Progress towards a molecular-level structural understanding of amyloid fibrils

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The problem of determining and understanding the molecular structures of amyloid fibrils has attracted considerable attention and effort over the past several years. Although complete, high-resolution structures have not yet been obtained, key features of protein and peptide conformations and supramolecular organization within amyloid fibrils have been elucidated using a variety of novel experimental methods, including magnetic resonance spectroscopies, electron microscopy, X-ray and neutron scattering, and biochemical techniques. The experimental data are beginning to shed light on issues such as the nature of the intermolecular interactions that stabilize amyloid structures, the molecular structural basis for polymorphism in amyloid fibrils, the universality of amyloid structures, and the balance between structural order and disorder within amyloid fibrils. Recent structural data will contribute to an improved understanding of the mechanisms of amyloid formation and to the development of therapeutic agents for amyloid diseases.

Introduction

Amyloid fibrils are self-assembled filaments, typically 0.1–10 μm long and approximately 10 nm wide in electron microscopy (EM) images, formed by the spontaneous aggregation of a wide variety of peptides and proteins (Figure 1a). Current interest in amyloid fibrils within the biomedical research community arises from their association with amyloid diseases, including Alzheimer’s disease, type 2 diabetes, prion diseases, Parkinson’s disease, senile systemic amyloidosis and Huntington’s disease.

Interest within the biochemical and biophysical research communities arises additionally from fundamental questions regarding the nature of the interactions that make amyloid fibrils a stable structural state for polypeptide chains and the mechanisms by which amyloid fibrils form from monomeric or oligomeric species. A defining characteristic of amyloid fibrils is the presence of the cross-β structural motif, originally revealed by X-ray fiber diffraction [1–3], in which ribbon-like β-sheets, extending over the length of the fibril, are formed by β-strands that run nearly perpendicular to the long axis of the fibril, with backbone hydrogen bonds that run nearly parallel to the long axis (Figure 1b). Apart from the existence of the cross-β motif, little was known until recently about the molecular-level structures of amyloid fibrils. Questions such as ‘does the cross-β motif contain a well-ordered pattern of intermolecular hydrogen bonds?’, ‘do peptides and proteins have well-ordered conformations in amyloid fibrils?’, ‘which peptide segments participate in the cross-β motif?’, ‘do amyloid fibrils contain non-β secondary structures?’ and ‘to what extent do amyloid fibrils formed by different peptides share a common molecular structure?’ have been difficult to answer. Information about the molecular structures of amyloid fibrils will lead to a better understanding of the intermolecular interactions that stabilize these structures, is likely to provide important clues about the mechanisms of fibril formation and may facilitate the development of therapeutic strategies for amyloid diseases.

Over the past several years, considerable progress has been made towards the elucidation of the molecular structures of amyloid fibrils. Solid-state NMR methods have proven to be particularly valuable as direct structural probes of amyloid fibrils, because these methods can provide constraints on interatomic distances and torsion angles at a site-specific level in noncrystalline materials with complex chemical structures [4–6,7,9,10,11,12,13]. Important recent contributions have also been made by electron paramagnetic resonance (EPR) spectroscopy [14,15,16,17], EM [8,18–21,22,23], X-ray and neutron scattering [24,25,26,27,28–33], and biochemical methods [28–33]. Some of these developments and their implications are discussed below.

Experimental approaches

Solid-state NMR

The term ‘solid-state NMR’ simply means the application of NMR spectroscopy to solids, solid-like materials (e.g. highly aggregated species such as amyloid fibrils) and samples that are not isotropic liquids or solutions.
Because the individual molecules in such samples do not tumble rapidly and isotropically, as they do in solutions of monomeric peptides or proteins, the spectral resolution of solid-state NMR is generally not as high as that of liquid-state NMR, the dominant nuclear spin interactions in solid-state NMR are different from those in liquid-state NMR, and the techniques employed and information obtained using solid-state NMR are somewhat different from those using liquid-state NMR. Over the past 10–15 years, a variety of solid-state NMR techniques have been developed that permit measurements of the interatomic distances (e.g. $^{13}$C–$^{13}$C or $^{15}$N–$^{13}$C distances up to approximately 6 Å) and torsion angles (e.g. peptide backbone $\phi$ and $\psi$ angles) that define the structure of a biopolymer, in samples that are either isotopically labeled at specific pairs of carbon or nitrogen sites or are labeled at all sites in multiple residues [12*]. Beginning with the work of Griffin, Lansbury and co-workers [4], who used solid-state NMR data to construct a model for amyloid fibrils formed by residues 34–42 of the full-length $\beta$-amyloid (A$\beta$) peptide associated with Alzheimer’s disease (A$\beta$34–42, where A$\beta$$_{m-n}$ indicates residues m–n of full-length A$\beta$), and Lynn, Meredith, Botto and co-workers [5,34], who first demonstrated the existence of cross-$\beta$ structures with parallel $\beta$-sheets in their studies of fibrils formed by A$\beta$$_{10-35}$, it has been found that amyloid fibrils in general are amenable to the most sophisticated solid-state NMR methods and that these methods yield structural constraints at a level of detail that has otherwise been inaccessible.

