Published in final edited form as:

Org Biomol Chem. 2017 August 30; 15(34): 7063–7071. doi:10.1039/c7ob01170a.

Amyloid Scaffolds as Alternative Chlorosomes

Rolando F. Rengifo, Noel X. Li, Anthony Sementilli, and David G. Lynn*

Emory University, Departments of Biology and Chemistry, 1515 Dickey Dr. NE, Atlanta, GA, 30322, USA

Abstract

Living systems contain remarkable functional capability built within sophisticated self-organizing frameworks. Defining the assembly codes that coordinate these systems could greatly extend nanobiotechnology. To that end, we have highlighted the self-assembling architecture of the chlorosome antenna arrays and report the emulation and extension of their features for the development of cell-compatible photoredox materials. We specifically review work on amyloid peptide scaffolds able to (1) organize light-harvesting chromophores, (2) break peptide bilayer symmetry for directional energy and electron transfer, and (3) incorporate redox active metal ions at high density for energy storage.

Graphical Abstract

1. Introduction

Biochemical ingenuity is beautifully displayed in photosynthesis. Complex pigments arrayed in intricate protein networks capture solar energy with near perfect quantum yield due to the precise arrangement of chromophores and electron transfer sites.¹ Designing and constructing precise mesoscale arrays presents a significant challenge, particularly when

*To whom correspondence should be addressed: Emory University, Department of Chemistry, 1515 Dickey Dr. NE, Atlanta, GA, 30322, USA. David G. Lynn, dlynn2@emory.edu. Tel: 1-404-727-9348, Fax: 1-404-727-5686.

considering high-energy photoredox processes.² The elegant chlorosome is a photosynthetic organelle found in anaerobic autotrophs like green sulfur bacteria that inspires the design of light-harvesting materials that might be extended and employed as parts for new functional cellular machines.³

As shown in the structural models of Figure 1A, chlorosomes contain over 250,000 chlorophyll and carotenoid pigments packed into multilamellar nanotubes.^{4, 5} This repeating architecture underlies a remarkably efficient light-harvesting capability, powering green sulfur bacteria in the low-light conditions found one hundred meters below sea level.^{6, 7} We hope to expand our increasing understanding of assembly pathways for constructing ordered cross- β amyloids ranging from nanotube,^{8–13} ribbon,^{14–16} sheet,^{17–19} and fiber^{14, 20–24} architectures for building chlorosome-like arrays. Templating chromophore arrays on protein scaffolds able to sustainably self-propagate in living cells could significantly extend the functions of extant biology. Here, we outline our view of the critical steps open to self-propagating amyloid scaffolds for templating chromophore organization and capturing physical energy for bioorthogonal yet cell-compatible photoredox catalysis. We review the development of self-assembling and self-healing bionanomaterials capable of light-harvesting, energy transfer, and access to membrane asymmetry for charge separation; combining each capability sets the stage for developing materials capable of directional net electron transfer and energy storage on a cell-compatible scaffold.

2. Toward Conducting and Energy-Storing Amyloids

2.1 Designing an Amyloid Antenna

The folding pathway for the nucleating core of the A β peptide of Alzheimer's disease (AD), L¹⁷VFFA²¹, may be the most widely studied amyloid, both empirically and through simulation.^{10, 25–45} Notably, when constructed as Ac-KLVFFAE-NH₂, nanotubes form from antiparallel β -sheets with strands shifted out-of-register by the N-terminal residue. This organization creates grooves that run the length of the internal and external surfaces that define the hollow assembly (Figure 1B). The predicted dimensions of these grooves are large enough to bind aromatic ligands (Figure 2).⁴⁶ More specifically, the nanotube grooves have been shown to organize Congo Red (CR) molecules end-to-end and side-by-side, spacing the chromophores in tracks one nanometer apart along the length of the hollow nanotube's inside and outside surfaces. This density approaches that seen in the chlorosome and benefits from organization on a peptide scaffold that can be further tailored.

