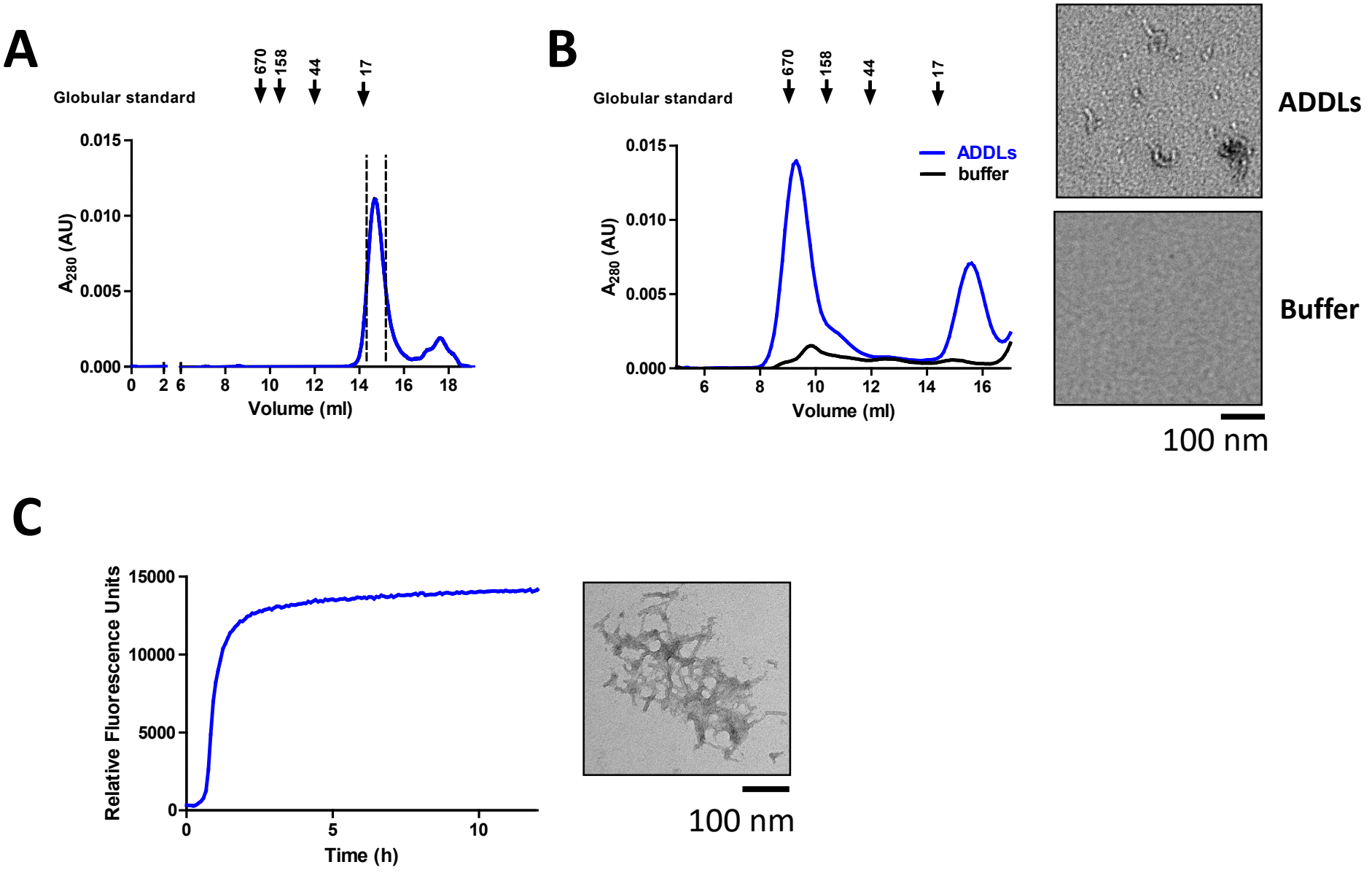
Supplementary Figure 1. Characterization of distinct Aβ preparations. (A) To generate aggregate-free monomer, Aβ1-40 was incubated at room-temperature in 7 M GuHCl for 16 hours, and monomer isolated using a Superdex 75 column eluted with 50 mM ammonium bicarbonate buffer, pH 8.5. Absorbance was measured at 280 nm and dashed lines indicate the fractions collected. **(B)** Aβ1-42 monomer was isolated and allowed to aggregate as described in the Material and Methods. Aggregation was monitored by following ThT fluorescence. The reaction was stopped after 12 hours, and negative contrast EM revealed the presence of abundant amyloid fibrils. The scale bar is 100 nm. **(C)** Aβ-derived diffusible ligands (ADDLs) were prepared as described in the Material and Methods and characterized by SEC and negative contrast EM. The buffer control is shown in the lower panel. The scale bar is 100 nm.

