

A recombinant human IgM prevents neuronal injury in multiple animal models of CNS disease

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Abstract

We discovered rHIgM12, a recombinant form of a neuron-binding human antibody that induced neurite extension and neuronal protection *in vitro* and proved effective in delaying deterioration in multiple animal models of CNS injury. Identified in a patient with Waldenstrom's macro globulinemia, the antibody was sequenced and re-expressed in CHO cells to generate a fully human GMP-quality monoclonal antibody. We tested rHIgM12 in three experimental models of CNS injury: 1) chronic, demyelinating/axonal model of multiple sclerosis induced by Theiler's virus infection; 2) genetic model of ALS caused by transgenic expression of superoxide dismutase (SOD) human mutation; and 3) a model of thromboembolic stroke. In the chronic demyelinating axonal injury model, a single peripheral treatment of antibody improved spontaneous neurological function and prevented axonal loss at the mid-thoracic spinal cord. In the ALS model, antibody treatment prolonged survival and prevented loss of NeuN-stained anterior horn cells. In the thromboembolic stroke model, antibody treatment given 30 minutes post ischemic insult, improved neurologic function closely mimicking clinical application. Studies of mixed brain glial cells *in vitro* in normoxic and hypoxic conditions showed rHIgM12 in the media activated microglial cells and prevented cell apoptosis by down-regulating caspase expression. Using surface plasmon resonance (SPR), we quantitated binding kinetics of therapeutic antibodies to antigens within the cell membrane. In summary, these results present the first clear demonstration of a recombinant human monoclonal antibody that can ameliorate neuronal injury across experimental models of neuron-destructive human diseases during the evolution of the disease process.

Biography

Moses Rodriguez is a professor of Neurology and Immunology. He received his MD from Northwestern University. After Neurology residency at Mayo, he completed an NIH fellowship at UCSD and the Scripps Research Institute. His scientific interests include CNS remyelination and experimental neuropathology. Currently principal investigator of five grants and author of >370 peer-reviewed papers, he directs a prestigious National MS Society Center of Excellence and the Mayo Center for Multiple Sclerosis and Central Nervous System Demyelinating Diseases Research and Therapeutics. He is a Mayo Clinic Distinguished Investigator and received the Frontiers in Neuroscience award from the American Academy of Neurology.

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