD
7	3bb7A	0.62	0.50	0.80	1.02	-AFVIDGYN-
8	4zrpC	0.50	0.50	1.00	1.46	LTWRCDRDL
9	5g04S	0.30	0.30	1.00	2.64	RAALSDITNS
10	1v9uA	0.60	0.60	1.00	2.22	VSWRC DGEND

4. Sequence: A WVCDGDND C (TauRP1-3)

Rank	PDB Hit	I den1	I den2	Cov.	Norm. Z-Score	Sec. Struc. Seq CCCCCCCCC A WVCDGDND C
1	1jrfA	0.67	0.60	0.90	0.11	-WLC DGH PDC
2	7qbdD	0.60	0.60	1.00	1.45	TWRCDRDLDC
3	1n7d	0.60	0.60	1.00	1.11	FWRC D GQVDC

4	4zrpC	0.60	0.60	1.00	2.72	TWRCDRDLDC
5	4u8u	0.56	0.60	0.90	1.13	LFVCDGHKD-
6	3a7qB	0.60	0.60	1.00	1.73	VWRCEDEDDC
7	7qbdD	0.60	0.60	1.00	0.48	TWRCDGHPDC
8	6qxfK	0.44	0.40	0.90	3.08	RLVFLGDN-Y-
9	1f5yA	0.60	0.80	1.00	0.11	FWRCDGQVDC
10	1n7dA	0.40	0.40	1.00	0.11	SRQCDREYDC

5. Sequence: **WVCDGDNDCE (TauRP1-4)**

Rank	PDB Hit	Iden1	Iden2	Cov.	Norm. Z-Score	Sec. Struc. Seq CCCCCCCCC WVCDGDNDCE
1	1jrfA	0.60	0.60	1.00	0.10	WLCDSGHPDCD
2	7qbdD	0.60	0.60	1.00	1.79	WRCDRDLDCS
3	4u8u	0.60	0.60	1.00	0.92	FVCDGHKDCCH
4	1ajjA	0.60	0.60	1.00	2.80	WRCDGGPDCK
5	4u8u	0.67	0.60	0.90	1.10	FVCDGHKDC-
6	3a7qB	0.60	0.60	1.00	1.80	WRCEDEDDCL
7	7qbdD	0.60	0.60	1.00	0.49	WRCDGHPDCN
8	1ajjA	0.60	0.60	1.00	2.77	WRCDGGPDCK
9	1f5yA	0.67	0.60	0.90	0.10	WRCDGQVDC-
10	2m0pA	0.80	0.80	1.00	0.10	WVCDTDNDG

6. Sequence: **VCDGDNDCED (Tau RP 1-5)**

Rank	PDB Hit	Iden1	Iden2	Cov.	Norm. Z-Score	Sec. Struc. Seq CCCCCCCCC VCDGDNDCED
1	7nycB1	0.60	0.60	17.20	1.83	ECNGENDCGD
2	4zrpC1	0.60	0.60	17.20	3.10	RCDRDLDCSD
3	7qbdD1	0.60	0.60	17.20	1.81	RCDRDLDCSD
4	1d2iA	0.50	0.50	14.50	0.12	QCDREYDCKD
5	6h03C	0.70	0.70	19.90	0.44	LCNGDNDCGD
6	7nycC	0.70	0.70	19.90	0.59	VNCGDSDCDD
7	1ajjA	0.60	0.60	17.20	3.02	RCDGGPDCKD
8	1j8eA	0.78	0.70	19.80	0.50	TCGDNDCCG-
9	7qbdD2	0.60	0.60	17.20	0.36	LCDSGHPDCPD
10	3milA	0.38	0.30	8.90	0.10	IFLGANDA--

7. Sequence: **CDGDNDCEDN (TauRP1-6)**

Rank	PDB Hit	Iden1	Iden2	Cov.	Norm. Z-Score	Sec. Struc. Seq CCCCCCCCC CDGDNDCEDN
1	1n7dA	0.50	0.50	1.00	0.11	CDREYDCKDM
2	7qbdD	0.60	0.60	1.00	1.93	CDRDLDCSDG
3	7nyc	0.60	0.50	1.00	1.08	CNGDSDCDDS
4	1ajjA	0.60	0.60	1.00	2.76	CDGGPDCKDK
5	3t5oA	0.67	0.70	0.90	1.03	CNGENDCGD-
6	3a7qB	0.60	0.60	1.00	1.86	CDEDDDLCDH
7	7qbdD	0.70	0.70	1.00	0.51	CDGHPDCPDN
8	3iaxB	0.20	0.30	1.00	2.55	GDGTGWSSER
9	2gtlM	0.60	0.60	1.00	0.11	CDGEKDCRDG
10	1jrfA	0.67	0.60	0.90	0.11	CDGHPDCDD-