My own laboratory has concentrated primarily on fibrils formed by A$\beta$$_{1-40}$, the 40-residue form of the full-length $\beta$-amyloid peptide. On the basis of constraints from measurements of intermolecular $^{13}$C–$^{13}$C dipole–dipole couplings [6], $^{13}$C and $^{15}$N NMR chemical shifts [7**], and intramolecular correlations of backbone carbonyl orientations [11], combined with measurements of A$\beta$$_{1-40}$ fibril dimensions and mass-per-length (MPL) from EM [7**,8*,20], we have recently proposed the structural model for the A$\beta$$_{1-40}$ protofilament (i.e. the fibril with minimum dimensions and minimum MPL observed experimentally) shown in Figure 2 [7**]. This structural model is also consistent with fiber diffraction data and with the hydrogen-exchange, proteolysis and EPR data discussed below. From the biophysical perspective, an important consequence of this model is that it shows how favorable hydrophobic interactions can be maximized within the context of a cross-$\beta$ structure with parallel $\beta$-sheets, while simultaneously avoiding unfavorable interactions.
electrostatic interactions in the protofibril core. This model also reveals how an amyloid structure may contain both structurally ordered and structurally disordered regions, with a combination of β-strand and non-β-strand segments in the ordered region.

The power of sophisticated solid-state NMR techniques has been demonstrated particularly clearly by Jaroniec et al. [9,10**] in recent structural studies of amyloid fibrils formed by residues 105–115 of transthyretin (TTR105–113). In these studies, the peptide conformation in the fibrils, including sidechain conformations but not yet including supramolecular structure, was determined to high resolution using a combination of interatomic distance, torsion angle and chemical shift measurements (see Figure 3). Combined with recent solid-state NMR data on Aβ16–22 and Aβ11–25 fibrils [13,35,36**], these results show that short peptides in amyloid fibrils can have molecular structures that are nearly as well ordered as the molecular structures in peptide crystals. The high degree of structural order is manifested in the narrow 13C and 15N NMR lines (0.5–1.5 ppm) detected under magic-angle spinning (MAS) conditions. Although structural biologists accustomed to viewing the intricate structures of proteins and protein complexes revealed by crystallography and liquid-state NMR might assume that amyloid fibrils contain structurally ordered molecules, in fact it is only the observation of sharp lines in MAS NMR spectra of amyloid fibrils that puts this assumption on a firm experimental foundation.

In addition to placing constraints on molecular conformation within amyloid fibrils, solid-state NMR measurements have been used to establish the supramolecular structure, especially the nature and registry of β-sheets in the amyloid cross-β motif [4–6,8*,13,35,36**]. These measurements reveal that Aβ10–35, Aβ1–40 and Aβ1–42 fibrils contain in-register, parallel β-sheets [5,6,8*], whereas Aβ16–22 and Aβ11–25 fibrils contain antiparallel β-sheets [13,35,36**]. In Aβ16–22 and Aβ11–25 fibrils, the registry of intermolecular hydrogen bonds involving the central hydrophobic segment (residues 17–21, sequence LVFFA) varies, with F19 forming intermolecular backbone hydrogen bonds to V18, F19 or F20 in Aβ11–25 fibrils formed at pH 7.4, Aβ16–22 fibrils formed at pH 7.4 or Aβ11–25 fibrils formed at pH 2.3, respectively. In all cases, the hydrogen bond registry appears highly ordered, with ‘registry shift’ defects below detectable limits, that is, less than 10% for data reported to date [13,36**]. These observations of sequence- and pH-dependent supramolecular organization provide a basis for refining our understanding of the interactions that determine and stabilize amyloid structures. All solid-state NMR data on Aβ peptides are consistent with the idea that maximization of favorable hydrophobic contacts is a primary consideration, but electrostatic and other interactions apparently play a role in determining the finer details of the supramolecular organization. It is particularly interesting that the supramolecular organization within an amyloid fibril has been found to be highly ordered, given the diversity of β-sheet structures revealed by solid-state NMR and the resulting naïve expectation that peptide molecules might attach to the end of a growing fibril in multiple alternative registries. Perhaps this indicates that structural annealing after peptide attachment is a necessary step in amyloid fibril growth.

