Novel Small Molecule Inhibitors of IRE-1 for the Treatment of B-cell Cancer

This technology is a family of small molecule inhibitors of the IRE-1 enzyme, which is a novel target for chronic lymphocytic leukemia (CLL), the most common adult leukemia, and mantle cell lymphoma (MCL). These novel inhibitors target IRE-1 activity in whole cells in the nanomolar range and kill B-cell cancer cell lines and primary patient samples of CLL. One compound was found to effectively reduce tumor burden in a mouse model of CLL without any observed acute or systemic toxicity. This compound also exhibits strong cytotoxic synergy in cell culture with ibrutinib, an FDA-approved B-cell cancer therapeutic.

COMMERCIAL OPPORTUNITY

- CLL is the most common type of adult leukemia affecting 38% of all adult leukemia patients. An estimated 15,680 new cases are expected to occur in 2013 according to NCI figures with an annual prevalence of over 130,000 patients.
- CLL is considered an incurable disease with patients cycling through many currently available therapies depending on their age, physical fitness, and responses to previous therapies. This suggests that many patients take most therapies and that the market size for our IRE-1 inhibitors might be comparable to the currently approved therapies.
- This market size can be approximated from the estimated 2013 annualized sales of first-line therapy bendamustamine (Treanda, Cephalon/Teva Pharmaceuticals) at $162MM in the CLL market alone and second-line CLL therapy ofatumumab (Arzerra, GSK/Genmab) at $119MM.
- The market is attractive as evidenced by new CLL therapies with novel targets (ibrutinib (Approved), Pharmacyclics/Janssen and idelalisib (Phase 3 studies), Gilead Sciences).
- Our 2nd and 3rd generation derivatives work as single agents and synergize with ibrutinib in cell culture studies, and act upon a novel molecular target, creating potential for a first-in-class CLL therapeutic regimen.

TECHNOLOGY

Our family of inhibitors target the IRE-1/XBP-1 arm of the unfolded protein response (UPR) pathway; when the UPR is dysfunctional, as it is in CLL, it leads to increased protein degradation and escape from the stress-induced apoptosis that is often triggered by chemotherapy treatment. Proof of concept studies investigating the efficacy of targeting this pathway were done using 1st generation compounds in a transgenic mouse model of CLL and produced a response analogous to a partial clinical response in humans, as defined by 1996 NCIWG guidelines. Novel 2nd and 3rd generation derivatives inhibit XBP-1 expression in human cancer cell lines with IC_{50} values between 0.1 and 1.0μM, (~10 to 100-fold more potent than the 1st gen.) and exhibit cytotoxic IC_{50} values of ~30-32μM in CLL cell lines (~3-fold more potent than the 1st gen.). Combination studies in B-cell cancer cell lines also demonstrate significant synergy with ibrutinib. When used as a single agent in a mouse model of CLL, our lead compound inhibits IRE-1 RNase activity *in vivo*, reduces tumor burden by ~67% relative to control treatment, and exhibits no apparent acute or systemic toxicity.

PUBLICATION/PATENT

- Provisional patent applications filed on 09/08/2013 for Drs. Hu and Del Valle.

CONTACT

Haskell Adler PhD MBA
Senior Licensing Manager
Haskell.Adler@Moffitt.org
(813) 745-6596

LICENSING OPPORTUNITY

MOFFITT CANCER CENTER