

W0252

Modeling Studies of Anti-amyloid Antibodies Bound to A β . Anna S. Gardberg, Nathan Tanner, Israel Huff, Ronald Wetzel, Chris Dealwis, Dept. of Biochemistry, Cellular and Molecular Biology, Univ. of Tennessee, Knoxville, TN.

WO1 and WO2 are conformation-specific monoclonal IgMs that bind the fibril state of the amyloid A β peptide (1-40), as well as amyloid fibrils of other disease-related proteins. Significantly, the antibodies (abs) do not bind the soluble, monomeric state of A β (1-40) or the precursor form of other amyloids. The Abs have been sequenced and analyzed to study the role of the unique and unusual residues in WO1 and WO2. Three-dimensional models of the Fv fragments of WO1 and WO2 were generated with Web Antibody Modeling. A left-handed, six-rung structural model of the A β amyloid core was evaluated by docking it with the Fv models of WO1 and WO2. The results predict binding of WO1 and WO2 to A β *via* hydrogen bonds and ionic pairing between the CDRs and the protofilament face consisting of residues 23-27. WO1 and WO2 bind the model in similar configurations; binding to WO2 is predicted to rely less on ion pairing. The results support the A β model. Binding of WO1 experimentally determined to be sensitive to salt and pH conditions, suggesting electrostatic interactions are important for binding; this result supports the proposed docking model for WO1.