Supplementary Information

Supplementary Methods

GdnHCl denaturation performed by reversed titration- Briefly, the titration was performed by titrating Aβ solution in Buffer A containing <0.1 M GdnHCl into an unfolded Aβ solution in Buffer A containing 1.5 or 2 M GdnHCl. The desired metal ion concentration, 25 μM of Aβ, and 5 μM of Bis-ANS were present in both solutions. The duration for each titration was approximately 30 s and each set of denaturation experiment was less than 1 h. The Bis-ANS fluorescence emission at 490 nm was collected, averaged, and normalized. The normalized emission intensity versus GdnHCl concentration was plotted.

GdnHCl denaturation monitored by tyrosine emission- The equilibrium unfolding was performed as described in "Experimental Procedures" except the samples were in the absence of Bis-ANS and the intrinsic tyrosine fluorescence were monitored. The samples were excited at 270 nm and emission intensities at 300 nm were collected. The signals were plotted against GdnHCl concentration.

Supplementary Figure Legends

Supplementary Fig. 1. Normalized Bis-ANS spectra of Aβ in the absence and presence of the metal ions. Aβ in the absence (●) and presence of 200 μM Zn^{2+} (▽), 200 μM Cu^{2+} (△), 200 μM Fe^{3+} (○), and 500 μM Al^{3+} (□) are shown. The data were normalized to Bis-ANS fluorescence intensity at 500 nm of Aβ without the metal ions. Panel (A) and (B) show the spectra of all conditions in two ranges of wavelength: 450-550 and 465-515 nm. Panel (C) and (D) show the spectra of Aβ alone and Aβ with Cu^{2+} (△) or Fe^{3+} in two ranges of wavelength: 450-550 and 465-515 nm.

Supplementary Fig. 2. Tyrosine fluorescence spectra of Aβ in various concentrations of (A) Zn^{2+}, (B) Cu^{2+}, (C) Fe^{3+}, and (D) Al^{3+}. The concentrations of the metal ions are colored as indicated.

Supplementary Fig. 3. Binding kinetics of Zn^{2+}, Cu^{2+}, Fe^{3+}, and Al^{3+} with Aβ. Intrinsic tyrosine fluorescence of Aβ in the absence (●) and presence of Zn^{2+} (▽), Cu^{2+} (△), Fe^{3+} (○), Al^{3+} (□) were monitored with excitation at 270 nm. Exponential fits for Zn^{2+}, Fe^{3+}, and Al^{3+} are shown in solid lines and the residuals are shown above.

Supplementary Fig. 4. Bis-ANS fluorescence, tyrosince fluorescence, and far-UV CD spectra of Aβ in native (<0.12 M GdnHCl) and denatured (3 M GdnHCl) condition. (A) Bis-ANS fluorescence, (B) tyrosine fluorescence, and (C) far-UV CD spectra of "native" and unfolded Aβ are shown in solid and dashed lines, respectively.

Supplementary Fig. 5. GdnHCl denaturation of Aβ in the absence and presence of the metal ions. (A) GdnHCl denaturation of Aβ monitored by Bis-ANS fluorescence. Data obtained from forward titration are shown as follows: Aβ in the absence (◇) and the presence of 25 μM Zn^{2+} (▽), 25 μM Cu^{2+} (△), 50 μM Fe^{3+} (○), and 100 μM Al^{3+} (□). Data obtained from reverse titration are colored as follows: Aβ in the absence (◆, black) and the presence of 25 μM Zn^{2+} (▼, green), 25 μM Cu^{2+} (▲, blue), 50 μM Fe^{3+} (●, orange), and 100 μM Al^{3+} (■, red). (B) GdnHCl denaturation of Aβ monitored by tyrosine fluorescence. Aβ in the absence (●) and the presence of 25 μM Zn^{2+} (▽), 25 μM Cu^{2+} (△), 50 μM Fe^{3+} (○), and 100 μM Al^{3+} (□) are shown. The data scattering was primarily due to the small differences resided in tyrosine fluorescence between "native" and unfolded Aβ.

