Supporting Information for:

Elucidating the Structures of Amyloid Oligomers with Macrocyclic β-Hairpin Peptides: Insights into Alzheimer's Disease and other Amyloid Diseases

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Early History of Amyloid Fibril Structure Determination

Aβ is the most extensively characterized of the more than thirty known amyloidogenic peptides and proteins and has served as the archetype for studying the structures of amyloid assemblies. X-ray diffraction measurements initially revealed that amyloid plaques produced a "cross-β" pattern, indicating that the proteinaceous components of the plaques have a "pleated sheet" conformation and providing a glimpse into the molecular structures of amyloid fibrils.[1,2,3] The determination of the sequences of the 40- and 42-amino acid alloforms of Aβ ($A\beta_{40}$ and $A\beta_{42}$) provided the next piece of the puzzle.[4,5] Solid-state NMR spectroscopy (ss-NMR) and X-ray diffraction of fibrils established that the fibrils are composed of an extended network of in-register parallel β-sheets, with the β-strands running perpendicular to the long axes of the fibrils and the hydrogen bonds running parallel.[6,7,8,9,10,11,12,13,14,15,16] These studies produced the first molecular models of amyloid fibrils.

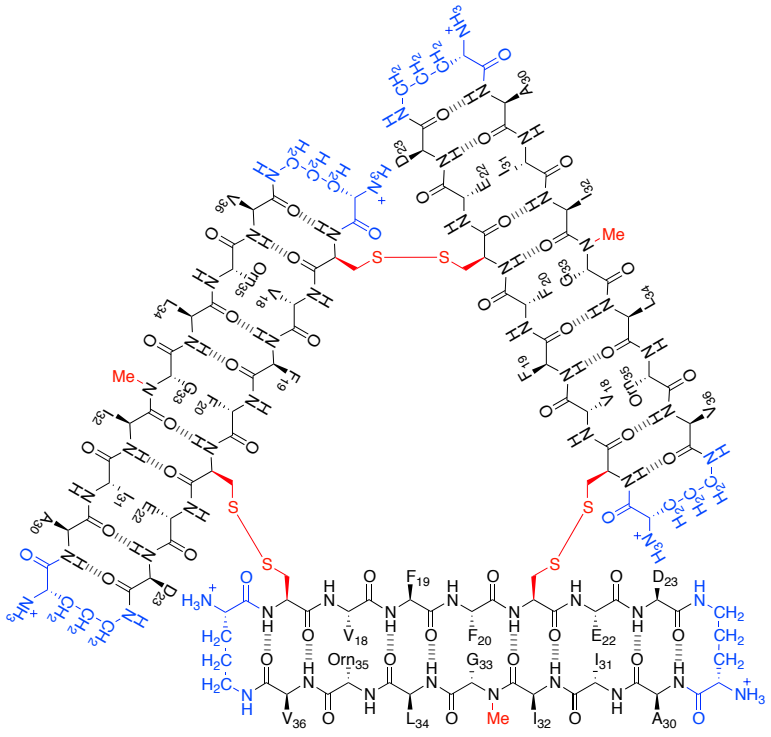

Figure S1. Chemical structures of trimers **4** and **5**.

Table S1. Amyloid fibril structures deposited in the PDB.

