# GILZ-mimics as novel therapeutic agents for progressive multiple sclerosis

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**Abstract:**
Multiple sclerosis (MS), a leading cause of neurological disability is an inflammatory demyelinating disease of the central nervous system (CNS). The clinical course of MS is highly variable ranging from isolated neurologic episodes to frequently relapsing or progressive disease. Currently there are no effective treatments for progressive MS. The long-term goal of this project is to evaluate a novel therapeutic strategy for progressive MS. Under physiological conditions signaling via the transcription factor, nuclear factor-kappa B (NF-κB) and glucocorticoid (GC) stimulation pathways regulate the immuno-inflammatory responses of the CNS resident glial cells. While NF-κB induces transcriptional activation, signaling via GC receptor functions to suppress immune responses. Persistent activation of NF-κB in the glial cells precipitates neuronal degeneration and axonal loss characteristic of progressive MS. Interactome analysis between the GC and NF-κB pathways suggested a novel strategy to inhibit NF-κB. Glucocorticoid-induced leucine zipper (GILZ) is a GC inducible protein that binds p65, the functionally critical subunit of NF-κB, and prevent transactivation of pathological mediators. The sites of interaction are localized to the proline rich region of the GILZ protein and the p65 transactivation domain. A 23 residue GILZ peptide prevented nuclear translocation of p65 and suppressed disease in an animal model of MS. Structurally GILZ peptide adopted polyproline type II (PP$_{II}$) helical conformation, a favorable feature for drug development. The objective of this study is to optimize the lead peptide and develop drug like analogs. Specific features of the GILZ-p65 interactions were adapted in the design of over 25 GILZ analogs such that each exhibit optimum PP$_{II}$ helix, bind p65 transactivation domain and potentially accommodate modified residues that enhance the binding specificity with the p65. The analogs were ranked after passing through the Lipinski filter to determine the drug like properties. The top ranked analogs will be evaluated for functional efficacy.