NX-5948, a Selective Degradator of BTK, Significantly Reduces Inflammation in a Model of Autoimmune Disease

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Introduction
- Bruton’s tyrosine kinase (BTK) transduces signals downstream of the B cell receptor (BCR), toll-like receptors, and Fc receptors in B cells and myeloid cells.
- Overexpression of BTK in B cells can lead to hyperactive BCR signaling, plasma cell generation, and autoantibody secretion
- Ablation of B cells and autoantibody mediated tissue damage are hallmarks of autoimmune diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA).
- NX-5948 is a chimeric targeting molecule (CTM) that engages the E3 ligase cereblon (CRBN) to promote the selective degradation of BTK

Results
- NX-5948 is a potent degrader of BTK in primary human B cells (DC50 = 0.34 nM) and inhibits BCR signaling
- NX-5948 is highly selective for BTK degradation by proteomic analysis with limited activity toward the CRBN neo substrate Aiolos (DC50 > 10 µM)
- In vivo, once oral administration of NX-5948 in mice and cynomolgus monkey demonstrated potent degradation of BTK in circulating B cells
- NX-5948 demonstrated significant anti-inflammatory activity and resulted in improvement of clinical symptoms in a mouse collagen-induced arthritis (CIA) model

Conclusions
- NX-5948 mediates potent anti-inflammatory activity via BTK degradation with resultant inhibition of B cell activation
- Preclinical animal models support clinical development of NX-5948 to treat autoimmune diseases

NX-5948 Catalyzes Rapid BTK Degradation in Lymphoma Cells

NX-5948 is a Potent Inhibitor of Anti-IgM-Mediated B Cell Activation

NX-5948 is a Potent Inhibitor of TLR7-Mediated B cell Activation

NX-5948 is a Selective BTK Degrader

NX-5948 is Efficacious and Well-Tolerated in a Mouse Collagen-Induced Arthritis Model and Suppresses Antibody Titers and Cytokine Levels