8. Sequence: DGDNDCEDNS (TauRP1-7)

Rank	PDB Hit	Icen1	Icen2	Cov.	Norm. Z-Score	Sec. Struc. Seq CCCCCCCCC DGDNDCEDNS
1	6qbjA	0.30	0.30	1.00	0.09	SGP N KK E SRG
2	7qbdD	0.60	0.60	1.00	1.50	RD L D C SDGS
3	7nyc	0.70	0.70	1.00	1.10	NG E N D C G DNS
4	3a7qB	0.60	0.60	1.00	2.70	DE D D D CLDH S
5	3ojvA	0.56	0.60	0.90	0.93	NG D Q D CLDG-
6	3a7qB	0.60	0.60	1.00	1.81	DE D D D CLDH S
7	7qbdD	0.50	0.60	1.00	0.47	D G HP D CPDTN
8	6tdwT	0.22	0.20	0.90	2.82	-NY N FIN N T
9	5azaA	0.30	0.40	1.00	0.11	KGTGT C SDGN
10	2zaqA	0.30	0.40	1.00	0.09	KGTGT C SDGN

9. Sequence: GDNDCEDNSD TauRP (1-8)

Rank	PDB Hit	Icen1	Icen2	Cov.	Norm. Z-Score	Sec. Struc. Seq CCCCCCCCC GDNDCEDNSD
1	1k7bA	0.50	0.50	1.00	0.08	GHP D C D DGRD
2	7qbdD	0.60	0.60	1.00	1.28	R D L D C S DG S D
3	3t5o	0.80	0.80	1.00	1.17	GE N D C GDN S D
4	3a7qB	0.60	0.60	1.00	2.79	ED D D D CLDH S D
5	7nyc	0.78	0.80	0.90	0.96	GE N D C GDN S -
6	3a7qB	0.60	0.60	1.00	1.86	ED D D D CLDH S D
7	7qbdD	0.60	0.60	1.00	0.46	GHP D CP D SSD
8	5hkpC	0.30	0.30	1.00	3.27	SPRG C ADGRD
9	7nycB	0.80	0.80	1.00	0.11	GE N D C GDN S D
10	2m96A	0.40	0.50	1.00	0.08	GKD D C G NGAD

10. Sequence DNDCEDNSDE TauRP (1-9)

Rank	PDB Hit	Icen1	Icen2	Cov.	Norm. Z-Score	Sec. Struc. Seq CCCCCCCCC DNDCEDNSDE
1	7nycB1	0.80	0.80	22.60	1.22	EN D C G DNS D E
2	3a7qB	0.70	0.70	19.90	2.72	DD D CLDH S D E
3	7qbdD1	0.70	0.70	19.90	1.09	LD L CS D GS D E
4	5xnll	0.30	0.30	9.10	0.09	SN D PGR N PGR
5	7nycB	0.80	0.80	22.60	0.42	EN D C G DNS D E
6	3t5oA	0.80	0.80	22.60	0.67	EN D C G DNS D E
7	2fvlB2	0.90	0.90	25.30	2.64	DN D C G DNS D E
8	3a7qB	0.67	0.60	17.10	0.48	DD D CLDH S D-
9	7qbdD2	0.60	0.60	17.20	0.33	HP D CP D SS D E
10	7ojjL	0.50	0.50	14.50	0.12	AN G CE H NS D E