peptide/protein	disease	approach	PDB ID	technique	comments and mutations
$A\beta_{40}$	AD	A	2M4J[17], 2LMP, 2LMQ, 2LMN and 2LMO[18,19]	ss-NMR	
$A\beta_{40}$	AD	A	2LNQ[20]	ss-NMR	D23N (Iowa mutant)
$A\beta_{40}$	AD	A	2MVX[21]	ss-NMR	E22Δ (Osaka mutant)
$A\beta_{42}$	AD	A	2NAO[22], 5KK3[23], 2MXU[24], 5AEF[25], 2BEG[26], 5OQV[27]	ss-NMR, cryo-EM	
$A\beta_{15-40}$	AD	B	2MPZ[28]	ss-NMR	D23N (Iowa mutant)
$A\beta_{15-23}$	AD	C	4Q8D[29]	X-ray	
$A\beta_{15-36}$	AD	D	5V64[30]	X-ray	$F19F^{p\text{-iodo}}$, $A\beta_{22-29}$ omitted
$A\beta_{16-21}$	AD	B	2Y2A, 3OW9, and 2Y29[31]	X-ray	
$A\beta_{27-32}$	AD	B	3Q2X[31]	X-ray	
$A\beta_{29-34}$	AD	B	3PZZ[31]	X-ray	
$A\beta_{35-40}$	AD	B	2OKZ and 2ONA[32]	X-ray	
$A\beta_{35-42}$	AD	B	2Y3K and 2Y3L[32]	X-ray	
$A\beta_{37-42}$	AD	B	2ONV[32]	X-ray	
α-syn	PD	A	2N0A[33]	ss-NMR	
$\alpha\text{-syn}_{47-56}$	PD	B	4ZNN[34]	EC	A53T
$\alpha\text{-syn}_{69-77}$	PD	B	4RIK[34]	X-ray	
$\alpha\text{-syn}_{68-78}$	PD	B	4RIL[34]	EC	
$\alpha\text{-syn}_{72-78}$	PD	B	4R0U[35]	X-ray	
$\alpha\text{-syn}_{70-76}$	PD	B	4R0W[35]	X-ray	
tau	AD	A	5O3O, 5O3T[36]	cryo-EM	
tau_{VQIVYK}	AD	B	5K7N[37], 4NP8[38], 2ON9[32]	EC, X-ray	
$IAPP_{15-25}$	T2D	B	5KO0[39]	EC	
$IAPP_{19-29}$	T2D	B	5KNZ[39]	EC	S20G
$IAPP_{22-28}$	T2D	B	5E5V[40]	X-ray	
$IAPP_{13-18}$	T2D	B	5E5X[40]	X-ray	
$IAPP_{16-21}$	T2D	B	5E5Z[40]	X-ray	
$IAPP_{23-29}$	T2D	B	5E61[40]	X-ray	
$IAPP_{18-23}$	T2D	B	3FPO[38]	X-ray	
$IAPP_{14-19}$	T2D	B	3FR1[38]	X-ray	
$IAPP_{14-20}$	T2D	B	3FTH[38]	X-ray	
$IAPP_{31-37}$	T2D	B	3FTK[38]	X-ray	
$IAPP_{28-33}$	T2D	B	3DG1[41]	X-ray	
$IAPP_{21-27}$	T2D	B	3DGJ[41]	X-ray	
$TTR_{105-115}$	SSA, FAP, FAC	B	1RVS[42], 2M5K, 2M5M, 2M5N, and 3ZPK[43]	ss-NMR, EM	
$TTR_{106-121}$	SSA, FAP, FAC	D	5HPP	X-ray	$TTR_{113-114}$ omitted
$TTR_{111-116}$	SSA, FAP, FAC	B	4XFN[44]	X-ray	
$TTR_{139-144}$	SSA, FAP, FAC	B	4XFO[44]	X-ray	
$hPrP_{170-175}$	CJD	B	2OL9[32]	X-ray	
$\alpha B\ crystallin_{95-100}$	N/A	B	3SGS[62]	X-ray	
$B2M_{20-41}$	DRA	B	2E8D[45]	ss-NMR	
$B2M_{74-79}$	DRA	B	3LOZ[46]	X-ray	
$HETs_{218-289}$	N/A	B	2KJ3[47], 2RNM[48]	ss-NMR	

disease: AD = Alzheimer's disease, PD = Parkinson's disease, T2D = type 2 diabetes, DRA = dialysis related amyloidosis, SSA = senile systemic amyloidosis, FAP = familial amyloid polyneuropathy, FAC = familial amyloid cardiomyopathy, CJD = Creutzfeldt Jakob disease, N/A = not applicable

approach: A = full-length peptide or protein, B = peptide fragment, C = macrocyclic β-sheet peptide, D = macrocyclic β-hairpin peptide

technique: X-ray = X-ray crystallography, ss-NMR = solid-state NMR spectroscopy, EM = electron microscopy, cryo-EM = cryo-electron microscopy, EC = electron crystallography

Table S2. Amyloid monomer structures deposited in the PDB.