The assembly characteristics of this peptide were extended via covalent attachment of chromophores in the peptide-pigment chimera Rho110-KLVFFAE-NH₂. With rhodamine 110 (Rho110) grafted to the N-terminus, the chimera assembles as pigmented twisted fibers.⁴⁷ When co-assembled with Ac-KLVFFAE-NH₂ in a 1:250 molar ratio, nanotubes form as shown in Figure 3. These nanotubes are morphologically indistinguishable from the Ac-KLVFFAE-NH₂ assemblies by TEM and WAXS, with the fluorophores randomly distributed along the nanotube surfaces.⁴⁸ The same homogeneous structure and fluorescence are observed when the Rho110-KLVFFAE-NH₂ ratio is increased to 1:75, but the fluorescence lifetime of Rho 110 becomes heterogeneous by fluorescence-lifetime imaging microscopy (FLIM).^{49, 50} While a decrease in lifetime might arise from

chromophore self-quenching, the dense chromophore composition in chlorosomes suggests that self-quenching can be circumvented in a well-organized chromophore arrays. Given the organization constraints achieved on the surface of the amyloid nanotubes, the domains of fluorescence lifetime may instead arise from subtle structural variations that propagate as the nanotubes grow due to differences in side chain packing. Variation along individual nanotubes has been shown to form in mixed peptide assemblies with single amino acid variation in the peptides and even from conformational changes in single amino acids.^{13, 51, 52} Such packing differences could lead to a conformational mutation that continues to propagate until another mutation occurs. Such events would open the possibility of controlling the architecture laterally along the growing nanotube and using dynamic packing differences to regulate energy and electron transfer efficiencies within defined regions of the nanotubes.^{10, 39}

Like CR, the negatively charged Alexa 555 (A555) binds the positively charged Ac-KLVFFAE-NH₂ nanotube surface, and when bound to the Rho110-KLVFFAE-NH₂-seeded nanotubes, Förster resonance energy transfer (FRET) is demonstrated,⁴⁷ paralleling the energy transfer achieved with chlorosomes. When introduced at a 4:1 Rho110-KLVFFAE-NH₂:A555 molar ratio, this system achieves 11% FRET efficiency.⁴⁷ Other chromophore organizing assemblies driven by electrochemical associations have also been reported^{53, 54} using the biologically relevant tetra-(p-hydroxyphenyl) porphyrin. The π - π interactions and electrostatics between the negatively charged porphyrin and positively charged dipeptides (KK) collectively drive solution phase assembly of these components into powerful light-harvesting antennae with the potential for hydrogen evolution.^{55–57} The amyloid templates provide a well-defined peptide scaffold with the potential for self-propagation and evolutionary selection within a cellular matrix. To extend the chlorosome model, we needed to increase the architectural and functional capability of amyloid nanotube assemblies.

2.2 Breaking Amyloid Assembly Symmetry

Biological phospholipids assemble into membranes that are symmetric across the bilayer but asymmetric across each individual leaflet. In contrast, amphiphilic peptides assemble with antiparallel strand arrangements that give more symmetric cross- β leaflets. The resulting bilayered leaflets contains antiparallel β -sheets that pack half the protonated lysine residues within the bilayer interface.⁵² Sequestering these charges from the aqueous environment represents a major energetic constraint on assembly,²¹ nevertheless, the hydrophobic Ac-KLVFFAL-NH₂ peptide forms these bilayer membranes when the interface is sufficiently passivated. Trifluoroacetic acid (TFA) provides the counterion to assemble the K-rich bilayer interface by passivating each interfacial amine stoichiometrically as observed by ¹⁹F-NMR.^{13, 52}

To explore the extent of this leaflet electrochemical constraint, the phosphorylated Ac-pYLVFFAL-NH₂ was constructed and shown to assemble as bilayer nanotubes with triethylammonium (TEA) as the counterion. This phosphorylated peptide then forms homogeneous negative charged nanotubes, greatly extending the general approach to assemble more complex scaffolds.⁵¹ The co-assembly of these two complementarily charged peptides (Ac-KLVFFAL-NH₂ and Ac-pYLVFFAL-NH₂) at equimolar concentrations, forms

nanotube bilayers with self-passivating leaflets.¹³ There are two limiting ways of structurally achieving the self-passivated leaflet interface: (1) laminating two homogeneous leaflets, one containing only Ac-KLVFFAL-NH₂ and the other only Ac-pYLVFFAL-NH₂ or (2) a complete inter-digitation of the lysine (K) and phosphotyrosine (pY) peptides in both leaflets. Electrostatic force microscopy establishes that all the assembled nanotubes maintain a homogeneous negative surface charge, and solid-state NMR analyses confirm that both limiting assemblies are equally represented in the nanotube assemblies. Most strikingly, these limiting structures exist as distinct blocks within individual nanotubes, appearing by TEM as block co-polymer nanotubes. As with the fluorescent lifetime blocks mentioned in section 2.1 above, the block architecture appears to be acquired during propagation where the lengths of each block are defined by the mutation rates.

