

Expression of WEE1 and PAXIP1 Can Select Patients who Respond to WEE1 Inhibitor Therapy

The biomarker PAXIP1 was identified in screens of lung cancer tumors to be co-expressed with the cell cycle regulator WEE1 in 19-30% of patients. The presence of both of these proteins resulted in increased cell death when cells were treated with the WEE1 inhibitor, AZD-1775, and data suggest that there is synergy between a WEE1 inhibitor and cisplatin when WEE1 and PAXIP1 levels are both increased. Overexpression of both WEE1 and PAXIP1 might therefore be useful to determine which lung cancer patients are more likely to respond to WEE1 inhibitor therapy leading to improved treatment choices for patients.



COMMERCIAL OPPORTUNITY

- Lung cancer will account for approximately 224,000 new cases in the US in 2016 and 158,000 patient deaths. Clinical trials for cancer therapeutics using randomized designs in unselected patient populations have a 28% failure rate. Hence, biomarker based clinical trial designs are essential to develop personalized cancer therapy.
- Recent success of Xalkori (Pfizer), which received accelerated approval from the FDA, is targeted to only 5% of NSCLC patients, and generated \$488 million in revenue in 2015 demonstrates the promise of biomarker based therapy. The present Moffitt technology would allow physicians to distinguish the 30% of lung cancer patients that have the best chance of responding to a WEE1 inhibitor. Additionally, WEE1 overexpression has been demonstrated in many other cancers, including breast, ovarian, glioblastoma, and melanoma, where it has been linked with decreased progression free survival.
- AstraZeneca's WEE1 inhibitor, AZD-1775, was licensed from Merck for an upfront payment of \$50M. This compound is currently in Phase IIa clinical trials for patients with p53 deficient ovarian cancers and achieved a 27% response rate. Additionally, PAXIP1 was found to be elevated in 12% of ovarian cancers. Using PAXIP1 as a biomarker, physicians can increase their prognostic accuracy for the selection of WEE1 inhibitors for these patients.

TECHNOLOGY

The current technology utilizes detection of PAXIP1 expression in a tumor biopsy sample as a biomarker for the selection of WEE1 kinase inhibitors, such as AZD-1775, or combination treatment of patients with WEE1 inhibitors and an antineoplastic agent. IHC staining of 106 lung tumor tissue microarrays found that 31% of lung tumors demonstrated both PAXIP1 and WEE1 expression. In 15 lung cancer cell lines, co-expression of PAXIP1 and WEE1 correlated with WEE1 inhibitor-dependent repression of CDC2 phosphorylation. PAXIP1 overexpression in H322 lung cancer cells and subsequent treatment with AZD-1775 led to an increased mitotic index at the G2/M checkpoint and a sustained increase in cleaved caspase-3 mediated apoptosis over a 72 hour time course when compared to cells with low levels of PAXIP1. Using the Bliss model of independence, strong synergy between AZD-1775 and cisplatin treatment resulting in a 10-30% increase in cell viability inhibition was found in lung cancer cell lines expressing both PAXIP1 and WEE1, while no synergism occurred in cells expressing just one of these proteins.

PUBLICATION/PATENT

- PCT application filed on March 12, 2015 for Drs. Alvaro Monteiro, Uwe Rix, and Ankita Jhuraney.
- Jhuraney *et al.* (2016) *Molecular Cancer Therapeutics*.

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