Preliminary Title: Discovery of Selective, CNS-Penetrant Covalent Inhibitors of Bruton's Tyrosine Kinase for the Treatment of Multiple Sclerosis.

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Abstract:

Multiple sclerosis (MS) is an inflammatory and degenerative disorder of the central nervous system (CNS) that presents as either a relapsing-remitting or progressive condition. B Cells are clinically validated targets for the treatment of MS as demonstrated by B cell-depleting monoclonal antibodies. Bruton's tyrosine kinase (BTK) is a critical signaling molecule in B cells, where it mediates proliferation and differentiation, and in myeloid cells where BTK promotes inflammation that can drive disease progression. Inhibition of BTK in the CNS and periphery may recapitulate modulatory effects on B cells without cell depletion while also allowing for additional therapeutic benefits via reduction of inflammation mediated by myeloid cells. This presentation will describe the discovery of a series of CNS-penetrant covalent inhibitors of BTK, which exhibit improved TEC-family kinase selectivity as compared to current clinical molecules via specific interactions within the ATP binding site.