This evidence supports molecular-level mutations emerging from assembly propagation, opening new levels of longitudinal variation and extending the structural and functional diversity of these scaffolds. Mechanistic evidence for conformational mutation during fiber and nanotube propagation has been achieved by mapping the existence of a two-step pathway for the assembly of mature amyloids.^{14, 58} The initial phase transition of monomer to particle creates a nucleation site; however, the initial strand arrangement is unstable when the growing end emerges in the solution phase during propagation. As the growing strands shear, the structural mutation is autocatalytically amplified at the expense of the initial particle phase assembly.⁵⁹ This mechanistic understanding suggests that tuning such conformational mutations could provide new and powerful approaches for selecting specific nanotube domains that localize specific chemistry to defined regions of a supramolecular assembly.

Nowhere might such spatial control be more important than in buffering reactive photo-redox chemistries along hollow nanotubes. For example, Ac-KLVFFAL-NH₂ and Ac-pYLVFFAL-NH₂ co-assemble into nanotubes that have already been differentially decorated on their internal and external surfaces with complementary positive and negatively charged fluorophores.¹³ To our knowledge, these nanotubes are the first to extend the concept of expanding membrane-like assembly to create innate electrochemical gradients. The control of membrane asymmetric domains at both the inner and outer surfaces of the nanotube would significantly expand chlorosome mimics. Having defined functional domains buffered by regions maintaining different functions might achieve directed energy and electron flow along a photoredox network approaching the sophistication of biological systems. Such networks will require the ability to store the acquired energy, and one system is outlined in the following section.

2.3 Metalloamyloid Arrays

One-third to one-half of all proteins depend on inorganic cofactors for their function, and capturing these cofactors on amyloid scaffolds may broaden their functions in disease^{60–67} and in health.^{66, 68} The controlled incorporation of metal ions at a high density in functional material design has blossomed over the past twenty years.⁶⁹ Specifically, metal organic frameworks (MOFs) are functional nanoporous materials that house metal ions ranging from transition metals to lanthanides within organic frameworks. The structural versatility

afforded to MOFs by the diversity of its building blocks has allowed for new applications in gas/vapor sorption, separation, drug delivery, and heterogeneous catalysis.⁷⁰ In 1966, Gramaccioli further expanded the frontiers in MOF design, being the first to use biomolecules as the organic linkers to a material he termed bioMOFs. Since their inception, several structures have been developed.⁷¹ However, a significant limitation in the design of these metal-organic materials is controlling growth along a specific selected dimension. While new strategies are emerging,⁷² amyloids and the energetic code embedded in the cross- β structure allows for the introduction of new materials whose growth can now be controlled along a single dimension in assemblies we term metalloamyloid arrays.

The A β -derived amyloid precursor protein regulates divalent metal ions, notably Zn²⁺ and Cu²⁺,^{73–76} and these same metals have been shown to induce the nucleation of amyloid assemblies.^{60, 77} For example, as shown in Figure 5A, the peptide H-YEVHHQKLVFFA-NH₂ (A β (10–21)) forms a mixture of fibers and particles.⁷⁷ In the presence of Zn²⁺, the peptide assembles more homogeneously (Figure 5B). Even though the metal and peptide are introduced in equimolar amounts, the resulting fibrils contain 0.03 molar equivalents of the metal – no more than 3% of the total metal present. At such a low degree of incorporation, we hypothesize that the Zn²⁺-peptide complexes only nucleate fiber growth. We reasoned that higher Zn²⁺ incorporation may be inhibited as the likely metal-binding HH-dyad lies near the middle of the peptide sequence, restricting Zn²⁺ accessibility. In an effort to increase metal ion access to the HH-dyad, the peptide was truncated to begin with an N-terminal HH-dyad.⁷⁸ Shortening the peptide also removed two amino acid side chains which could compete with the HH-dyad for metal binding, tyrosine (Y) and glutamic acid (E).