11. Sequence NDCEDNSDEE – TauRP (1-10)

Rank	PDB Hit	Icen1	Icen2	Cov.	Norm. Z-Score	Sec. Struc. Seq CCCCCCCCC NDCEDNSDEE
1	2jm4A	0.40	0.40	1.00	0.10	D D C G NQA D E D
2	7nycB	0.80	0.80	1.00	1.16	ND C GDN S DER
3	3t5o	0.80	0.80	1.00	1.14	ND C GDN S DER
4	3a7qB	0.60	0.60	1.00	2.76	DD D CLDH S DE D
5	5f0eA	0.56	0.50	0.90	0.70	CD C CDGT D E-
6	3a7qB	0.60	0.60	1.00	1.93	DD D CLDH S DE D
7	7qbdD	0.60	0.60	1.00	0.45	PD D CP D SS D EN
8	5hkpC	0.30	0.30	1.00	3.33	RG C ADGRD A D
9	1f5vA	0.56	0.50	0.90	0.12	-D C DN G S D E Q
10	2m96A	0.50	0.50	1.00	0.09	D D C G NGA D E E

12. Sequence DCEDNSDEEN – TauRP (1-11)

Rank	PDB Hit	Icen1	Icen2	Cov.	Norm. Z-Score	Sec. Struc. Seq CCCCCCCCC DCEDNSDEEN
1	7nycB	0.70	0.70	1.00	1.07	D C G D N S D E R D
2	3t5o	0.70	0.70	1.00	1.10	D C G D N S D E R D
3	3a7qB	0.60	0.60	1.00	2.91	D C L D H S D E D D
4	5w4kA	0.30	0.30	1.00	2.13	N A S S N S A S A N
5	5hkpC	0.33	0.30	0.90	2.98	G C A D G R D A D -
6	7kx0D	0.20	0.30	1.00	1.07	H C N S G L L V R N
7	7nyc	0.70	0.80	1.00	1.10	D C G D N S D E R D
8	5w4kA	0.30	0.30	1.00	2.72	N A S S N S A S A N
9	3a7qB	0.60	0.60	1.00	1.96	D C L D H S D E D D
10	1uf2K	0.44	0.40	0.90	2.65	- S E P F S D K E R

13. Sequence CEDNSDEENC – TauRP (1-12)

Rank	PDB Hit	Icen1	Icen2	Cov.	Norm. Z-Score	Sec. Struc. Seq CCCCCCCCC CEDNSDEENC
1	7nycB1	0.70	0.70	19.90	1.09	C G D N S D E R D C
2	3a7qB	0.60	0.60	17.20	2.76	C L D H S D E D D C
3	7pg0A6	0.30	0.30	9.10	1.07	C S Q P D D P T K C
4	2m96A	0.60	0.60	17.20	0.11	C G N G A D E E N C
5	7nycB	0.70	0.70	19.90	0.39	C G D N S D E R D C
6	7nycB	0.70	0.70	19.90	0.64	C G D N S D E R D C
7	1aijA	0.80	0.80	22.60	2.67	C K D K S D E E N C
8	1aijA	0.78	0.70	19.80	0.64	C K D K S D E E N-
9	7qbdD2	0.60	0.60	17.20	0.36	C P D S S D E L G C
10	3oijB1	0.70	0.70	19.90	0.12	C G D Q S D E A N C

14. Sequence EDNSDEENCE – TauRP (1-13)

Rank	PDB Hit	Icen1	Icen2	Cov.	Norm. Z-Score	Sec. Struc. Seq CCCCCCCCC EDNSDEENCE
1	7pg0A6	0.20	0.20	6.40	1.16	S Q P D D P T K C V
2	2fylB2	0.60	0.60	17.20	2.41	G D N S D E A G C S
3	1uf2k	0.50	0.50	14.50	2.94	E P F S D K E R S E
4	7nycB1	0.60	0.60	17.20	0.97	G D N S D E R D C G
5	2im4A	0.44	0.40	11.70	0.07	G N Q A E D N C -
6	6h04D	0.60	0.60	17.20	0.35	E D S A E D R C E
7	3t5oA	0.60	0.60	17.20	0.60	G D N S D E R D C G
8	3a7qB	0.56	0.50	14.40	2.18	L D H S D E D D C-
9	3a7qB	0.56	0.50	14.40	0.50	L D H S D E D D C-
10	6ae8c	0.44	0.40	11.70	2.48	- D E D E E D D D