Elevated levels of the 42-residue form of full-length Aβ, brought about by certain genetic mutations, are associated with familial forms of Alzheimer’s disease [37]. In vitro studies have shown that Aβ1–42 fibrillizes more rapidly and at lower concentrations than Aβ1–40 [38], and that the early stages of oligomerization and aggregation of the two forms are also qualitatively distinct [39**]. One might guess that these differences would imply differences in the molecular structures of Aβ1–40 and Aβ1–42 fibrils, but solid-state NMR and EM measurements on Aβ1–42 fibrils have not revealed structural differences [8*].

Electron paramagnetic resonance
EPR spectroscopy, applied to samples with nitroxide spin labels at cysteine residues that have been introduced by site-directed mutagenesis or direct synthesis, has been applied to the problem of defining the locations and contacts of β-strand segments within amyloid fibrils. Serag et al. [14,15*] have reported a series of EPR measurements on the native tetrameric and amyloid forms of TTR that indicate changes in the β-strand interfaces upon fibril formation. In the native tetramer, the C, B, E and F β-strands of TTR dimers form an approximately continuous eight-stranded β-sheet, following the pattern

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**Figure 3**

Molecular conformation of TTR105–115 within amyloid fibrils, determined from solid-state NMR data [9,10**], represented (a) as an average structure and (b) as a bundle of structures that are each consistent with the experimental constraints on interatomic distances and torsion angles. Figure created with MOLMOL [63].
CBEFF′E′B′C′. Electron–electron dipole–dipole couplings extracted from EPR spectra of spin-labeled tetramers are consistent with this pattern, but EPR spectra of spin-labeled TTR amyloid are consistent with the pattern BEFF′E′B′BEFF′E′B′ within a cross-β motif, suggesting that the C strands loop out and the B strands form new contacts upon fibril formation.

Török et al. [16 † † ] have reported EPR measurements on spin-labeled Aβ1–40 and Aβ1–42 fibrils that support an in-register, parallel alignment of peptide chains within the cross-β motif. In these measurements, which were performed at ambient temperature on fully hydrated fibrils, the EPR line shapes indicate local variations in sidechain mobility that correlate well with secondary structure. In particular, the greatest mobility is observed in the N-terminal and central segments of the fibrillized Aβ peptides, which are the non-β-strand segments in the Aβ1–40 protofilament model in Figure 2. In addition, Török et al. showed that the EPR spectra of fibrils formed by diluting spin-labeled Aβ1–40 in either unlabeled Aβ1–40 or unlabeled Aβ1–42 are nearly indistinguishable, proving that Aβ1–40 and Aβ1–42 co-fibrillize with molecular-level mixing and strongly suggesting that the molecular structures of the Aβ1–40 and Aβ1–42 fibrils are essentially the same. Again, these results are consistent with the solid-state NMR data discussed above.

EPR measurements on spin-labeled α-synuclein, a 140-residue protein associated with Parkinson’s disease, are consistent with a natively unfolded monomeric state and indicate that approximately residues 30–70 become structurally ordered with in-register, parallel alignment in the fibrillar state [17].

Hydrogen exchange and proteolysis

Hydrogen/deuterium (H/D) exchange techniques have been developed by several groups as an indirect means of probing the molecular structures of amyloid fibrils. Although H/D exchange measurements do not provide specific geometric constraints on molecular structures, they do provide valuable information about the nature and extent of the structural rearrangements that proteins with stable native folds undergo upon conversion to an amyloid form, and about the presence and location of peptide segments in the amyloid form that are not involved in stable secondary structure elements. Kheterpal et al. [30] have reported H/D exchange data for Aβ1–40 fibrils, showing that between 48% and 55% of backbone amide protons are highly protected from exchange. This result is consistent with the solid-state NMR model in Figure 2, in which the two β-strand segments approximately span residues 12–24 and 30–40, and the remaining residues are in disordered or loop segments.