Supplementary Fig. 6. Oligomerization and fibrillization of Aβ in the presence of Al^{3+} in neutral pH monitored by ThT, dot blotting, and TEM. The samples were prepared in 10 mM Tris-HCl, pH 7.85, to insure neutral pH in the solution after addition of Al^{3+}. (**A**) ThT assay. Aβ in the absence and presence of 100, 250, and 500 μM of Al^{3+} are shown in black, blue, magenta, and green. (**B**) The end-point products were subjected to dot blotting probed by A11 and 6E10 antibodies. (**C**) The end-point products of Aβ in the presence of 250 μM Al^{3+} were centrifuged as described in text. The supernatant and pellet were subjected to A11 and 6E10 dot blotting. (**D**) TEM images of the total protein before centrifugation (scale bar = 200 nm) as well as the supernatant and pellet after centrifugation (scale bar = 100 nm).

Supplementary Fig. 7. Far-UV CD of the end-point products of Aβ aggregation with and without the metal ions. Aβ in the absence (●) and in the presence of 25 μM Zn^{2+} (▽), 25 μM Cu^{2+} (△), 50 μM Fe^{3+} (○), and 250 μM Al^{3+} (□) are shown.

Supplementary Table 1. The pHs of various aluminum concentrations prepared in 10 mM Tris-HCl, pH 7.4 or pH 7.85, at room temperature. The acidic pHs are underlined.

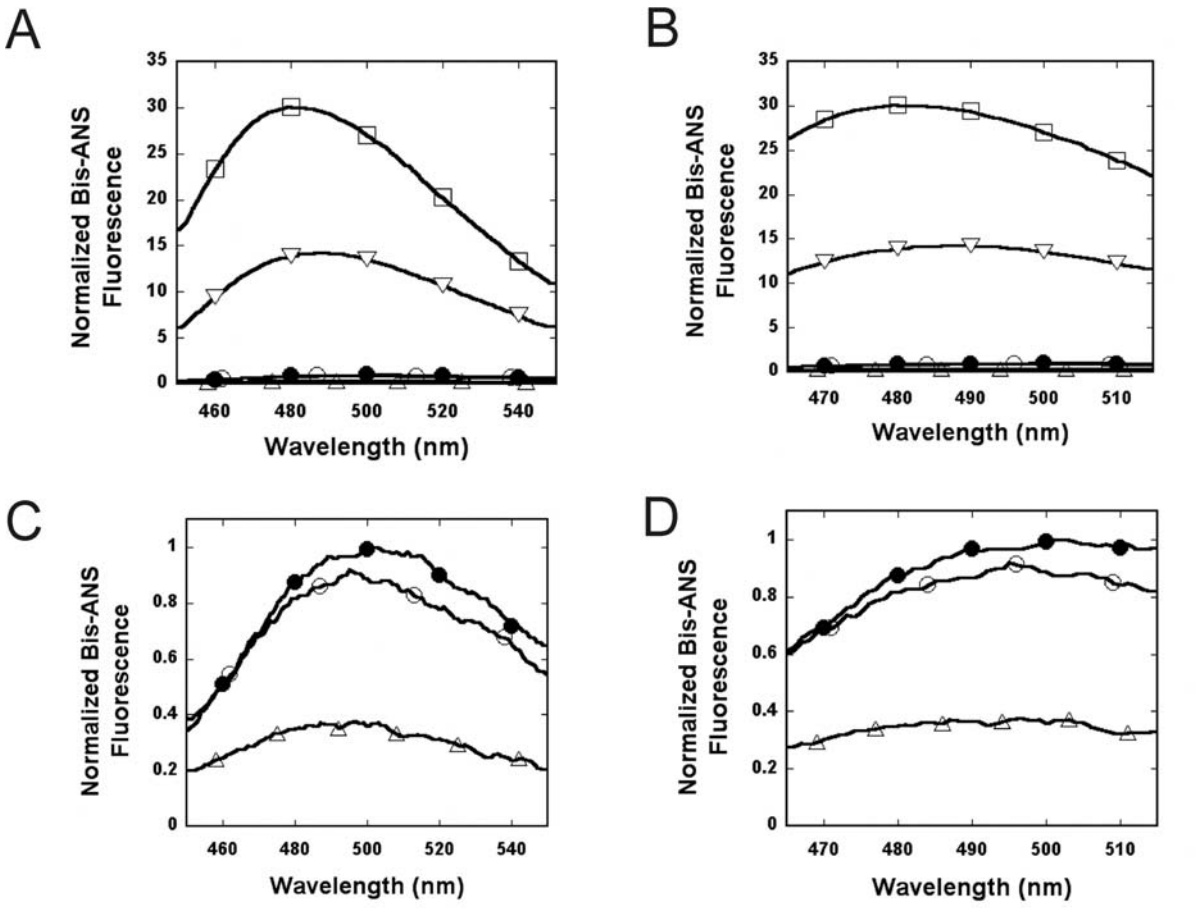
[Al^{3+}] (μM)	**Tris buffer, pH 7.4**	**Tris buffer, pH 7.85**
0	7.4	7.85
25	7.37	7.82
50	7.32	7.79
100	7.26	7.74
200	7.08	7.68
300	6.86	7.64
400	6.45	7.58
500	5.25	7.5
600	4.91	7.39
700	4.78	7.28
800	4.70	7.14
900	4.65	6.95
1000	4.59	6.65