15. Sequence DNSDEENCES – TauRP (1-14)

Rank	PDB Hit	Icen1	Icen2	Cov.	Norm. Z-Score	Sec. Struc. Seq CCCCHHCCCC DNSDEENCES
1	1n7dA	0.50	0.50	1.00	0.08	D M S D E V G C V N
2	7jpmA	0.30	0.30	1.00	1.05	C K S D D D C P R
3	3t5o	0.60	0.90	1.00	1.04	D N S D E R D C G R
4	1n7dA	0.50	0.50	1.00	1.94	D M S D E V G C V N
5	2fylA	0.44	0.50	0.90	1.00	D R S D E S A S C-
6	1cr8A	0.60	0.60	1.00	1.56	D S S D E K S C E G
7	7qbdD	0.50	0.50	1.00	0.45	D S S D E L G C T N
8	6ae8C	0.40	0.40	1.00	3.13	D D E D E E D D D F
9	1jrfA	0.40	0.50	1.00	0.12	D G R D E W G C G T
10	2i1pA	0.60	0.60	1.00	0.07	D N S D E A G C P T

Those residues in template which are identical to the residue in the query sequence are highlighted in color. Polar residues are bright colored while non-polar residues are colored darker. Ident1 indicates the % sequence identity of templates in the threading aligned region with

the query sequence while Ident2 is the % sequence identity of the whole template chains with query sequence. Cov is the coverage of the threading alignment and is equal to the number of aligned residues divided by length of query protein. Norm. Z. Score = Z-score of the threading alignments. The top 10 alignments reported (in order of their ranking) are mostly from the following threading programs and are shown for each of the sequences below. 1: FFAS-3D 2: SPARKS-X 3: HHSEARCH2 4: Neff-PPAS 5: HHSEARCH 6: pGenTHREADER 7: wdPPAS 8: PROSPECT2 9: SP3 10: FFAS03. (<https://zhanggroup.org/I-TASSER/>).

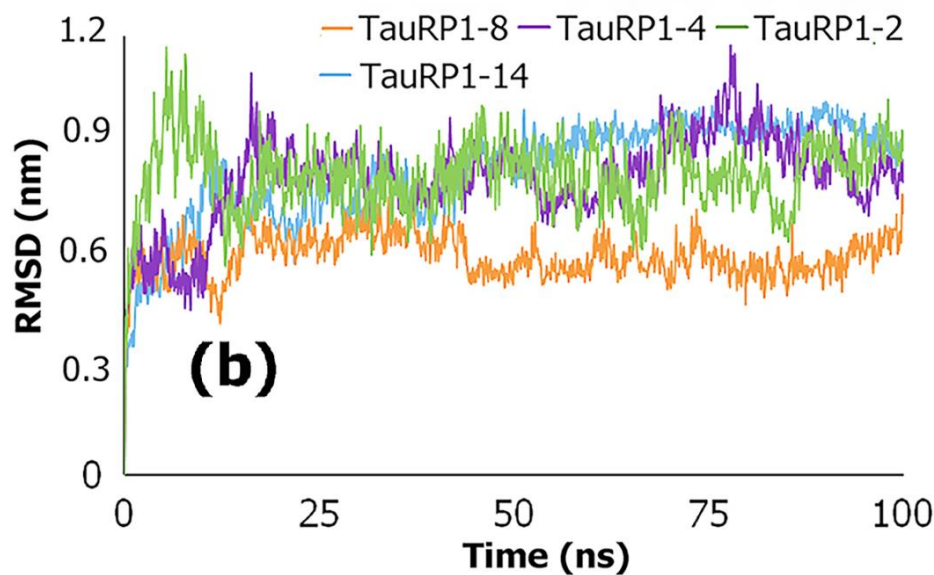


Figure S1. Comparison of RMSDs of peptide bound complexes with PHF Tau over 100 ns simulations.

