A Specific Glycan Biomarker and Potential   Drug Target for Amyotrophic Lateral Sclerosis (ALS) (BGN)
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Amyotrophic Lateral Sclerosis (ALS) also named Lou Gehrig's disease, is a fatal neurodegenerative disease characterized by the progressive degeneration of cortical brain neurons, brainstem and, upper and lower motor neurons. Within short time, the disease leads to limb paralysis, compromise of speech and swallow, respiratory failure and death. The disease is relatively rare with an incidence of 2 per 100,000/year and prevalence average 5.2 per 100,000. Currently about 30,000 have the disease in the USA and another 30,000 in Europe. The cause of ALS is unknown and to date there is no cure. Existing treatments may extend life for a couple of months are palliative and multi-disciplinary aimed to improve as much as possible the patient quality of life. The diagnosis of ALS is very difficult and to date there is no test or procedure, which can ultimately diagnose ALS. It is through a clinical examination and series of tests for ruling out other diseases that mimic ALS, that a diagnosis can be established. Therefore the diagnostic of ALS is very costly, cumbersome and stressing to the patient and its family. It is estimated that the amount of people undergoing initial diagnosis of ALS reach 20,000/year in the USA alone with an annual cost for USA and Europe alone of around USD 100 M if considering only initial diagnosis. Early and accurate diagnosis of ALS is of outmost importance to enable the patient and care surroundings to prepare and to receive supportive treatment. Robust biomarkers might also help to assess drug efficacy in trials. Hence, biomarker discoveries will change the way ALS is investigated and how patients are treated.

The Technology
Increasing evidence points to the involvement of the immune system in ALS pathogenesis, with accumulation of IgG in the spinal cord motor neurons and in pyramidal cells within the motor cortex of ALS patients. It has been suggested that by simultaneously binding antigens through their variable domains (F(ab)2) and interacting through their Fc domain with Fcc receptors (FccR) on immune cells, IgG play a role in motor neuron degeneration by activating an immune response. The binding capacity of IgG to Fc receptors (CD16) was found to be lost after cleaving or preventing glycosylation at a single site in the IgG Fc domain. Furthermore, the nature of the glycans affects the affinity of the CD16 interaction and thus governs antibody cytotoxicity. The findings that aberrant glycosylation relates to pathogenesis in other neurodegenerative diseases encouraged us to explore the glycome of ALS in patient sera. We found high levels of sialylated glycans and low levels of core fucosylated glycans in serum derived N-glycans of patients with ALS, compared to sera from healthy volunteers and we further identified a distinct glycan, A2BG2. We suggest that the frequent presence of IgG containing a neuron-antigenic domain and an Fc domain carrying the A2BG2 glycan in ALS patients induces neuronal death and that IgG glycans such as A2BG2 may serve as a biomarker for the disease.

Applications
Biomarker for early detection of ALS
Potential Target for ALS therapeutics

Patent Status
Pending

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