

Novel Small Molecule Histone Deacetylase 6 Inhibitor with a Substituted Aryl Urea Cap Group



Novel, selective, small molecule inhibitors of histone deacetylase 6 (HDAC6) activity. The most promising molecule inhibits HDAC6 activity with an IC_{50} of 2.5nM in vitro. In a series of compounds, higher binding specificity for HDAC6 correlated with stronger antiproliferative activity. The lead inhibitor significantly slows melanoma tumor growth in a mouse xenograft model significantly better than Tubastatin A, another HDAC6 inhibitor. Tubastatin A has also been shown to strongly inhibit mantle cell lymphoma growth in a mouse xenograft model.

COMMERCIAL OPPORTUNITY

- Our lead HDAC6 inhibitor is active against melanoma cells and may show efficacy against mantle cell lymphoma, organ transplant rejection, and Charcot–Marie–Tooth disease.
- The market size for advanced metastatic melanoma therapies can be estimated from vemurafenib, a mutant-Raf kinase inhibitor, and ipilimumab, a T-cell targeted immunotherapy, that have world-wide annualized revenues of \$282MM and \$648MM, respectively.
- Better drugs are needed because Vemurafenib has a high rate of resistance within 7-9 months after initial response, and less than 25% of patients treated with ipilimumab respond and 90% of those will eventually relapse.
- Many HDAC inhibitors are in development, and two pan-HDAC inhibitors, Merck's vorinostat and Celgene's romidepsin, have been approved for the treatment of lymphoma with 2012 annualized revenues for romidepsin of \$50MM.
- The attractiveness of this target is evidenced by Celgene's recent \$100MM deal with Acetylon for the rights to 3 drug candidates including ACY-1215, a selective HDAC6 inhibitor. This deal follows Celgene's \$15MM equity investment in Acetylon in Feb 2012.

TECHNOLOGY

Our inhibitor consists of a cap-linker-zinc binding group system. A key feature of this compound is the use of an aryl urea cap group incorporated into a benzyl hydroxamic acid scaffold. These features lead to a compound that is 284 times more selective for HDAC6 (IC_{50} =2.54nM) when compared to HDAC1 (IC_{50} =0.721 μ M). The lead inhibitor also stops growth as a single compound in B16 murine melanoma cells and stalls melanoma xenograft growth in a mouse model at a 25mg/kg dosage (78% reduction in tumor volume at 20 days compared to vehicle treated mice, $p<0.00005$). Tubastatin A only reduced tumor size by 41% over the same time frame.

PUBLICATION/PATENT

- PCT application filed on 3/7/13 and provisional patent application filed on 7/30/13 for Drs. Sotomayor, Woan and Villagra
- *J. Med. Chem.* (2012), Nov 26; 55(22): 9891-9.

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LICENSING OPPORTUNITY



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