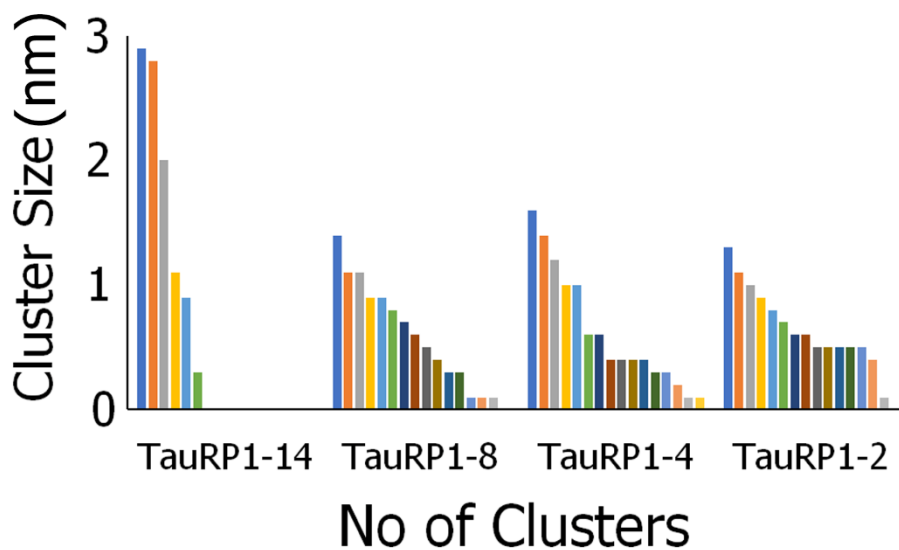


Figure S2. Comparison of size and number of clusters formed for TauRP (1-2); TauRP (1-4); TauRP (1-8) and TauRP (1-14) based on clustering results obtained from the trajectory images of the last 25 ns of 100 ns MD simulations upon binding to PHF Tau calculated from the RMSD matrices.

