## **Supporting Information**

## Detailed method for model construction and differences between models

The heterogeneous A $\beta$ -tau mixtures were constructed based on Lührs ssNMR model of A $\beta_{17.42}$ , which protein data bank (PDB) ID is 2BEG for A $\beta$  monomer and mutated A $\beta_{17.42}$  for tau monomers. Lühr's A $\beta$  model has 10 different coordinates in one PDB file, because of the fluctuation of atoms. That fluctuation induces the different compositions of residues, so it can change the interior feature of monomer. To consider that impact, we used 2 types of tau models which are mutated Lühr's A $\beta$  models. They are called as WT1 and WT2 in the main paper. The different conformation of those is that the Valine (VAL) residue is located at different side. V287 (VAL) of WT1 is located at the outside of the loop and that of WT2 is at inside of the loop. Other mutated models are prepared by replace the residues of A $\beta$  into tau's residues. Since K280 (LYS) residue is deleted and the other residues are shifted to fill the empty place, so each models have different interior conditions from that of WT models.

## Characters of binding interactions for each models

Composed amino acids for each models have four main features that are hydrophobic, hydrophilic, polar uncharged and special cases. For intuitive insights of binding features, direct interacting features are organized at table S2. Every possible combinations are considered and represented with various colors. Especially, complementary interactions between  $A\beta$  and tau layers seem to initiate the breakage of interactions and allow water molecules to access into the interior regions.



Fig S1. Different configurations at initial steps and final steps for each models are represented after the stabilizing simulations were performed. Blue layers are representing the Tau proteins and red layers represent  $A\beta$  proteins.



**Fig S2.** Different arrangement of oligomers which are stacked with the different directions. (a) A scheme of oligomer. Arrows show directions of tilted interior residues. (b) shows interacting features between Tau (blue) and A $\beta$  (red) layers. (c) Inter and inter salt-bridge interactions between A $\beta$  and tau mixtures for each model. (d) Average number of hydrogen bonds between A $\beta$  and tau mixture interfaces from last 5 ns. (e) Average SASA between A $\beta$  and tau mixture interfaces from last 5 ns.



**Fig S3.** Final configurations for mixtures after the 20ns MD simulations were performed. (a) binding type 1 models are represented. (b) binding type 2 models are described

Нус	Iropho	obic	А	V	Ι	L	М	F	Y	W																	
Hydrophilic			R	Н	к	D	Е																				
Uncharged		jed	s	Т	Ν	Q																					
Special cases		С	U	G	Ρ																						
ABETA	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	ResID
ABETA	1	0	1.	0	1	0	1	0	0	0	0	0	0	0	0	1	0	1	0	1	0	0	0	1	0		
WT1	1	0	1	0	1	0	1	0	T	0	0	0	T.	0	0	1	0	1	0	1	0	I	0	1	0	1	11
ABETA	1	0	L	0	1	0	1	0	0	0	0	0	0	0	0	T.	0	1	0	1	0	0	0	1	0	1	_
WT1	1	0	- L	0	1	0	1	0	1	0	0	0	1	0	0	1	0	Ĩ.	0	1	0	I	0	1	0	1	12
ABETA	1	0	1	0	1	0	1	0	0	0	0	1	0	0	0	- T	0	1	0	1	0	0	0	1	0		
WT2	1	0	1	0	1	0	1	0	Т	0	0	1	0	0	0	1	0	1	0	1	0	1	0	1	0	1	11
ABETA	1	0	1	0	1	0	1	0	0	0	0	1	0	0	0	1	0	1	0	1	0	0	0	-	0	1	70
WT2	1	0	<u>I</u>	0	1	0	1	0	T	0	0	1	0	0	0	1	0	1	0	1	0	I	0	1	0	1	12
ABETA	1	0	I	0	1	0	1	0	0	0	0	0	0	0	0	1	0	1	0	1	0	0	0	1	0	1	74
M1	1	0	1	0	1	0	1	0	1	0	0	0	I	0	0	1	0	0	0	1	0	1	0	1	0	$\times$	] ''
ABETA	1	0	1	0	1	0	1	0	0	0	0	0	0	0	0	1	0	1	0	1.1	0	0	0	1	0	0	TO
M1	1	0	1	0	1	0	1	0	1	0	0	0	Ι	0	0	1	0	1	0	1	0	1	0	1	0	$\ge$	] '2
ABETA	1	0	1	0	1	0	1	0	0	0	0	0	0	0	0	1	0	1	0	1.	0	0	0	1	0	0	τ.
M31	1	0	1	0	1	0	1	0	-1	0	0	0	I	0	0	0	0	1	0	1	0	t.	0	0	1	1	
ABETA	1	0	1	0	1	0	1	0	0	0	0	1	0	0	0	1	0	I.	0	1	0	0	0	1	0	0	T2
M31	1	0	1	0	1	0	1	0	1	0	0	0	ļ	1	0	0	0	I.	0	1	0	1	0	1	0	0	12
ABETA	1	0	Ť	0	1	0	Ť	0	0	I	0	0	0	0	0	1	0	T	0	1	0	0	0	1	0	T	т1
M41	0	0	Ι	0	1	0	1	0	1	0	0	0	1	0	0	1	0	0	0	1	0	Ι	0	0	0	1	
ABETA	1	0	1	1	0	0	1	0	0	0	0	0	0	0	0	1	0	1	0	1	0	0	0	1	0	0	т2
M41	0	0	1	0	1	0	1	0	T	0	0	0	1	0	0	1	0	0	0	1	0	I	0	0	1	0	12
TAU	275	276	277	278	279	280	281	282	283	284	285	286	287	288	289	290	291	292	293	294	295	296	297	298	299	300	ResID

