Therapeutic Methods, Treatment of Genetic Diseases

AB008. Bifunctional antibody as a surrogate molecular linker for the treatment of alpha-dystroglycan related muscular dystrophies

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Background: Alpha-dystroglycan related muscular dystrophies are a subgroup of rare congenital muscular dystrophies that present with a spectrum of neurologic and physical impairments. Eighteen genes have been identified that contribute to the development of these diseases; all cause hypoglycosylation of O-linked glycans on alpha-dystroglycan that renders it defective in binding several ligands (e.g., laminin-211 in skeletal muscles, agrin in neuromuscular junctions, neurexin in the central nervous system and pikachurin in the eye).

Methods: To restore the link between the extracellular matrix and sarcolemma, a novel bifunctional antibody designed to recognize laminin-211 and beta-dystroglycan was developed. Such a bifunctional antibody could potentially then act as a surrogate molecular linker to mimic the function of alpha-dystroglycan. Recombinant human laminin-2 (alpha LG-4/5 domain) and beta-dystroglycan (extracellular domain) were generated and served as immunogens for the generation of antibodies recognizing the respective targets. The Vh and Vl sequences of the corresponding antibodies to laminin-2 and beta-dystroglycan were then engineered into a bifunctional antibody format. Resultant bifunctional antibodies were selected based on their characteristics and functionality using a variety of assays.

Results: Treatment of Largemyd-3j mice, a mouse model of alpha-dystroglycanopathy, with the bifunctional antibodies demonstrated significant improvements in muscle function as assayed using grip strength and wire hang assays. Treated mice also showed dose-dependent decreases in muscle membrane damage (by Evans Blue dye staining) following exercise-induced injury.

Conclusions: Collectively, the results provide preclinical proof-of-concept of a bifunctional antibody to laminin-211 and beta-dystroglycan as a potential treatment for the non-neurological forms of alpha-dystroglycan related muscular dystrophies.

Keywords: Alpha-dystroglycanopathy; bispecific antibodies; congenital muscular dystrophies; laminin-211; alpha-dystroglycan

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