

Targeted Secretion Inhibition (TSI) as a Novel Therapeutic Strategy in Plasma Cell Disorders

Abstract :

Multiple myeloma (MM) and AL amyloidosis (AL) are diseases of clonal plasma cell (PC) proliferation and hyper-secretion of monoclonal immunoglobulin (paraprotein) and/or free light chain (FLC). MM is the second most frequent blood cancer in the western world, with a peak incidence in the 7th decade of life. AL is a rare, rapidly fatal disorder characterized by deposition of amyloidogenic FLC in target organs, leading to failure and eventually death. Despite novel therapies such as proteasome inhibitors (PI), MM/AL are incurable. My prior work showed that MM cells have baseline excess protein synthesis/misfolding in the face of limited proteasome-mediated degradation. PI exacerbate this imbalance, leading to proteotoxicity and apoptosis. Proteotoxicity similarly underlies PI sensitivity in AL. While PI are effective in treating MM/AL, resistance is inevitable, underscoring an important, unmet therapeutic need. Botulinum toxin (BoNT) proved effective in reducing paraprotein secretion in PC, suggesting its utility in MM/AL treatment. I hypothesize that: targeted inhibition of paraprotein/FLC secretion via chimeric BoNT is a feasible and effective therapeutic strategy in MM/AL, leading to decreased paraprotein/FLC secretion and direct cytotoxicity against MM/AL cells via exacerbation of baseline proteotoxicity. In this proposal, I present an experimental plan to test these hypotheses in well-established MM/AL *in vitro* and *in vivo* models. The support of Harvard Catalyst and IPSEN is crucial for the successful design and proof of concept of chimeric BoNT targeting paraprotein/FLC in MM/AL, with the ultimate goal of bench to bedside translation of chimeric BoNT for patients with MM/AL and/or other paraprotein/FLC-related disorders.