Small Molecule Inhibitor of the Rb/Raf-1 Interaction as a Targeted Therapeutic for Cancer

Potent, selective, non-toxic and orally bioavailable small molecule disruptor of the retinoblastoma tumor suppressor protein (Rb) and Raf-1 serine/threonine protein kinase interaction (Rb/Raf). Disruption of the Rb/Raf interaction leads to inhibition of cellular signaling pathways involved in cell proliferation, angiogenesis, and metastasis. Inhibition of the Rb/Raf interaction alone in murine xenograft models displays efficacy in arresting melanoma and lung tumor growth to a similar extent as the clinically approved Raf kinase inhibitors vemurafenib, sorafenib, and regorafenib.

COMMERCIAL OPPORTUNITY

- Our lead compound, RRD-251, has shown preclinical efficacy against metastatic melanoma and metastatic lung cancer, regardless of Raf mutation, and has demonstrated synergistic efficacy with dacarbazine, a first-line chemotherapeutic against advanced melanoma.
- The market size for advanced metastatic melanoma therapies can be estimated from the two drugs Vemurafenib, a mutant-Raf kinase inhibitor, and ipilumumab, a T-cell targeted immunotherapy, that have world-wide annualized revenues of $282M and $648M, respectively.
- Better drugs are needed because Vemurafenib has a high rate of resistance within 7-9 months after initial response, and is detrimental to the 40% of melanoma patients without the Raf mutation, and ipilumumab only has responses in 25% of patients treated and 90% of those will eventually relapse.
- RRD-251 is a first-in-class therapy that specifically inhibits the physical interaction between Raf-1and Rb, and shows efficacy similar to approved Raf kinase inhibitors in xenograft tumor models.

TECHNOLOGY

RRD-251 selectively disrupts the binding of Rb to Raf-1, but not Rb binding to other proteins necessary for its tumor suppressor functions. RRD-251 is in preclinical development and has shown strong efficacy in reducing growth of melanoma xenograft tumors (0% vs. 200% growth, $p=0.003$) and 2 NSCLC xenograft tumor types (0% vs. 500% growth, $p<0.01$ and 17% vs. 800% growth, $p=0.003$). SCID mice treated with RRD-251 also exhibited 80% fewer metastases to the lung and surrounding tissues than vehicle-treated controls. As a toxicity indicator, mice showed no difference in body weight between pre- and post-treatment with RRD-251 for melanoma. In a dacarbazine-resistant exposure produced an 8-fold increase in apoptosis over dacarbazine alone.

PUBLICATION/PATENT

- PCT applications filed in 2009 for Drs. Sebti, Chellapan, and Lawrence
- Cancer Res(2012),72:516-26; Mol Cancer Ther(2010),9:3330-41; Cancer Res(2008), 68:3810-18

CONTACT

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

LICENSING OPPORTUNITY

MOFFITT CANCER CENTER

05B126.2012.09