Nazabal et al. [31] have reported H/D exchange data for fibrils formed by the HET-s fungal prion protein, showing that only the 70-residue C-terminal segment has a reduced exchange rate in the fibrillar form. Exchange rates for the remainder of the protein, which forms a globular domain in the monomeric form of HET-s, are not significantly altered upon fibril formation. This result suggests that only the C-terminal segment participates in the cross-β core of HET-s fibrils, while the globular domain retains its native fold. Similar behavior is indicated in experiments by Baxa et al. [40 † † ], in which the enzymes carbonic anhydrase, barnase and glutathione S-transferase were fused to the 65-residue N-terminal domain of the Ure2p yeast prion protein. The enzymatic activities of amyloid fibrils formed by the three fusion proteins were found to be almost identical to those of the native enzymes, indicating that amyloid formation did not significantly perturb the molecular structures of the globular enzymatic domains. Thus, amyloid formation by a bona fide protein, as opposed to a relatively short peptide without a stable monomeric structure (such as Aβ1–40), does not require the entire protein to participate in the amyloid core structure. In the amyloid state, the structures of amyloid-forming segments of proteins may closely resemble the structures of fibrillized peptides.

H/D exchange techniques with residue-specific resolution have been described by Hoshino et al. [29] and Ippel et al. [32]. In these experiments, amyloid fibrils were subjected to H/D exchange under controlled conditions and for controlled periods, dissolved under conditions that largely prevented further exchange and then examined by liquid-state NMR in an apotic solvent. For β2-microglobulin amyloid fibrils [29], the H/D exchange data indicate that certain loop segments in the native fold become highly protected in the amyloid form, suggesting conversion to β-strands. Additionally, certain β-strands in the native fold exchange more rapidly in the amyloid form. Data such as these place strong constraints on any structural model of β2-microglobulin fibrils.

Proteolysis experiments have also been used as probes of amyloid structure. Kheterpal et al. [28] have reported in vitro trypsin and chymotrypsin digestion results for Aβ1–40 fibrils, showing that the F4–R5, R5–H6 and Y10–E11 peptide bonds are susceptible to proteolysis. These results are consistent with the H/D exchange and solid-state NMR data described above. The N-terminal segment of full-length Aβ has previously been found to undergo proteolysis in vivo [41]. The in vitro proteolysis data indicate that in vivo N-terminal digestion can occur after fibrillization of Aβ, rather than being a requisite step for in vivo amyloid deposition.

Polymorphism in amyloid fibrils

EM images of amyloid fibrils formed by a given peptide or protein commonly show a mixture of fibril morphologies. For example, detailed analyses of these morphologies have been reported for Aβ1–40 amylin and insulin fibrils.
It has been unclear whether these morphological variations arise from structural variations at the molecular level or merely from different modes of lateral association of the same protofilament. Recently, we have found that the predominant morphology of Aβ_{1-40} fibrils can vary in response to subtle variations in fibrillization conditions and that samples with different predominant morphologies also exhibit differences in their solid-state NMR spectra [7**,12**]. These findings suggest that variations in fibril morphology result from underlying molecular structural variations. The precise nature of these structural variations remains to be elucidated.

Structural polymorphism in amyloid fibrils has obvious implications for a variety of experiments that probe molecular structure. For example, the finding that approximately 20% of the Aβ_{1-40} fibrils in samples investigated by Kheterpal et al. [28] were resistant to proteolysis may be a consequence of the structural features of a particular Aβ_{1-40} fibril polymorph in these samples. The observation of incomplete reductive alkylation at K28 in Aβ_{1-40} fibrils in the experiments of Iwata et al. [33] may also reflect differences in molecular structure (i.e. solvent exposure versus sequestration of the K28 ε-amino group) for different polymorphs.

Structural polymorphism in amyloid fibrils has important implications for the phenomenon of strains in prion diseases. In both mammals [42] and yeast [43–45], single prion proteins have been found to give rise to multiple disease strains with somewhat different manifestations. It has been suggested that different prion strains correspond to different structural forms of the prion proteins in aggregated states [46,47]. In support of this suggestion, we have found that both the morphological features of Aβ_{1-40} fibrils seen in EM images and the molecular-level structural features sensed by NMR spectroscopy can be passed down from one generation of fibrils to the next by using sonicated fragments of ‘parent’ fibrils as seeds for subsequent growth of ‘daughter’ fibrils in in vitro experiments.

The identification of structurally and morphologically distinct forms of Aβ_{1-40} fibrils may help explain why a strong correlation between cognitive impairment in Alzheimer’s disease and total amyloid deposition has not been observed [48]. Perhaps certain polymorphs are more neurotoxic than others.

