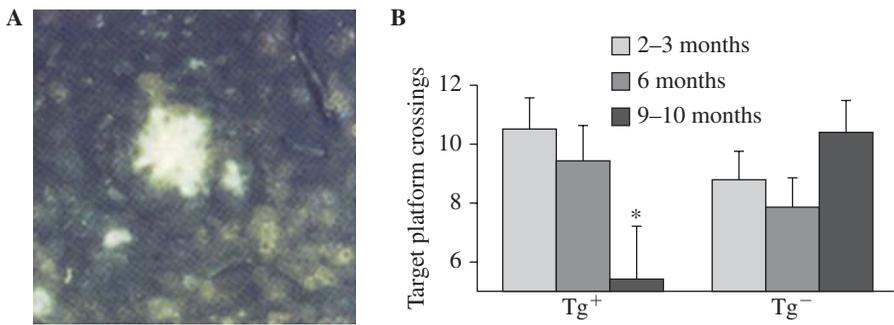
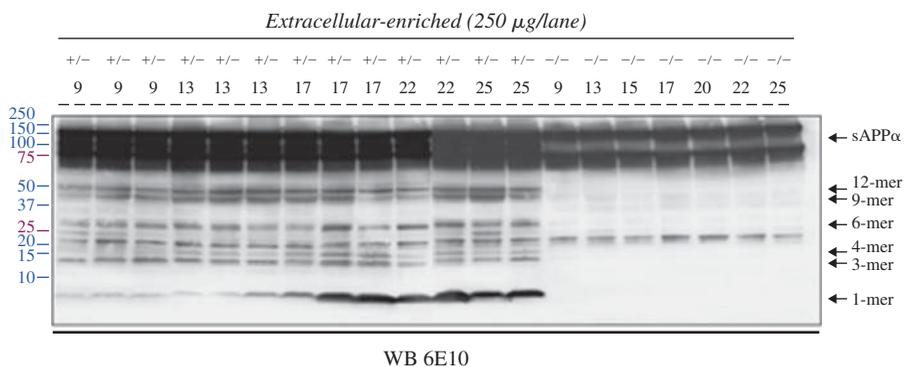