To completely isolate the HH-dyad, lysine (K) replaces alanine (A) to give H-HHQALVFFA-NH₂, (K16A). This peptide assembles as fibers (Figure 5C), and in the presence of equimolar Zn²⁺, assembles as fibers, helical ribbons of varying sizes, and nanotubes (Figure 5D). These assemblies contain 60 – 80% of the added Zn²⁺, contrasting the longer peptide (Figure 5B). The high degree of Zn²⁺ incorporation opened possibilities in creating new kinds of nanoscale materials incorporating high metal concentrations with extended redox functions.

While both K16A and a congener, Ac-HAQKLVFFA-NH₂ (H14A), form homogeneous fibers in metal-free environments (Figure 6A and C), Cu²⁺ inhibited K16A fiber formation but improved the rate of H14A assembly without affecting morphology (Figure 6B). Cu²⁺ binding was confirmed by a spectroscopic blue shift in the λ_{max} of Cu²⁺, apparent for both Cu²⁺-peptide mixtures. Furthermore, electron paramagnetic resonance (EPR) confirmed metal coordination for H14A fibers. Electron spin echo envelope modulation (ESEEM) spectroscopy provided evidence that Cu²⁺ ions are arrayed continuously along the long-axis of the micron-long H14A fibers, positioning the Cu²⁺ ions 9.4 Å apart on the fiber surface (Figure 7).⁷⁹ The high density of Cu²⁺ ions incorporated in single tracks is unprecedented and resembles the proximal binding of CR along the laminate groove of amyloid. Recently, a reexamination of the K16A-Cu²⁺ assembly conditions found that with longer assembly times a unique morphology emerges (Figure 6D). K16A-Cu²⁺ complexes form ribbons that isolate Cu²⁺ ions within the peptide bilayer leaflet interface, much like TFA in the nanotubes

formed by Ac-KLVFFAL-NH₂ described in section 2.2 of this review. Using the H residues as binding sites, Cu²⁺ passivates the leaflet interface and stabilizes the bilayer. Computational models for this organization bury the Cu²⁺ ions within extended rows of metal ions spaced closely enough to function as unique redox catalysts and as bionanomaterials capable of electron storage and transfer (Rengifo et. al, under review). Such capability might greatly extend the function of the chlorosome-like assemblies as self-propagating photoredox organelles for extending the options for new light-harvesting functions.

3. Outlook

The elegant arrangement of pigments in chlorosomes underlies the remarkable light-harvesting ability of these self-assembling structures. Similar ordered density has now been achieved on cross- β scaffolds, and the amyloid assemblies have revealed opportunities that greatly extend the functions of these efficient antenna. Our growing understanding of the energetic landscape has made it possible to create peptide bilayer asymmetry, opening distinct opportunities for directed energy and electron transport. Small changes to the peptide sequence allows for metals to nucleate amyloid assembly and propagate at high densities. Recent evidence suggests that the metals are protected in environments that facilitate redox cycling and energy storage. While all these functions have not yet been combined, the degree to which the chlorosome model can be used to guide the functional diversification of cross- β assemblies is just now beginning.

While Nature's biochemical ingenuity provides valuable insight into new materials design, the most immediate and potentially impactful lessons may be the energetic landscape that selects for specific assemblies within cellular matrices. Prions are critical in health and disease, but how the powerful information content of these self-propagating structures leads to cellular malfunction remains poorly defined after many decades of study. Strains, defined here as conformationally distinct propagating assemblies, are selected by their ability to spread deleterious information from cell to cell in disease and health. In AD, as well as in many other neurodegenerative diseases, this seeming infection manifests as a progressive spread of information. Therapeutic approaches to limiting the initiation and spread of disease causing assemblies may depend on an understanding of nucleation and spread of these robust cross- β assemblies. The insights gained by the design of these materials should continue to reveal critical sights for intervention of disease progression while continuing to provide new beneficial self-organizing assemblies for creating alternative functions new to extant biology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the Robert P. Apkarian Electron Microscopy Core of Emory University for TEM training and data collection, the Emory X-ray Center for powder diffraction with specific gratitude to John Bacsá, the Integrated Cellular Imaging core with specific notation of Neil Anthony, and the Emory NMR center for all Solid-State NMR analysis. We acknowledge support from NSF CHE-1507932 and NSF/DMR-BSF 1610377 for synthesis and design

of materials, and the NIH Alzheimer's Disease Research Center: P50AG025688 for studies designed to define the amyloid assembly code.