Supplementary Table 2. Kinetic parameters of Aβ and the metal ion binding in the millisecond time scale.

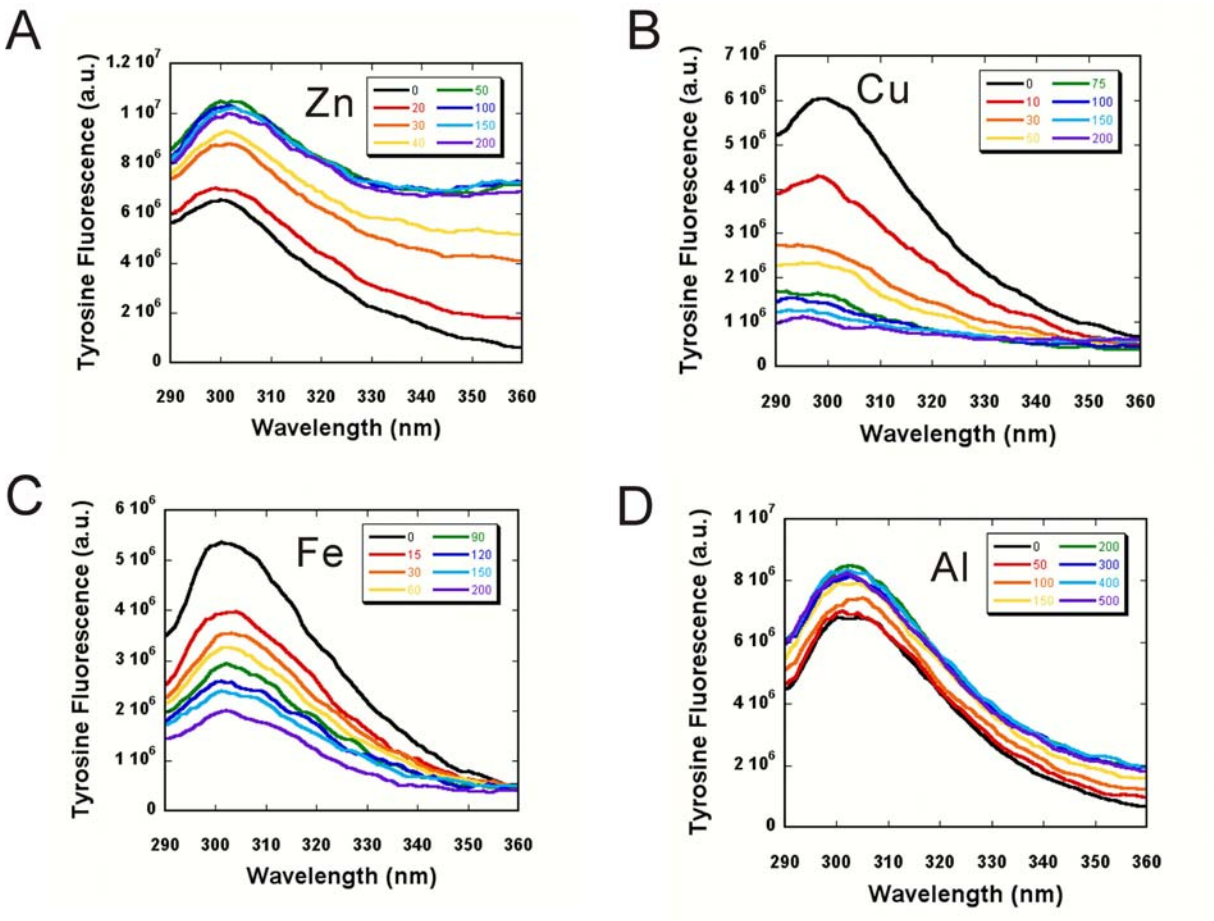
	c_1	**k_1 (sec^{-1})**	**c_2**	**k_2 (sec^{-1})**
Zn^{2+}	-0.127	0.125	N/A	
Cu^{2+}	N/A			
Fe^{3+}	0.0712	3.455	0.1243	0.4345
Al^{3+}	-0.0267	6.067	-0.0186	0.0915