peptide/protein	disease	approach	PDB ID	technique	comments and mutations
$A\beta_{40}$	AD	A	2LFM[49]	NMR	
$A\beta_{40}$	AD	A	1BA4[50]	NMR	
$A\beta_{40}$	AD	A	2OTK[51]	NMR	$A\beta_{40}$/affibody complex
$A\beta_{1-28}$	AD	B	1BJB and 1BJC[52]	NMR	
$A\beta_{17-34}$	AD	B	2MJ1[53]	NMR	
α-syn	PD	A	4BXL[54]	NMR	α-syn/affibody complex
α-syn	PD	A	2KKW[55]	NMR	α-syn/micelle complex
α-syn	PD	A	1XQ8[56]	NMR	α-syn/micelle complex
IAPP	T2D	A	5MGQ[57]	NMR	
IAPP	T2D	A	5K5G[58]	NMR	IAPP/affibody complex
IAPP	T2D	A	2KJ7[59]	NMR	
IAPP	T2D	A	2KB8[60]	NMR	IAPP/micelle complex
IAPP	T2D	A	2L86[61]	NMR	IAPP/micelle complex

disease: AD = Alzheimer's disease, PD = Parkinson's disease, T2D = type 2 diabetes
approach: A = full-length peptide, B = peptide fragment
technique: NMR = solution-state NMR spectroscopy

Table S3. Amyloid oligomer structures deposited in the PDB.

peptide/protein	disease	approach	PDB ID	technique	comments and mutations
αB crystallin$_{90-100}$	N/A	B	3SGN, 3SGO, 3SGP, and 3SGR[62]	X-ray	antiparallel β-sheet cylindrin
SOD1$_{28-38}$	ALS	B	5IIW[63]	X-ray	antiparallel β-sheet corkscrew, P28K
hPrP$_{177-182}$	CJD	B	4E1I and 4E1H[64]	X-ray	disulfide stabilized antiparallel β-sheet
$A\beta_{15-23}$	AD	C	4IVH[65]	X-ray	
$A\beta_{16-36}$	AD	D	5V63[30]	X-ray	F19F$^{p\text{-iodo}}$, $A\beta_{23-29}$ omitted
$A\beta_{16-36}$	AD	D	5W4H[66]	X-ray	$A\beta_{23-29}$ omitted
$A\beta_{17-21}$	AD	C	3Q9H[67]	X-ray	F19F$^{p\text{-iodo}}$, $A\beta_{23-29}$ omitted
$A\beta_{17-36}$	AD	D	4NTR and 4NW9[68]	X-ray	M35Orn, $A\beta_{24-29}$ omitted
$A\beta_{17-36}$	AD	D	5SUT and 5SUR[69]	X-ray	stabilized trimers, M35Orn, $A\beta_{24-29}$ omitted
$A\beta_{17-36}$	AD	D	5V65[30]	X-ray	F19F$^{p\text{-iodo}}$, $A\beta_{24-29}$ omitted
$A\beta_{17-36}$	AD	E	5HOX[70]	X-ray	V24C, G29C
$A\beta_{30-34}$	AD	C	3Q9J[4]	X-ray	G33F
$A\beta_{30-36}$	AD	C	3T4G[71]	X-ray	
α-syn$_{36-55}$	PD	D	5F1T[72]	X-ray	G36A and Y39F$^{p\text{-iodo}}$, α-syn$_{42-49}$ omitted
tau$_{VQIVY}$	AD	C	3Q9G[67]	X-ray	
tau$_{SVQIVYK}$	AD	C	4E0M, 4E0N, and 4E0O[73]	X-ray	
B2M$_{58-63}$	DRA	C	4E0K[73]	X-ray	
B2M$_{62-68}$	DRA	C	4E0L[73]	X-ray	
B2M$_{63-69}$	DRA	D	4P4V, 4P4W, 4P4X, 4P4Y, 4P4Z, 4WC8, and 4X0S[74]	X-ray	Y66F$^{p\text{-iodo}}$
IAPP$_{11-17}$	T2D	C	5UHR[75]	X-ray	R11Cit

disease: ALS = amyotrophic lateral sclerosis, CJD = Creutzfeldt Jakob disease, AD = Alzheimer's disease, PD = Parkinson's disease, DRA = dialysis related amyloidosis, T2D = type 2 diabetes, N/A = not applicable
approach: B = peptide fragment, C = macrocyclic β-sheet peptide, D = macrocyclic β-hairpin peptide, E = stabilized β-hairpin
technique: X-ray = X-ray crystallography

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