Discovery of JNJ-64264681: a Potent and Selective Covalent BTK Inhibitor for Treating Hematological Malignancies

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Bruton's tyrosine kinase (BTK) is a Tec family kinase that plays an essential role in B-cell receptor (BCR) signaling as well as Fcγ receptor signaling in leukocytes. Pharmacological inhibition of BTK has been shown to be effective in treating hematological malignancies and is hypothesized to provide an effective strategy for the treatment of autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus. In this talk we will discuss the discovery and preclinical properties of JNJ-64264681 a covalent, irreversible BTK inhibitor with potent whole blood activity and exceptional kinome selectivity. BTK inhibitors were profiled by determining the second order rate constant k_{inact}/K_I, demonstrating the improvement in potency was achieved by optimizing the initial reversible binding affinity (K_I) and not to an increase in electrophile reactivity. JNJ-64264681 demonstrated excellent oral efficacy in both cancer and autoimmune models with sustained *in vivo* target coverage amenable to once daily dosing and has advanced into human clinical studies to investigate safety and pharmacokinetics.