c and *k* are the amplitudes and rate constants for the kinetic phases occurred between 0.005 to 100 sec .

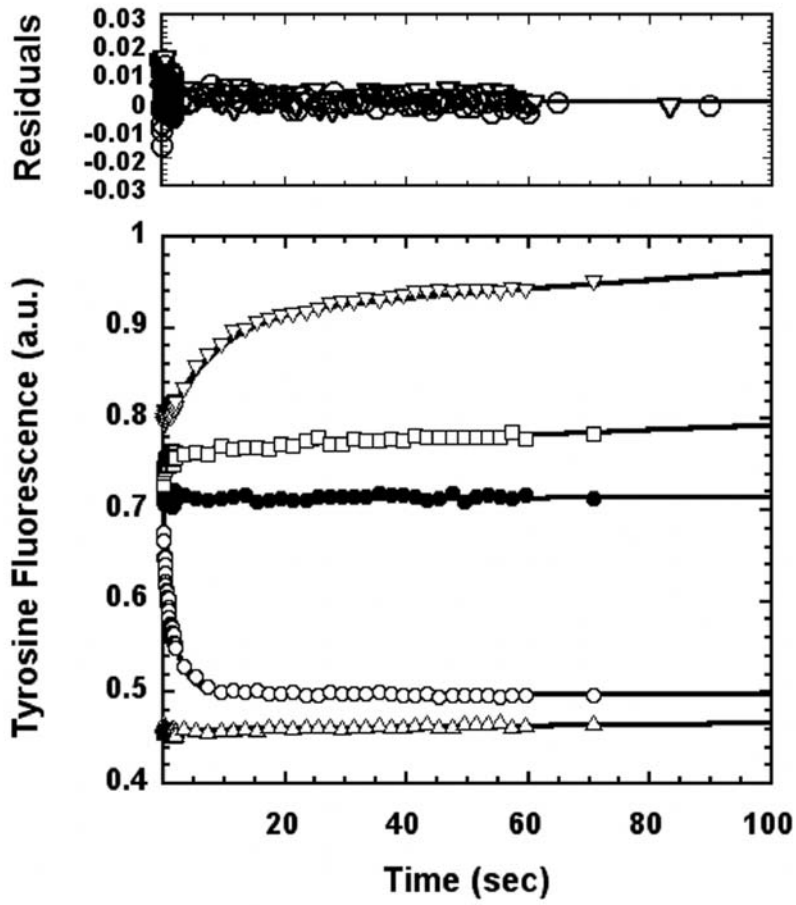
