

Recombinant Human Monoclonal Antibodies for the Disease-Modifying Treatment of Neurodegenerative Diseases

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Abnormal protein misfolding, or aggregation of endogenous proteins in the brain characterizes several neurodegenerative diseases including Alzheimer's and Parkinson's diseases as well as ALS and frontotemporal degeneration. The abnormal protein aggregates are stable, they can be involved in cell-to-cell propagation of pathology, and some forms can adopt conformations with neurotoxic activities. They include, for example, beta-amyloid, tau, alpha-synuclein, TDP-43, C9orf72, SOD-1 and huntingtin. Recombinant human monoclonal antibodies designed to selectively target pathological neo-epitopes within the abnormal structures can be effective in neutralizing toxicity, in blocking cell-to-cell propagation and in removing abnormal aggregates by microglia-mediated phagocytosis. Pharmacologic activities of therapeutically effective antibodies include high selectivity for abnormal neo-epitopes over normal physiological forms of the proteins, high affinity, long plasma-half life, the abilities to diffuse through the blood-brain-barrier and migrate through brain parenchyma, as well as to bind, over extended time periods, to the target structures. Immunologically active Fc regions are required for triggering Fcγ-receptor-mediated phagocytosis. Aducanumab, an example for such a recombinant human monoclonal antibody, removes brain beta-amyloid in a time- and dose-dependent fashion. Antibody-mediated removal of beta-amyloid was associated with initial signs of clinical stabilization in patients with Alzheimer's diseases (Sevigny *et al.*, Nature 2016). Aducanumab is currently in clinical phase 3 development for the treatment of Alzheimer's disease. The results of our studies provide the scientific basis for a technology in recombinant human monoclonal antibody design resulting in a novel class of efficacious and safe biopharmaceutical products.