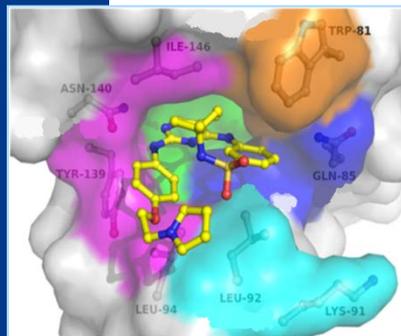


Novel BRD4/JAK2 Dual Inhibitors as Cancer Therapeutics



Our technology is a family of small molecules that inhibit Bromodomain-containing protein 4 (BRD4) at an IC_{50} of at least 4nM. BRD4 is an epigenetic regulator that supports aberrant proliferation through promotion of oncogenes such as c-Myc and Bcl-2. As such, inhibitors of BRD4 are being explored for the treatment of solid and hematologic cancers. In addition to inhibiting BRD4, our compounds are potent inhibitors of JAK2 and FLT3, and several groups have shown synergistic promotion of apoptosis in cancer cells both in vitro and in vivo when the kinase and bromodomain proteins are inhibited together.

COMMERCIAL OPPORTUNITY

- A synergistic increase in apoptosis occurs when myeloproliferative neoplasm primary cells are treated simultaneously with inhibitors of BRD4 and JAK2, and when AML cell lines are treated with inhibitors of BRD4 and FLT3. Moreover, in vitro studies suggest that JAK1/JAK2 inhibitor resistant cells remain sensitive to BRD4 inhibitor-induced apoptosis suggesting our dual inhibitor may be useful in JAK1/JAK2 sensitive or resistant cancers.
- The market for BRD4 inhibitors is attractive as evidenced by five companies developing small molecules that inhibit BRD2-4 and BRD3-4 for hematologic malignancies, NUT midline carcinoma, and advanced solid cancers. At least one inhibitor, OncoEthix's OTX015, has successfully completed Phase I clinical studies, suggesting that inhibition of BRD4 is not deleterious. Moreover, Merck acquired OncoEthix in December 2014 for \$110M upfront and \$265M in future milestones.
- Our dual BRD4/JAK2 inhibitors have IC_{50} s for JAK2 that are comparable to those of the JAK2 inhibitors currently in the clinic and on the market. Ruxolotinib, Incyte's and Novartis' JAK1/JAK2 inhibitor, has already been approved for myelofibrosis, a rare bone cancer, as well as psoriasis, and rheumatoid arthritis. Several other JAK2 inhibitors are in Phase II & III clinical trials, alone and in combination, for a number of solid tumors and hematologic malignancies.

TECHNOLOGY

A kinase inhibitor library was screened to identify potential BRD4-inhibitor scaffold(s). It was known that the Bis-anilinopyrimidine scaffold in TG101209 interacts with the hinge-region of the ATP site of JAK2 and FLT3, and we showed it is also necessary for binding to residues in the KAc region of all bromodomain and extraterminal proteins (BETs). IC_{50} s were determined by MTT assay after MM1.S cells were treated with the compound for 72 hours, and western blots of pSTAT2 (JAK2) and c-MYC (BRD4) post six hours of treatment validated the dual kinase inhibitory properties. Over 100 compounds have been synthesized; the most promising candidates are highly selective for BRD4, with four new compounds with IC_{50} s below 4nM. Additionally, one compound is currently being analyzed in a xenograft model of multiple myeloma.

PUBLICATION/PATENT

- Provisional patent applications have been filed for Drs. Schönbrunn, Lawrence, and Lawrence beginning on 8/3/2014

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LICENSING OPPORTUNITY