References

- Govindjee, J., Kern, F., Messinger, J., Whitmarsh, J. eLS. John Wiley & Sons, Ltd; 2001.
- Kim JH, Lee M, Lee JS, Park CB. *Angew Chem Int Ed*. 2012; 51:517–520.
- Ganapathy S, Oostergetel GT, Wawrzyniak PK, Reus M, Chew AGM, Buda F, Boekema EJ, Bryant DA, Holzwarth AR, de Groot HJM. *Proc Natl Acad Sci USA*. 2009; 106:8525–8530. [PubMed: 19435848]
- de Groot, HJM. *Solid-state NMR studies of biopolymers*. Vol. ch. 30. Wiley; 2010. p. 509-517.
- Ansari-Oghol-Beig D, Rostami M, Chernobrovkina E, Saikin SK, Valleau S, Mosallaei H, Aspuru-Guzik A. *J Appl Phys*. 2013; 114:164315.
- Manske AK, Glaeser J, Kuypers MAM, Overmann J. *Appl Environ Microbiol*. 2005; 71:8049–8060. [PubMed: 16332785]
- Oostergetel GT, van Amerongen H, Boekema EJ. *Photosynth Res*. 2010; 104:245–255. [PubMed: 20130996]
- Scanlon S, Aggeli A. *Nano Today*. 2008; 3:22–30.
- Valery C, Artzner F, Paternostre M. *Soft Matter*. 2011; 7:9583–9594.
- Anthony, NR., Berland, KM., Mehta, AK., Lynn, DG., Seth Childers, W. *Bio-nanoimaging*. Uversky, VN., Lyubchenko, YL., editors. Academic Press; Boston: 2014. p. 27-36.<http://dx.doi.org/10.1016/B978-0-12-394431-3.00003-1>
- Hamley IW. *Angew Chem Int Ed*. 2014; 53:6866–6881.
- Pachahara SK, Nagaraj R. *Biochem Biophys Rep*. 2015; 2:1–13.
- Li S, Mehta AK, Sidorov AN, Orlando TM, Jiang Z, Anthony NR, Lynn DG. *J Am Chem Soc*. 2016; 138:3579–3586. [PubMed: 26942690]
- Childers WS, Anthony NR, Mehta AK, Berland KM, Lynn DG. *Langmuir*. 2012; 28:6386–6395. [PubMed: 22439620]
- Guo Q, Mehta AK, Grover MA, Chen W, Lynn DG, Chen Z. *Appl Phys Lett*. 2014; 104:211102.
- Castelletto V, Hamley IW, Hule RA, Pochan D. *Angew Chem Int Ed*. 2009; 48:2317–2320.
- Xie L, Luo Y, Wei G. *J Phys Chem B*. 2013; 117:10149–10160. [PubMed: 23926957]
- Jiang T, Xu C, Liu Y, Liu Z, Wall JS, Zuo X, Lian T, Salaita K, Ni C, Pochan D, Conticello VP. *J Am Chem Soc*. 2014; 136:4300–4308. [PubMed: 24571053]
- Dai B, Li D, Xi W, Luo F, Zhang X, Zou M, Cao M, Hu J, Wang W, Wei G, Zhang Y, Liu C. *Proc Natl Acad Sci USA*. 2015; 112:2996–3001. [PubMed: 25713359]
- Paramonov SE, Jun HW, Hartgerink JD. *J Am Chem Soc*. 2006; 128:7291–7298. [PubMed: 16734483]
- Liang Y, Pingali SV, Jogalekar AS, Snyder JP, Thiagarajan P, Lynn DG. *Biochemistry*. 2008; 47:10018–10026. [PubMed: 18759497]
- Ivanova MI, Sievers SA, Sawaya MR, Wall JS, Eisenberg D. *Proc Natl Acad Sci U S A*. 2009; 106:18990–18995. [PubMed: 19864624]
- Paparccone R, Sanchez J, Buehler MJ. *J Comput Theor Nanosci*. 2010; 7:1279–1286.
- Jayawarna, V., Ulijn, RV. *Supramol Chem*. John Wiley & Sons, Ltd; 2012.
- Pan, Y-x, Liu, C-j, Zhang, S., Yu, Y., Dong, M. *Chem Eur J*. 2012; 18:14614–14617. [PubMed: 22996562]
- Balbach JJ, Ishii Y, Antzutkin ON, Leapman RD, Rizzo NW, Dyda F, Reed J, Tycko R. *Biochemistry*. 2000; 39:13748–13759. [PubMed: 11076514]
- Klimov DK, Straub JE, Thirumalai D. *Proc Natl Acad Sci USA*. 2004; 101:14760–14765. [PubMed: 15465917]
- Li G, Pomès R. *J Phys Chem B*. 2013; 117:6603–6613. [PubMed: 23627280]
- Gehman JD, Separovic F, Lu K, Mehta AK. *J Phys Chem B*. 2007; 111:7802–7811. [PubMed: 17583943]

