The ability of antibodies to recognize target antigens with high affinity and specificity is central to their widespread use in diagnostic and therapeutic applications. The binding activity of antibodies is encoded in up to six of their solvent-exposed peptide loops that directly contact antigens. Antibodies are generated by randomly varying the sequences of their antigen-binding loops and selecting rare variants that are complementary to target antigens. Due to the daunting number of possible antibody sequences with variation only within their antigen-binding loops ($>10^{30}$ variants), it seems unlikely that the needles (antibodies with desired binding activity) in the haystack (all possible antibody variants) can be predicted instead of being selected. We have challenged this conventional wisdom by reducing the seemingly intractable problem of designing multiple antibody loops to cooperatively bind antigens to a tractable one in which we design individual antibody loops with binding activity. Using this simplified design strategy, we find that high-affinity antibodies can be readily engineered to recognize diverse misfolded (aggregated) proteins linked to neurodegenerative disorders by targeting unique structural features within such protein antigens. Our innovative approach generates single- and multidomain antibodies that recognize misfolded proteins not only based on their sequence, but also based on their conformation. We also find that our antibodies recognize sequence epitopes that are difficult to target using conventional approaches for selecting antibodies, and that these novel antibodies are unusually potent inhibitors of protein aggregation. Our long-term goal is to use these and related antibodies to prevent and/or reverse toxic protein aggregation associated with several neurodegenerative diseases.