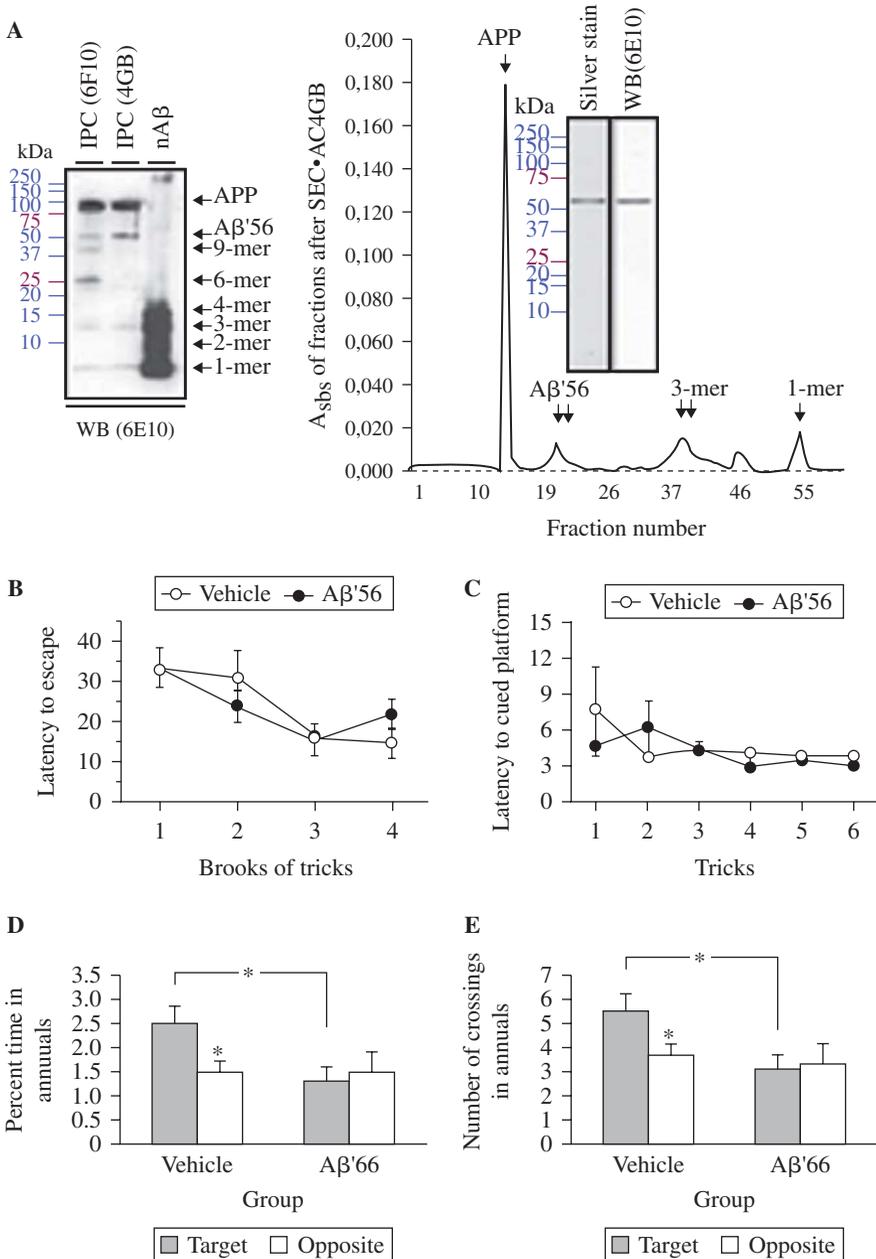
**FIGURE 11.1** Age-related changes in the brain associated with Alzheimer disease. (A) Plaques and tangles in a human brain from a patient with Alzheimer disease. Plaques are extracellular deposits of proteins (left panel); neurofibrillary tangles are fibrous collections of proteins within neurons (right panel). (From K. H., Ashe, Alzheimer's disease: transgenic mouse models, in *Encyclopedia of Neuroscience* with permission of Elsevier. Copyright © 2009). (B) The heterogeneity of A $\beta$  proteins in the brain becomes more complex with age. The amyloid precursor protein (APP) undergoes posttranslational processing by  $\alpha$ -,  $\beta$ -, and  $\gamma$ -secretases to generate A $\beta$  and other APP cleavage products. Monomers and trimers have been identified inside neurons. Larger assemblies of A $\beta$  are found extracellularly, including A $\beta$ \*56, a potentially important A $\beta$  oligomer involved in disrupting memory formation. The monomers and oligomeric forms of A $\beta$  are soluble in aqueous buffers. In contrast, the plaques contain A $\beta$  fibrils that are insoluble in aqueous and detergent-containing buffers. Solubilized plaques contain monomers and low- $n$  oligomers.



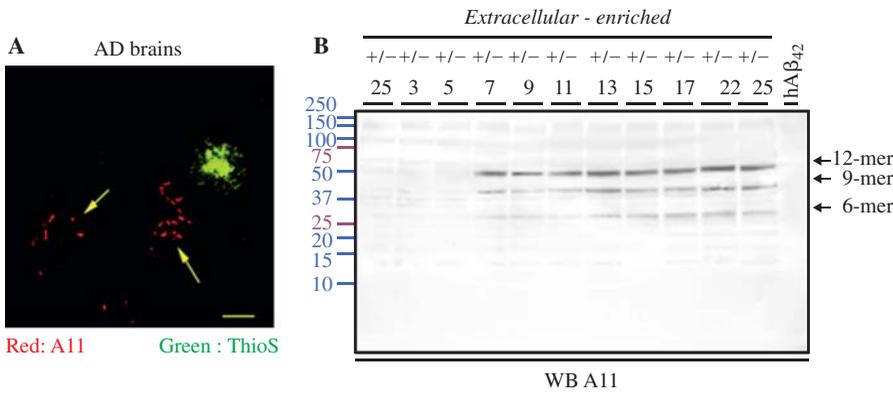
**FIGURE 11.2** Amyloid plaques and age-dependent memory loss in the Tg2576 APP transgenic mouse model of Alzheimer disease. (A) Plaques in a 354-day-old mouse stain with thioflavin S, a dye that binds  $\beta$ -pleated sheets. (B) With increasing age, transgene-positive, but not transgene-negative animals performing in a water maze show a dramatic decrease in platform crossings. (From [17], with permission of AAAS.)