Supplementary Figure 2. PrP grafted antibodies immunoprecipitated PrP^{Sc} from scrapie infected mouse brain and recombinant PrP binds ADDLs, but not Aβ monomer. (A) Homogenates from scrapie infected mouse brain or an uninfected mouse brain were incubated with PrP grafted antibodies. Paramagnetic beads alone and the b12 antibody were used as negative controls and the anti-PrP mouse mAb, ICSM-35, was used a positive control. Human grafted b12 antibodies and mouse mAb were captured onto paramagnetic beads coupled to anti-human or anti-mouse IgG, respectively. Precipitated PrP was detected via Western Blot using the anti-PrP mAb, 6D11. Molecular weight markers are indicated on left, and the antibodies used for IP are indicated at the bottom of the gel. PrP specific bands migrate between ~25-35 kDa and blots are cropped accordingly. Results are representative of two independent experiments. **(B)** Direct binding of ADDLs, Aβ fibrils, and Aβ monomers was assessed using the same ELISA-like assay employed in Figure 1, except 6E10 was used to

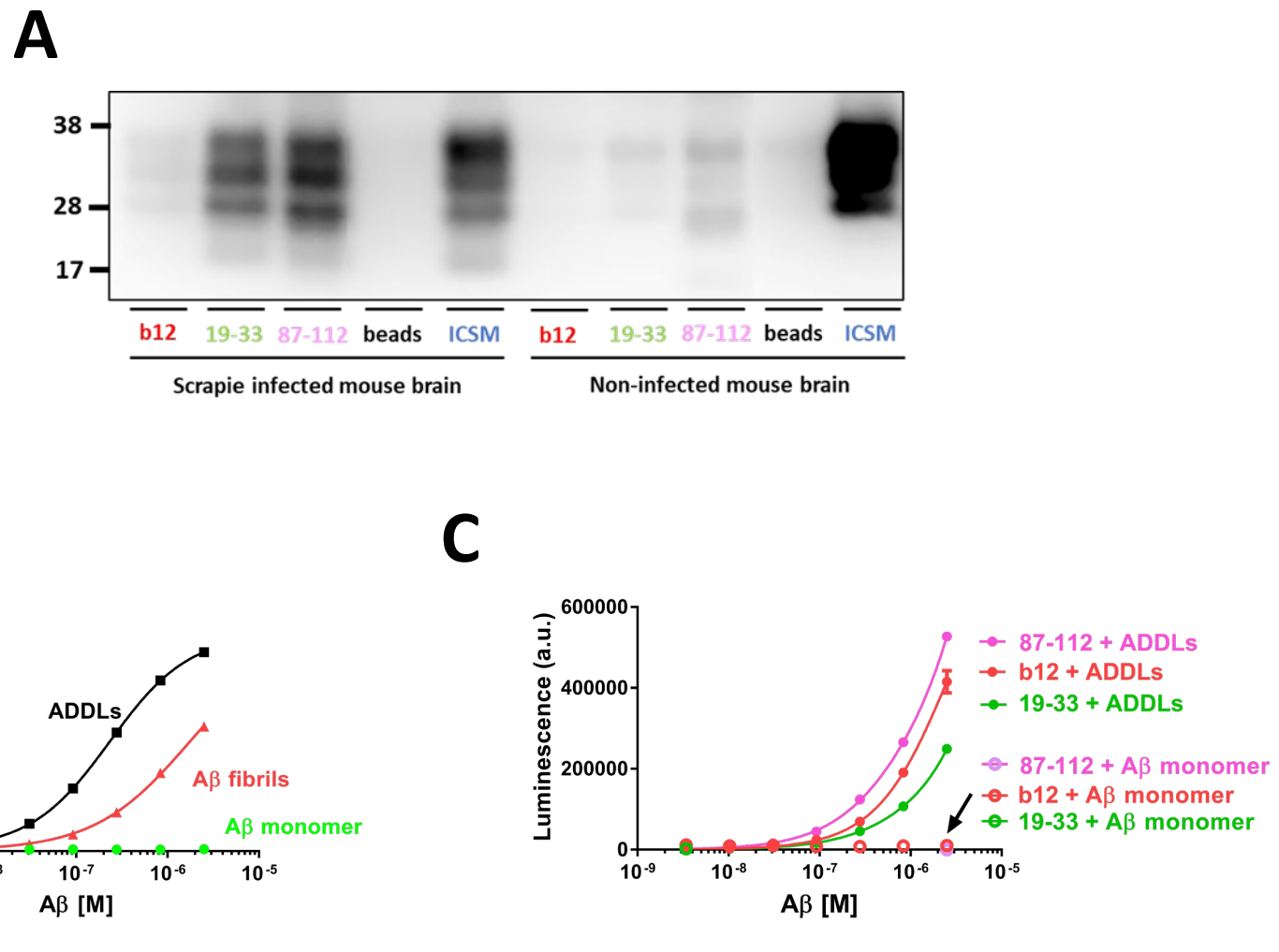
detect bound Aβ. Again, ADDLs bound PrP in a dose-dependent manner, whereas Aβ monomers showed little affinity for PrP. Each data point is the average ± SEM of three independent experiments. **(C)** Antibodies grafted with and without PrP motifs 19-33 and 87-112 were coated onto microtiter