30. Li H, Luo Y, Derreumaux P, Wei G. *Biophys J*. 2011; 101:2267–2276. [PubMed: 22067167]
31. Smith JE, Liang C, Tseng M, Li N, Li S, Mowles AK, Mehta AK, Lynn DG. *Isr J Chem*. 2015; 55:763–769.
32. Klimov DK, Thirumalai D. *Structure*. 2003; 11:295–307. [PubMed: 12623017]
33. Petty SA, Decatur SM. *J Am Chem Soc*. 2005; 127:13488–13489. [PubMed: 16190699]
34. Martinez AV, Małolepsza E, Rivera E, Lu Q, Straub JE. *J Chem Phys*. 2014; 141:22D530.
35. Debeljuh N, Barrow CJ, Byrne N. *PCCP*. 2011; 13:16534–16536. [PubMed: 21850354]
36. Santini S, Mousseau N, Derreumaux P. *J Am Chem Soc*. 2004; 126:11509–11516. [PubMed: 15366896]
37. Lin D, Luo Y, Wu S, Ma Q, Wei G, Yang X. *Langmuir*. 2014; 30:3170–3175. [PubMed: 24588450]
38. Shanmugam G, Polavarapu PL. *J Struct Biol*. 2011; 176:212–219. [PubMed: 21855637]
39. Anthony NR, Mehta AK, Lynn DG, Berland KM. *Soft Matter*. 2014; 10:4162–4172. [PubMed: 24763698]
40. Elgersma RC, van Dijk M, Dechesne AC, van Nostrum CF, Hennink WE, Rijkers DT, Liskamp RM. *Org Biomol Chem*. 2009; 7:4517–4525. [PubMed: 19830304]
41. Krone MG, Hua L, Soto P, Zhou R, Berne BJ, Shea JE. *J Am Chem Soc*. 2008; 130:11066–11072. [PubMed: 18661994]
42. Irbäck A, Mitternacht S. *Proteins: Struct Funct Bioinform*. 2008; 71:207–214.
43. Cheon M, Chang I, Hall CK. *Biophys J*. 2011; 101:2493–2501. [PubMed: 22098748]
44. Ma B, Nussinov R. *Proc Natl Acad Sci*. 2002; 99:14126–14131. [PubMed: 12391326]
45. Brovchenko I, Burri RR, Krukau A, Oleinikova A. *PCCP*. 2009; 11:5035–5040. [PubMed: 19562133]
46. Childers WS, Mehta AK, Lu K, Lynn DG. *J Am Chem Soc*. 2009; 131:10165–10172. [PubMed: 19569651]
47. Liang Y, Guo P, Pingali SV, Pabit S, Thiagarajan P, Berland KM, Lynn DG. *Chem Commun*. 2008; :6522–6524.doi: 10.1039/B814262A
48. Ni R, Childers WS, Hardcastle KI, Mehta AK, Lynn DG. *Angew Chem Int Ed*. 2012; 51:6635–6638.
49. Anthony, NR., Bisignano, AJ., Mehta, AK., Lynn, DG., Berland, KM. presented in part at the Proc. SPIE 8226; San Francisco, California, USA. February 9, 2012, 2012;
50. Anthony, NR., Berland, KM., Mehta, AK., Lynn, DG., Seth Childers, W. *Bio-nanoimaging*. Uversky, VN., Lyubchenko, YL., editors. Academic Press; Boston: 2014. p. 27–36.
51. Li S, Sidorov AN, Mehta AK, Bisignano AJ, Das D, Childers WS, Schuler E, Jiang Z, Orlando TM, Berland K, Lynn DG. *Biochemistry*. 2014; 53:4225–4227. [PubMed: 24955650]
52. Childers WS, Mehta AK, Ni R, Taylor JV, Lynn DG. *Angew Chem Int Ed*. 2010; 49:4104–4107.
53. Liu K, Xing R, Chen C, Shen G, Yan L, Zou Q, Ma G, Möhwald H, Yan X. *Angew Chem Int Ed*. 2015; 54:500–505.
54. Liu K, Kang Y, Ma G, Möhwald H, Yan X. *PCCP*. 2016; 18:16738–16747. [PubMed: 27270974]
55. Zou Q, Liu K, Abbas M, Yan X. *Adv Mater*. 2016; 28:1031–1043. [PubMed: 26273821]
56. Liu K, Xing R, Li Y, Zou Q, Möhwald H, Yan X. *Angew Chem Int Ed*. 2016; 55:12503–12507.
57. Liu K, Abbas M, Zou Q, Yan X. *Green Energy & Environment*. 2017; 2:58–63.
58. Dong J, Apkarian RP, Lynn DG. *Biorg Med Chem*. 2005; 13:5213–5217.
59. Liang C, Ni R, Smith JE, Childers WS, Mehta AK, Lynn DG. *J Am Chem Soc*. 2014; 136:15146–15149. [PubMed: 25313920]
60. Dong J, Canfield JM, Mehta AK, Shokes JE, Tian B, Childers WS, Simmons JA, Mao Z, Scott RA, Warncke K, Lynn DG. *Proc Natl Acad Sci USA*. 2007; 104:13313–13318. [PubMed: 17686982]
61. Allsop D, Mayes J, Moore S, Masad A, Tabner BJ. *Biochem Soc Trans*. 2008; 36:1293–1298. [PubMed: 19021543]
62. Hung YH, Robb EL, Volitakis I, Ho M, Evin G, Li QX, Culvenor JG, Masters CL, Cherny RA, Bush AI. *J Biol Chem*. 2009; 284:21899–21907. [PubMed: 19542222]
63. Hureau C, Faller P. *Biochimie*. 2009; 91:1212–1217. [PubMed: 19332103]