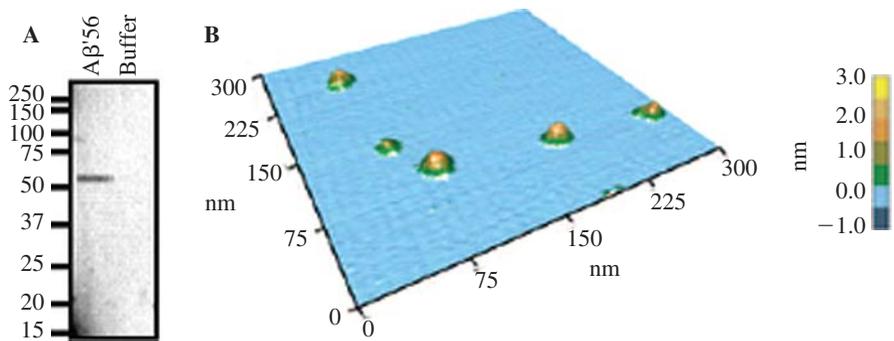
**FIGURE 11.8** Soluble extracellular-enriched A $\beta$  species assessed by immunoblot using 6E10 in Tg2576 mice between 9 and 25 months of age. The levels of the 56-kDa species, corresponding in size approximately to a theoretical A $\beta$  (1–42) dodecamer, remain relatively stable during this time period. In contrast, levels of soluble and insoluble Ab1–42 increase 50- and 100-fold, respectively [19]. (From [9], with permission of Macmillan Publishers Ltd.)



**FIGURE 11.9** Application of Aβ\*56 into the lateral ventricles impairs spatial reference memory in healthy, young rats. Aβ species were immunoaffinity-purified using monoclonal antibodies 6E10 or 4G8 (A, left), then separated by size-exclusion chromatography to yield fractions containing Aβ\*56 (A, right). When injected ICV into rats pretrained in the Morris water maze, Aβ\*56 had no effect on the animals' ability to locate a visible (B) or hidden (C) escape platform. However, in probe trials administered 24 hours later (after a second injection of Aβ\*56 or vehicle), Aβ\*56-treated rats spent significantly less time in the target quadrant than did vehicle-injected rats (D,E). hAβ42, Synthetic human Aβ (1–42) peptide was used as a size marker. (From [9], with permission of Macmillan Publishers Ltd.)



**FIGURE 11.10** The anti-oligomer antiserum A11 recognizes A $\beta$ \*56. (A) A11 staining of non-plaque-associated oligomers in brain tissue from an Alzheimer patient; (B) staining of high-N A $\beta$  oligomers with the anti-oligomer antiserum, A11. Note that the human A $\beta$  42 (hA $\beta$ 42) standards are not detected with the A11 antiserum (far right lane). [(A) From Kaye et al., *Science*, 2003; Apr 18; 300(5618);486–489, with permission of AAAS. (B) from [9], with permission of Macmillan Publishers Ltd.]



**FIGURE 11.11** Ex situ AFM height image and size distribution of Aβ\*56. (A) western blot analysis (6E10 antibody) of wild-type Aβ\*56 purified from detergent-soluble forebrain lysates of Tg2576 mice by tandem immunoaffinity/size-exclusion chromatography; (B) representative 1-μm<sup>2</sup> atomic force microscopy image of Aβ\*56, demonstrating ellipsoidal shapes. (From [35]. Copyright © 2007 American Society for Biochemistry and Molecular Biology.)