plate wells and incubated with ADDLs (filled circles) or Aβ monomers (open circles) for 1 hour, and detected using 6E10. Red circles denote the parent b12 control antibody. Antibodies grafted with PrP motifs 19-33 and 87-112 are colored in light green and pink, respectively. Each data point is the average ± SEM of two technical replicates. Where the error bars are not visible, the SEM is smaller than the size of the symbol. Results are representative of at least 2 individual experiments.

Supplementary Figure 3. Recombinant PrP 23-231 and PrP 23-109 (N1) bind ADDLs similarly. PrP_{23-109} (N1) and PrP_{23-231} were Western blotted with mAbs directed to **(A)** *Site I* (MI0131) and **(B)** *Site II* (ICSM35). PrP_{23-109} contains both binding *Sites I and II*, that are present in PrP_{23-231}. **(C)** Direct binding of ADDLs, Aβ fibrils, and Aβ monomer was assessed using an ELISA-like microtiter plate assay. PrP_{23-109} and PrP_{23-231} were coated at 0.5 µM. Aβ was added for 1 hour and bound Aβ was detected with biotinylated anti-Aβ mAb 4G8. ADDLs bind PrP in a dose-dependent manner, whereas Aβ monomers and fibrils show little affinity for PrP. The binding curves of both PrP constructs 23-109 (open symbols, dashed line), and 23-231 (filled symbols, continuous line) are highly similar.

Supplementary Figure 1



Supplementary Figure 2



Supplementary Figure 3