LICENSING OPPORTUNITY

Companion Diagnostic to Predict Response to Immunotherapy Based on the Methylation Status

Cancer immune evasion is achieved through multiple layers of immune mechanisms. Methylation of immune synapse genes is a crucial driver of tolerogenic immune landscapes and immune evasion in cancer. Notably, preclinical studies demonstrate the efficacy of demethylating agents to augment immunotherapy. This Moffitt technology is a diagnostic to predict response to immunotherapy based on the methylation status of immune synapse gene signature. This technology predicts a subset of patients with hypermethylated co-stimulatory genes ($PC1^{high}$) will benefit from combination therapy of PD1 blockade with 5-azacytidine and decitabine, while conversely, patients with hypermethylated immune checkpoint genes ($PC2^{high}$) may be adversely impacted.

COMMERCIAL OPPORTUNITY

- FDA has approved nivolumab (Opdivo®) and pembrolizumab (Keytruda®) to treat patients with unresectable or metastatic solid tumors that have progressed following prior therapy, with no satisfactory alternative treatment options.
- FDA recently also approved Onureg® (azacitidinetablets) and Dacogen® (decitabine), a DNA methyltransferase inhibitor, as continued treatment for adults in first remission with acute myeloid leukemia. Recent studies have shown promise combining Keytruda and Dacogen. However, their optimized application in solid cancer to overcome resistance to PD1 blockade requires careful patient selection as evidenced by negative preliminary findings from the phase II randomized clinical trial of oral 5-azacitidine plus pembrolizumab in lung cancer.
- Given negative preliminary findings from the phase II randomized clinical trial of oral **5-azacitidine plus pembrolizumab**, patient selection may be crucial to overcome resistance to PD1 blockade.
- Clinically, a major advantages to the use of methylation status for patient selection is that epigenetic changes are heritable while the DNA is stable, and degradation is less likely in formalin-fixed paraffin-embedded tissues, and thus anticipated to be more robust than RNA-based or histology-based approaches.

TECHNOLOGY

- TCGA Level 1 methylation data from 30 solid tumor types were studied. Twenty selected genes were divided into two groups, immune checkpoint genes (ICG) and co-stimulatory genes (CSG). Preliminary results from unbiased t-stochastic neighbor embedding (SNE) and hierarchical clustering analysis demonstrated that the methylation status of immune synapse genes can distinguish tumor vs. normal tissue and histologic subtypes. ICGs and CSGs demonstrated inverse methylation patterns reflecting their opposite immunomodulatory functions.
- A principal component analysis revealed two major principal components, PC1 and PC2, based on the methylation status. The dominant components of PC1 were CSGs and PC2 was mainly driven by ICGs. It was found that normal tissues exhibit hypomethylation of CSGs and hyper-methylation of ICGs. By contrast, tumor tissues manifested either hypermethylation of CSGs and/or hypomethylation of ICGs to deliberately suppress the immune system.
- This methylated gene signature was tested using a Moffitt melanoma patient dataset (29 patients) and the diagnostic predicted patients who are $PC1^{low}$ respond to immunotherapy. Importantly, we observed reversal of hypermethylation of CSGs by 5-azacytidine in the dataset of 26 epithelial cancer cell lines with a significant decrease in PC1 scores.
- This model also correlated with overall survival (OS) and DSS in other immunogenic cancers, including non-small cell lung cancer, renal cell carcinoma, head and neck cancer, breast cancer, and uterine cancer with microsatellite instability.

PUBLICATION/PATENT

Provisional application was filed for Dr. Sungjune Kim on 8/21/2019

CONTACT

Praba Soundararajan, PhD
Intellectual Property Manager
praba.soundararajan@moffitt.org
813.745.6776

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