**Table S1.** Interior and exterior residues are distinguished with their features. The feature of residues are categorized with 4 colors, which are red (hydrophobic residues), blue (hydrophilic residues), dark gray (uncharged residues) and green (special residues, such as Cysteine, Glycine and Proline).

Interaction Types	Color	Comb	ination
Hydrophobic-Hydrophobic			
Hydrophilic-Hydrophilic			
Hydrophobic-Special			
Hydrophilic-Special			
Hydrophobic-Hydrophilic			
Special-Special			
Hydrophobic-Uncharged			
Hydrophilic-Uncharged			
Uncharged-Uncharged			
Uncharged-Special			
Inside-Outside		1	0

Squences for Wild Type model																											
ABETA	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	ResID
ABETA	L	V	F	F	A	Е	D	V	G	S	N	К	G	A	1	1	G	L.	М	V	G	G	V	V	1	A	Residue
WT	V	Q	1.	1	N	к	К	L.	D	L	S	N	V	Q	S	к	С	G	S	к	D	N	1	к	н	V	Name
Binding Site Characters																											
WT1T1																											
WT1T2																											BC
WT2T1																											
WT2T2																											
TAU	275	276	277	278	279	280	281	282	283	284	285	286	287	288	289	290	291	292	293	294	295	296	297	298	299	300	ResID
Squences for Mutated model (M1)																											
ABETA	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	ResID
ABETA	L	V	F	F	A	Е	D	V	G	S	N	к	G	A	1	1	G	L	М	V	G	G	V	V	1	A	Desidue
M1	V	Q	1	1	N	к	L	D	L.	S	N	V	Q	S	к	С	G	S	к	D	N	1	к	н	V	$\times$	Name
Binding Site Characters																											
M1T1																										$\times$	
M1T2																					0 0					$\times$	BC
TAU	275	276	277	278	279	280	281	282	283	284	285	286	287	288	289	290	291	292	293	294	295	296	297	298	299	300	ResID
										6				- +		1-1 ()	(21)						-	-			
	17	10	10	20	24	22	22	24	25	Squ	ence	s for		ated	moc		131)	24	25	20	27	20	20	40	44	40	0
ABETA	17	18	19	20	21	22	23	24	25	20	21	28	29	30	31	32	33	34	35	30	37	38	39	40	41	42	RosiD
M21	L.	0			N	E		, v	6	0	N	N.	0	0		C	6	0	M	D	N	6	V V		V		Residue Name
IVIS I	v	ų				R		U		0	Bi	nding	n Site	Cha	racte	are		2	N.	U	14		K		×	- E.	-
M31T1										2		nunių	Jone	Ona	acte	15					4						
M31T2													-														BC
TAU	275	276	277	278	279	280	281	282	283	284	285	286	287	288	289	290	291	292	293	294	295	296	297	298	299	300	ResID
	210	210		210	2.10	200	201	2.02	200	201	200	200	201	2.00	200	200	201	202	200	201	200	200	201	200	200	000	
										Squ	ence	s for	Mut	ated	mod	del (I	M41)										
ABETA	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	ResID
ABETA	L.	V	F	F	A	E	D	V	G	S	N	к	G	A			G	L.	м	V	G	G	V	V		A	Residue
M41	к	V	Q	1.1	1	N	К	L.	D	L.	S	N	V	Q	S	К	С	G	S	К	D	N	1	К	н	V	reame
	_	_	_	_	_	_	1	_		_	Bir	nding	g Site	Cha	racte	ers	_	_			_	_	_	_	_	_	
M41T1																											BC
M41T2											8			-			1.		-								
TAU	275	276	277	278	279	280	281	282	283	284	285	286	287	288	289	290	291	292	293	294	295	296	297	298	299	300	ResID

Table S2. The features of binding regions are analyzed with the table. Each colors represents types of interactions.