64. Jomova K, Vondrakova D, Lawson M, Valko M. *Mol Cell Biochem.* 2010; 345:91–104. [PubMed: 20730621]
65. Liu B, Moloney A, Meehan S, Morris K, Thomas SE, Serpell LC, Hider R, Marciniak SJ, Lomas DA, Crowther DC. *J Biol Chem.* 2011; 286:4248–4256. [PubMed: 21147772]
66. Roberts BR, Ryan TM, Bush AI, Masters CL, Duce JA. *J Neurochem.* 2012; 120(Suppl 1):149–166. [PubMed: 22121980]
67. Jiang DL, Zhang L, Grant GPG, Dudzik CG, Chen S, Patel S, Hao YQ, Millhauser GL, Zhou FM. *Biochemistry.* 2013; 52:547–556. [PubMed: 23237523]
68. Mital M, Zawisza IA, Wiloch MZ, Wawrzyniak UE, Kenche V, Wróblewski W, Bal W, Drew SC. *Inorg Chem.* 2016; 55:7317–7319. [PubMed: 27409140]
69. Gangu KK, Maddila S, Mukkamala SB, Jonnalagadda SB. *Inorg Chim Acta.* 2016; 446:61–74.
70. Sabale S, Zheng J, Vemuri RS, Yu XY, McGrail BP, Motkuri RK. *Synthesis and Catalysis.* 2016; 1:1–8.
71. Rojas S, Devic T, Horcajada P. *J Mater Chem B.* 2017; doi: 10.1039/c6tb03217f
72. Lee J, Kwak JH, Choe W. *Nat Commun.* 2017;8. [PubMed: 28364116]
73. Hesse L, Behr D, Masters CL, Multhaup G. *FEBS Lett.* 1994; 349:109–116. [PubMed: 7913895]
74. Barnham KJ, McKinsty WJ, Multhaup G, Galatis D, Morton CJ, Curtain CC, Williamson NA, White AR, Hinds MG, Norton RS, Beyreuther K, Masters CL, Parker MW, Cappai R. *J Biol Chem.* 2003; 278:17401–17407. [PubMed: 12611883]
75. Adlard PA, Bush AI. *J Alzheimer's Dis.* 2006; 10:145–163. [PubMed: 17119284]
76. Baumkötter F, Schmidt N, Vargas C, Schilling S, Weber R, Wagner K, Fiedler S, Klug W, Radzimanowski J, Nickolaus S, Keller S, Eggert S, Wild K, Kins S. *J Neurosci.* 2014; 34:11159–11172. [PubMed: 25122912]
77. Morgan DM, Dong J, Jacob J, Lu K, Apkarian RP, Thiagarajan P, Lynn DG. *J Am Chem Soc.* 2002; 124:12644–12645. [PubMed: 12392395]
78. Dong J, Shokes JE, Scott RA, Lynn DG. *J Am Chem Soc.* 2006; 128:3540–3542. [PubMed: 16536526]
79. Hernández-Guzmán J, Sun L, Mehta AK, Dong J, Lynn DG, Warncke K. *ChemBioChem.* 2013; 14:1762–1771. [PubMed: 24014287]