### Recent proposals regarding amyloid structures

#### Polar zippers

Certain amyloid-forming proteins, including huntingtin and yeast prion proteins, contain glutamine-rich or asparagine-rich segments in the portions of their sequences that form the cross-β fibril core. Perutz et al. [49,50] proposed that the cross-β structural motif is stabilized in these cases by intermolecular hydrogen bonds between sidechain amide and carbonyl groups, in addition to the backbone hydrogen bonds present in all amyloid fibrils. They used the term ‘polar zipper’ to describe the chain of sidechain hydrogen bonds envisioned in amyloid fibrils formed by glutamine-rich or asparagine-rich segments. This proposal has gained acceptance and has been incorporated into recent structural models of amyloid fibrils [51,52**], but has not yet been proven by direct structural measurements on amyloid fibrils. Related intermolecular sidechain hydrogen bonding has been observed in a crystal structure of domain-swapped RNase A [53]. Measurements of the aggregation kinetics for synthetic polyglutamine peptides with proline–glycine inserts suggest that polyglutamine fibrils contain β-strand segments of nine or ten residues, separated by turn conformations [54**].

### Domain swapping

Certain proteins that are principally monomeric in solution have been found to exist as domain-swapped dimers in crystalline form [55] or in solution after destabilization of the monomeric structure [56]. The observation of domain swapping by amyloid-forming proteins led to the proposal that domain swapping involving β-strand segments might be a mechanism by which proteins with stable monomeric structures convert to amyloid fibrils [55]. The true significance of domain swapping with respect to amyloid formation has not yet been determined experimentally, principally because molecular-level structural data on amyloid fibrils formed by proteins with stable monomeric structures remain scarce.

#### β-Helices

Proteins such as pectate lyase C [57] and P.69 pertactin [58] contain β-helices — tubular structures formed by a peptide chain with multiple β-strand segments (typically 4–6 residues in each β-strand) that are separated by short (typically 1–2 residues) bend segments. The idea that amyloid fibrils may be constructed from β-helices was first proposed by Lazo and Downing [59], who suggested antiparallel β-helical structures for Aβ and other amyloid fibrils, presumably because the existence of parallel β-sheets in amyloid fibrils had not yet gained wide acceptance. Subsequently, Wille et al. [22**] developed a parallel β-helical model for human prion protein aggregates observed to form ordered two-dimensional arrays in EM images. Perutz et al. [52**] proposed a related tubular structure for amyloid fibrils formed by polyglutamine peptides.

The β-helix is a plausible structural motif for amyloid fibrils, because it is a primarily β-sheet structure with the proper cross-β orientation and because it is known to occur in bona fide proteins. To be consistent with MPL measurements on Aβ fibrils [8*,20], at least two β-helices would have to associate laterally to form a fibril. Such a structure might then be consistent with the fibril...
dimensions observed in EM images. Perutz et al. [52**] proposed a bundle of three β-helical tubes as a model for polyglutamine fibrils, based on MPL data and the fibril morphology observed in negatively stained EM images. No definitive proof of β-helical structures within amyloid fibrils has been obtained to date. The structural model in Figure 2 might be considered a dimeric, flattened β-helical model if the C-terminal end of each peptide chain were closer to the N-terminal end of the next chain than to its own N-terminal end.

Universality of amyloid structures

The observation by solid-state NMR of both parallel and antiparallel β-sheets in amyloid fibrils means that there is no absolutely universal molecular structure for amyloid fibrils. To date, antiparallel β-sheets have only been demonstrated in amyloid fibrils composed of relatively short peptides (i.e. 15 residues or less) [4,35,36**]. However, the possibility of antiparallel β-sheets in fibrils formed by longer peptides or proteins certainly exists [54*]. Topological constraints imposed by intra-chain and interchain disulfide bridges, present in cases such as insulin fibrils [23**] but absent in other cases, further suggest that significant variations in molecular structure must exist. Although amyloid fibrils do not share a single common molecular structure (apart from the defining characteristic that a cross-β motif be present), it may eventually prove possible to group amyloid fibrils into classes based on common structural and morphological features.

O’Nuallain and Wetzel [60*] have reported the isolation of monoclonal murine antibodies that bind to amyloid fibrils in a sequence-independent manner, but do not bind to the corresponding soluble peptides or to fibrillar proteins that are not amyloid. These results suggest a common structural feature for amyloid fibrils formed by diverse peptides and proteins. The precise structural determinant of antibody recognition in these experiments is not yet known.