Supplementary Fig. 1



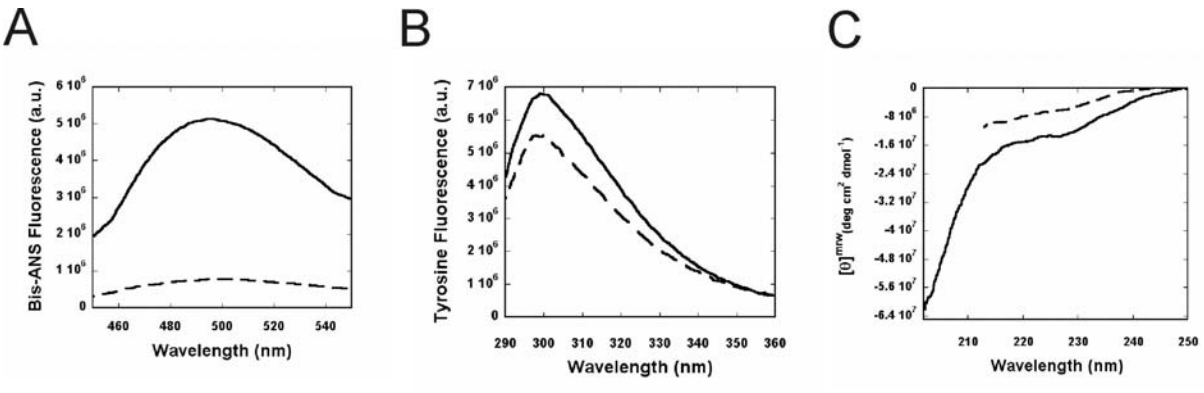
Supplementary Fig. 2



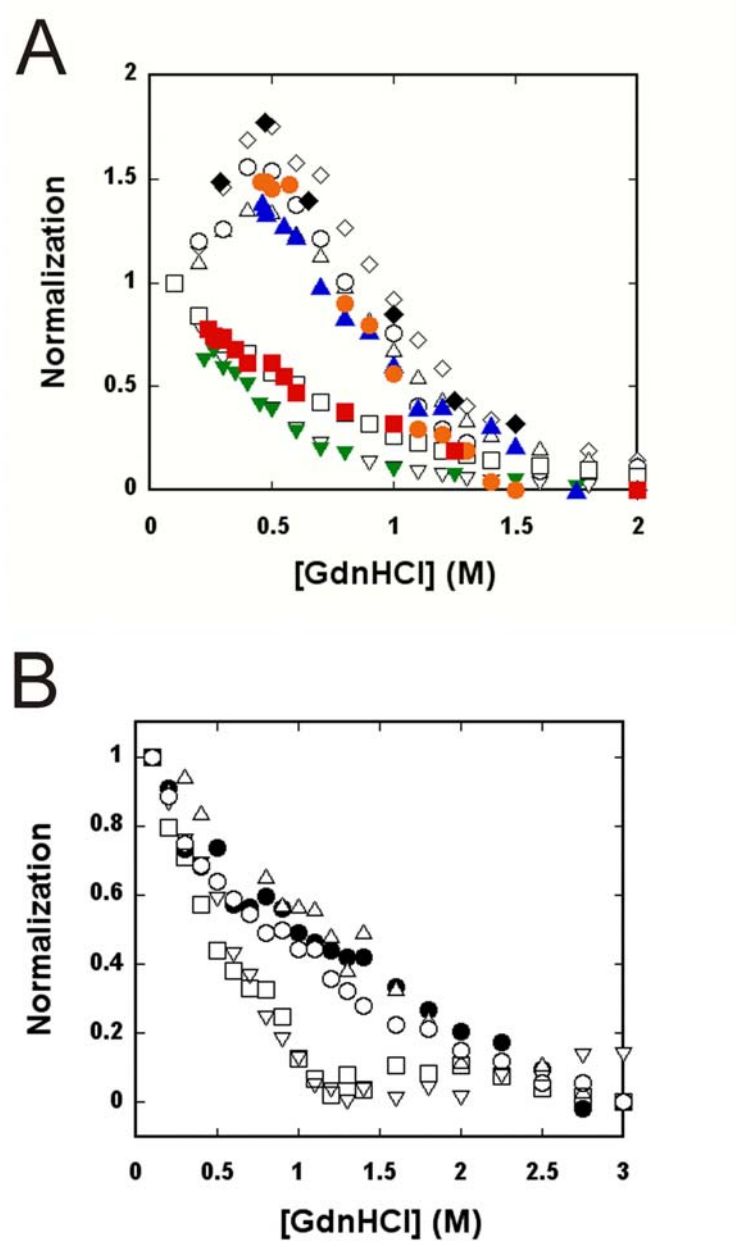
