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

**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\textsubscript{50}=2.54nM) when compared to HDAC1 (IC\textsubscript{50}=0.721µM). 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