Figure 1.

Schematic models of (A) bacteriochlorophyll pigments (green) organized as a nanotube in a chlorosome and (B) an engineered nanotube consisting of peptides self-assembled in a cross- β array. Peptides (e.g. Ac-KLVFFAL-NH₂), unlike simple amphiphiles, can form ordered arrays by pairing solubilizing groups (K, blue) with amyloidogenic domains (LVFFAL, gray). (Figure 1A reprinted from ref. 5 with the permission of AIP Publishing.)

Figure 2. Nanotube model depicting Congo Red (CR) binding to assembled Ac-KLVFFAE-NH₂. Surface coloring highlights the high density of CR adsorption in the nanotube hydrophobic grooves. A Congo Red molecule extends 19 Å.

Figure 3.

(A) Derivatizing Rho110 to the N-terminus of the A β truncation (Ac-KLVFFAE-NH₂), photofunctionalizes the ensuing nanotube. Assembly forces anchor Rho110 along the peptide array with dose-dependent density. (B) Covalently anchored Rho110 (left) and electrostatically bound A555 (middle) display antennae capabilities when both fluorophores are present on the nanotube surface (right). Unlike Rho110 and A555 in solution, when bound to the Ac-KLVFFAE-NH₂ nanotube scaffold, energy transfer across the 10 nm donor-acceptor distance gives 11% FRET efficiency. (Figure 3 adapted from ref. 4 with permission of Elsevier.)⁵³

Figure 4.

(A) Positively charged Ac-KLVFFAL-NH₂ and negatively charged Ac-pYLKLVFFAL-NH₂ co-assemble into asymmetric peptide membranes. (B) This dual peptide system forms nanotubes of monodisperse width (TEM) and height (AFM, left) with a preferred positioning of the negatively charged pY to the outer nanotube leaflet (EFM, right). (Figure 4B adapted with permission from ref. 13. Copyright 2016 American Chemical Society.)

Figure 5.

Electron micrographs of fibrils formed by Aβ(10–21), H-YEVHHQKLVFFA-NH₂ (A), Aβ(10–21) + 1 mM ZnCl₂ (B), H-HHQAALVFFA-NH₂ (K16A) (C) and K16A + 1mM ZnCl₂ (D). Peptides assembled in 25mM MES, pH: 5.6. Two-week incubation. Scale bar = 200 nm.

Figure 6.

(A and B) TEM images show that H14A does not undergo a morphological transition when co-assembled with CuCl_2 . (C and D) TEM images highlight the morphological transition K16A undergoes when Cu^{2+} is co-assembled with peptide monomers from $t = 0$ in the supramolecular assembly timeline. Scale bar = 100 nm.

Figure 7.

Representation of the molecular structure for the Cu²⁺-H14A fibers. Only the peptide backbone and Cu²⁺ ions (gold) are displayed. Distances correspond to the hydrogen-bonded, intra-sheet peptide spacing (4.7 Å), intra-sheet spacing of Cu²⁺ sites (9.4 Å), and β-sheet lamination distance (10 Å). Backbone color code: Oxygen red, carbon grey, nitrogen blue. Hydrogen atoms are omitted for clarity. (Figure 7 reprinted from ref. 79 with permission of John Wiley and Sons)