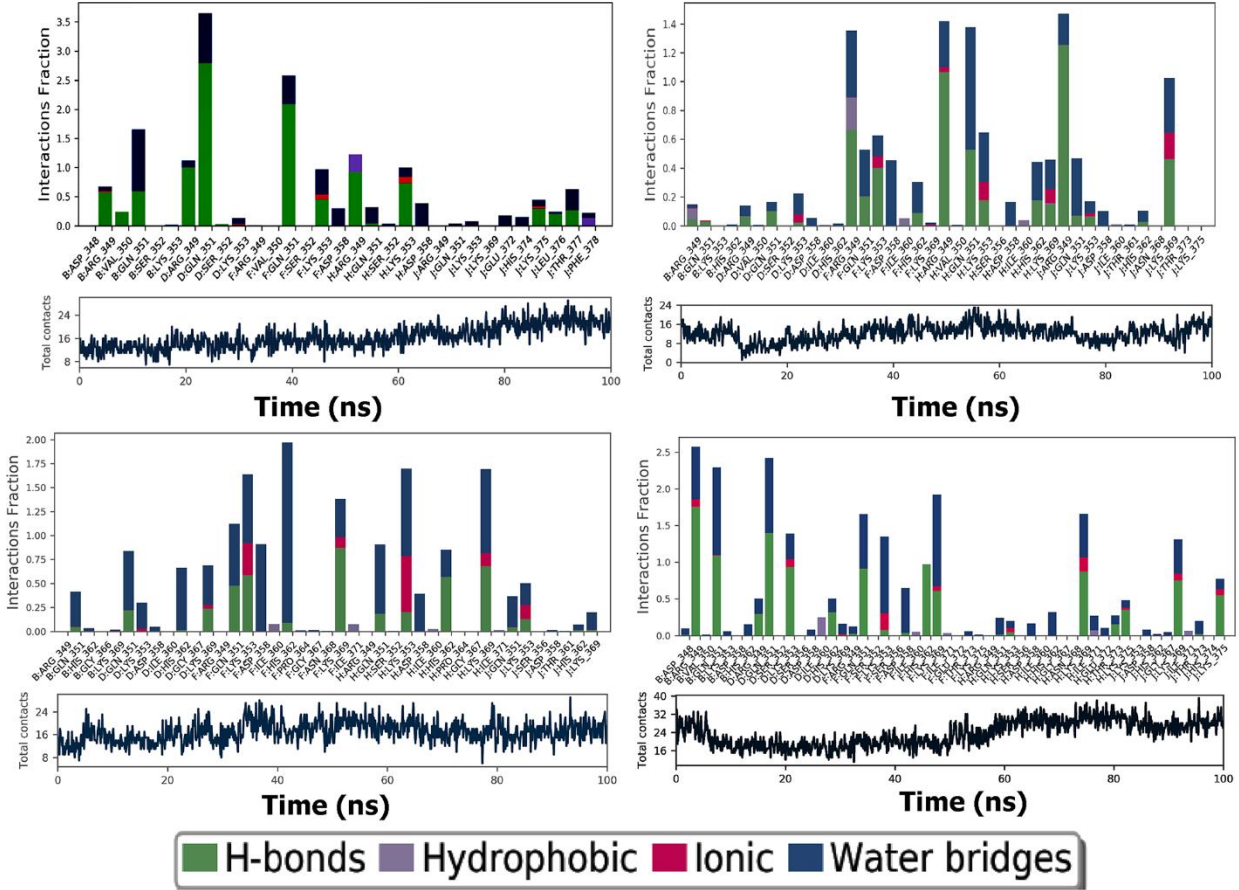


Figure S3. Protein-ligand contacts over 100 ns simulations between PHF Tau and top row (left) Tau (RP1-2) with total contacts; top row (right) Tau (RP1-4) with total contacts; Bottom row (left) Tau (RP1-8) with total contacts; Bottom row (right) TauRP 1-14 and total contacts.

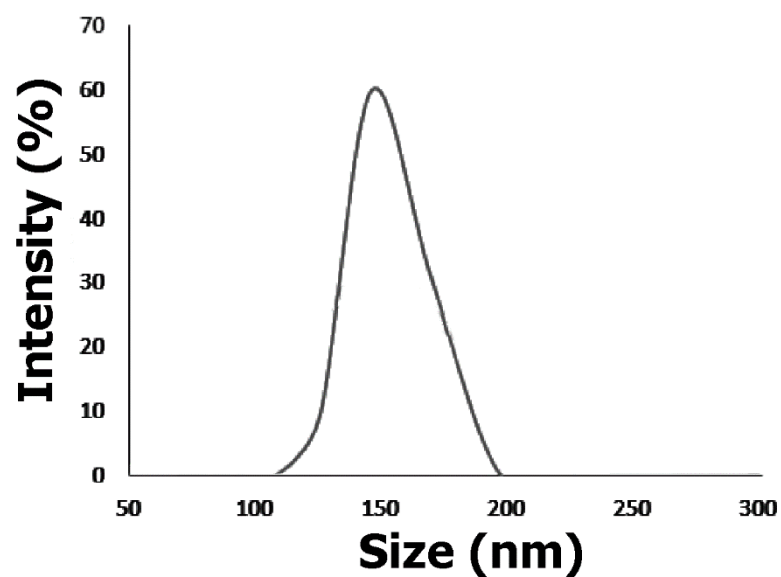


Figure S4. DLS analysis showing the formation of fibrillar Tau aggregates in the size range of 100 to 200 nm.

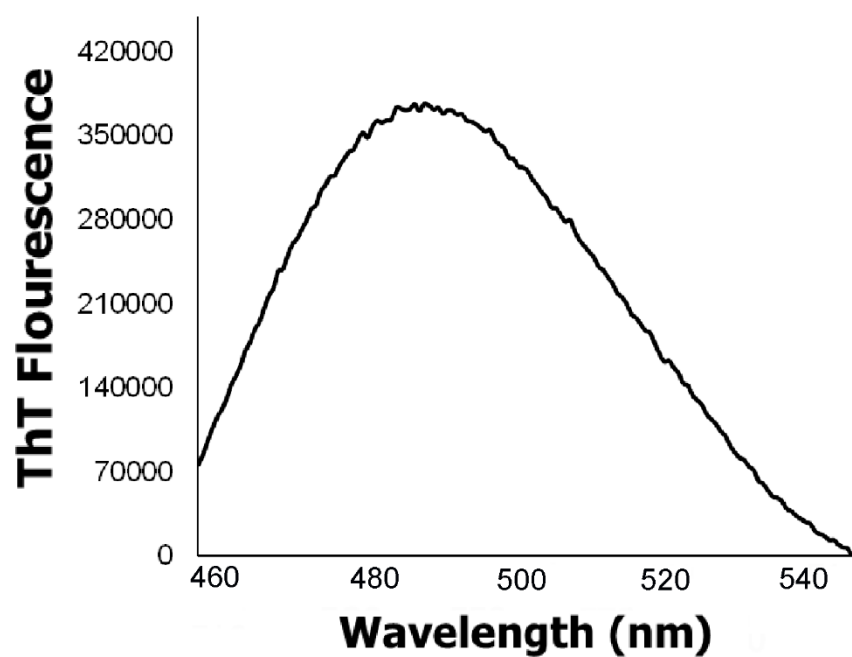


Figure S5. Emission spectrum ThT bound to fibrillar tau aggregates at excitation of 450 nm.