Small Molecule WEE1 Inhibitor (WEIN-159) that Inhibits WEE1 Phosphorylation of H2B but Not Cdc2 to Treat Cancer

A new allosteric orally available WEE1 inhibitor was developed that inhibits WEE1 from binding chromatin and phosphorylating Histone H2B. This may lead to more efficient chromatin packaging that may inactivate transcription of oncogenes while increasing transcription of tumor suppressor genes. The new inhibitor does not affect the phosphorylation of Cdc2 thereby avoiding potential side effects in normal cell division when the G2-M checkpoint is removed and cells enter into unscheduled mitosis. Prostate cell proliferation assays show that the WEE1 inhibitor has sub micromolar IC50s as low as 0.55 µM. Xenograft mouse models of prostate cancer show decreased tumor growth by as much as 96%.

COMMERCIAL OPPORTUNITY

- The American Cancer Society estimates that there will be 164,690 new cases of prostate cancer in 2018, and 29,430 deaths due to prostate cancer.
- Overexpression of WEE1 has been observed in several malignancies, including hepatocellular carcinoma, luminal and HER-2 positive breast cancers, glioblastoma, and malignant melanoma, where high expression has been shown to correlate with poor disease-free survival.
- The market is attractive as evidenced by the WEE1 inhibitor AZD1775 that is involved in 27 clinical trials that are currently recruiting. AstraZeneca licensed the Phase 2 drug from Merck in 2013 with a $50M upfront payment, with unspecified royalties and milestones.
- The Moffitt WEE1 inhibitor might not show toxicity in humans, except maybe in combination regimens, in light of the recent AZD1775 Phase 1 data. In the Phase 1 trial of AZD1775 10% of evaluable patients (17/176) achieved a partial response and 53% had stable disease. Responses were observed in patients with ovarian cancer, melanoma, breast cancer, head and neck cancer, colorectal cancer, and squamous cell carcinoma of the skin. AZD1775 monotherapy given as a single dose was well tolerated, and the maximum-tolerated dose was not reached. In the combination regimens, the most common adverse events were fatigue, nausea and vomiting, diarrhea, and hematologic toxicity.

TECHNOLOGY

The allosteric inhibitor WEIN-159 (WEE1 Epigenetic Inhibitor #159) was assayed in cell proliferation assays of LNCaP and LAPC4 cells that showed IC50s of 0.75 µM in LNCaP cells and 0.55 µM in LAPC4 cells. WEIN-159 was shown to inhibit prostate xenograft tumor growth when VCaP cells were implanted subcutaneously in male SCID mice (n=7), or when LAPC4 cells were implanted subcutaneously in male NOD-SCID mice (n=7). When tumors became palpable, mice were injected subcutaneously either with vehicle or WEIN-159 at 30 mg/kg of body weight for 5 days a week for 4 weeks. Data show 58.8% less tumor growth in the VCaP xenograft mice, and 96% less tumor growth in the LAPC4 mice. LAPC4 cells were also implanted subcutaneously in male NOD-SCID mice, and the mice were given oral gavage either with vehicle or WEIN-159 at 70 mg/kg of body weight for 5 days a week for 4 weeks (n=11). Data show 50% less tumor growth in the LAPC4 xenograft mice with oral dosing of WEIN-159.

PUBLICATION/PATENT

- Provisional patent filed August 3, 2018 for Dr. Nupam Mahajan and Dr. Nicholas Lawrence.

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