Supplementary Fig. 3



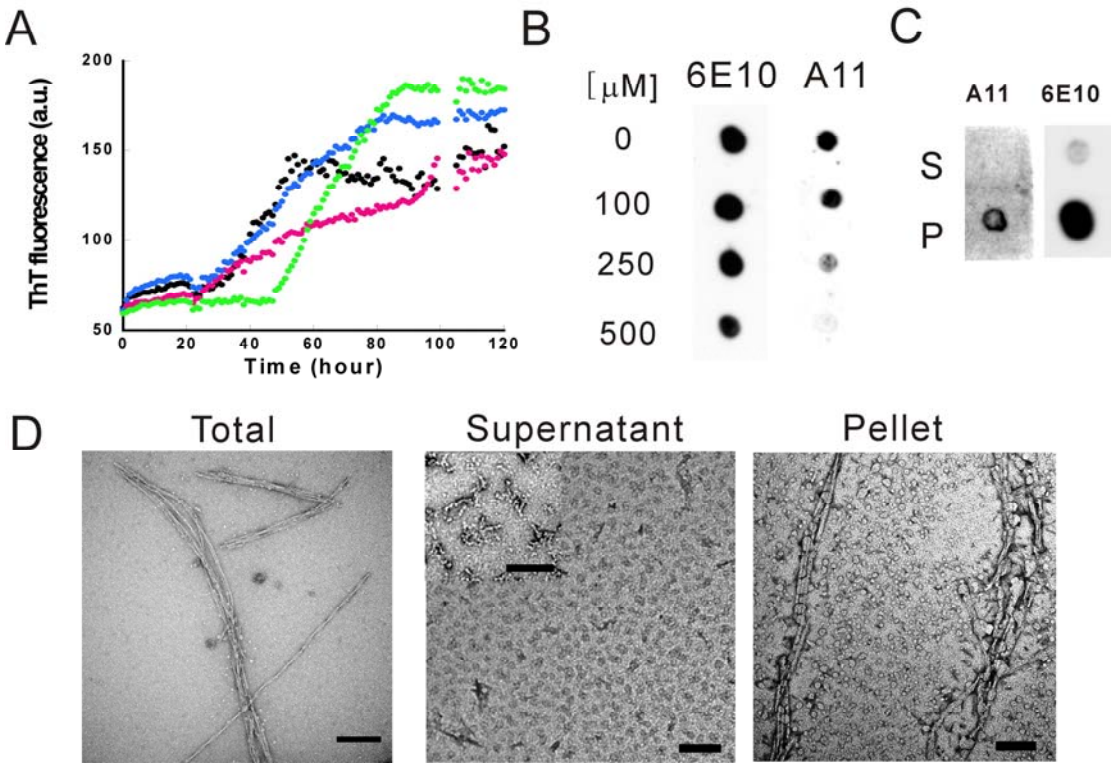
Supplementary Fig. 4



Supplementary Fig. 5



Supplementary Fig. 6



Supplementary Fig. 7