Amyloid fibrils as technological materials

From the standpoint of materials science, amyloid fibrils are self-assembled, quasi-one-dimensional structures that may prove useful as scaffolds or building blocks for biomimetic materials with technologically significant electronic, magnetic, optical or mechanical properties. Molecular structure determination is then a prerequisite for rational materials design. Along these lines, Reches and Gazit [61] have reported the fabrication of silver nanowires, with ~20 nm diameter, by casting within tubular fibrils formed by the dipeptide Phe–Phe. Scheibel et al. [62] have reported templated fabrication of gold/silver nanowires, with ~100 nm diameter, on amyloid fibrils formed by a fragment of the Sup35p yeast prion protein. In potentially related work, Lu et al. have described the assembly of Aβ16–22, which forms conventional amyloid fibrils near neutral pH [13,35], into hollow, tubular fibrils with homogenous, 52 nm diameter at low pH [27**].

Conclusions

Substantial progress has been made towards the elucidation of the molecular structures of amyloid fibrils through the development and application of novel and diverse experimental methods. Although the high-resolution molecular structure of an amyloid fibril (including both the molecular conformation and the supramolecular organization) has not yet been completely determined from experimental data, it appears likely that complete structure determination will be achieved in the near future, based on some combination of solid-state NMR, EM, EPR, X-ray and neutron scattering, and biochemical measurements. Further studies will probably lead to an improved understanding of the interactions that stabilize amyloid structures, the commonalities and differences among amyloid structures, the mechanisms by which amyloid fibrils form, and the potential technological utility of amyloid structures. Further structural studies will also most likely yield new insights into the etiology and treatment of amyloid diseases.

Acknowledgements

I thank RG Griffin and CP Jaroniec for providing TTR105-115 coordinates used to generate Figure 3. The EM image in Figure 1a was obtained by AT Petkova and RD Leapman. This work was supported by the Division of Intramural Research of the National Institute of Diabetes and Digestive and Kidney Diseases, and by the Intramural AIDS Targeted Antiviral Program of the National Institutes of Health.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

● of special interest
●● of outstanding interest


7. Petkova AT, Ishii Y, Balbach JJ, Antzutkin ON, Leapman RD, Delaglio F, Tycko R: A structural model for Alzheimer’s
Solid-state NMR measurements of intramolecular and intermolecular distances, backbone torsion angles, chemical shifts that correlate with secondary structure and NMR line-widths that correlate with structural order were used to construct a model for the protofibril within Aβ40 fibrils, in conjunction with constraints on fibril diameters and MPL from EM.


A large set of constraints on interatomic distances and torsion angles was used to determine the conformation of the TTR105-115 peptide in amyloid fibrils. Although the supramolecular organization was not determined, this is the highest resolution molecular structure within an amyloid fibril reported to date.


Structural constraints on Aβ1-40 fibrils were obtained from measurements of EPR line-widths and spin-spin couplings in a series of spin-labeled cysteine mutant samples. Conclusions about molecular structure and supramolecular organization drawn from these data agree well with the model in Figure 2. Data are also reported that indicate co-fibrillization of Aβ1-40 and Aβ1-42 with molecular-level mixing, supporting the absence of large structural differences between Aβ1-40 and Aβ1-42 fibrils.


Variants of a mammalian prion protein are reported to form ordered two-dimensional arrays of aggregates, for which an electron density distribution was determined. A parallel β-helical structural model was found to fit the electron density distribution.

Cryo-EM was used to construct models of electron density in insulin amyloid fibrils with several different morphologies. The possibility that the observed morphologies share a common protofibril structure is investigated.


Detailed analysis of X-ray scattering from Aβ11-25 fibrils that are nearly crystalline, leading to an antiparallel β-sheet model.


A rapid photochemical cross-linking technique was used to investigate the earliest stages of aggregation of amyloid-forming peptides. The distributions of oligomer sizes for Aβ1-40 and Aβ1-42 are found to be qualitatively different, suggesting a possible reason for the association of elevated Aβ1-42 levels with Alzheimer’s disease.


Amyloid fibrils formed by fusion proteins composed of the N-terminal ‘prion domain’ of Ure2 and several enzymes with globular structures are found to retain nearly full enzymatic activity. This demonstrates retention of the globular structure in the amyloid form and may place steric constraints on the amyloid structure.


Measurements of the aggregation kinetics of synthetic polyglutamine peptides with proline–glycin inserts, suggesting a molecular conformation with repeated β-hairpins in the amyloid fibril state.


Monoclonal antibodies raised against Aβ1-40 fibrils bind to a variety of amyloid fibrils, but not to nonamyloid controls.


