Soluble Aβ oligomers are suggested to exert the major pathological effects within Alzheimer's disease (AD). In strong support of this notion, immunological targeting of Aβ oligomers in AD mice-models shows that memory impairments can be restored without affecting the total burden of Aβ deposits. Consequently, a specific immunological targeting of Aβ oligomers is of high therapeutic interest. Previously the generation of conformational-dependent oligomer specific anti-Aβ antibodies has been described. However, to avoid the difficult task of identifying a molecular architecture only present on oligomers, we have focused on a more general approach based on the hypothesis that all oligomers expose multiple identical epitopes and therefore would have an increased binding to a multivalent receptor. Using the polyvalent IgM immunoglobulin we have developed a monoclonal anti-Aβ antibody (OMAB). OMAB demonstrates a weak interaction with Aβ monomers and dimers with fast kinetics. However, as an effect of avidity, its interaction with Aβ-oligomers results in a high affinity complex. Through this mechanism a high selectivity towards Aβ oligomers is acquired and OMAB fully inhibits the cytotoxic effect exerted by Aβ(1-42) at highly substoichiometric ratios. Through a screen of endogenous anti-Aβ IgM auto-antibodies from a group of healthy individuals we show that all displays a strong preference for oligomeric Aβ. Taken together we provide a simple and general mechanism for targeting of oligomers without the requirement of conformational-dependent epitopes. In addition, our results suggest that IgM anti-Aβ auto-antibodies may exert a more specific protective mechanism in vivo than previously anticipated.