Indian Institute of Science
Centre for BioSystems Science and Engineering
BSSE Seminar

2nd December 2019 (Monday), 4:00 PM, MRDG Seminar Hall, 1st floor, Biological Sciences Building

A CRISPR-Cas9 Screen Reveals Novel Mechanisms of PD-L1 Regulation in Human Lung Cancer

Dr. Shruthy Suresh Aggarwal

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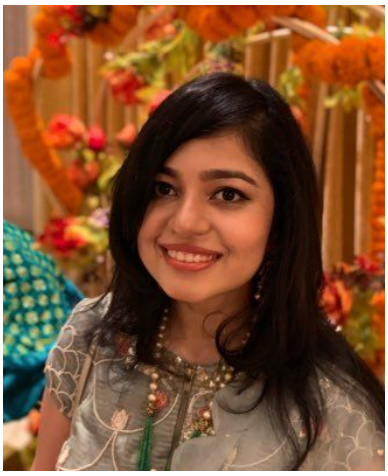
ABOUT THE SPEAKER



Dr. Shruthy Suresh Aggarwal was born and raised in Chennai for 21 years, and received a B.Tech in Biotechnology from IIT Madras in 2013. A summer of exciting research at Michigan State University as a Khorana Scholar motivated her to pursue graduate studies in the US. Shruthy recently obtained her Ph.D in Cancer Biology from the University of Texas, Southwestern Medical Center as an HHMI Med to Grad fellow in 2019. Her graduate work in Dr. Kathryn O'Donnell's laboratory has focused on using CRISPR based screening to identify regulators of the PD-L1 immune checkpoint in lung cancer. Her Thesis work contributed to the lab being awarded several grants: Welch Foundation Grant 2018, Friends of the Comprehensive Cancer Center Award in Cancer Research 2017 and NCI SPORE in Lung Cancer Career Development Award 2016.Currently, she is working as a postdoctoral fellow in the Department of Molecular Biology at the UT Southwestern Medical Center.

ABSTRACT

Cancer cells express high levels of PD-L1, a ligand of the PD-1 receptor on T cells, allowing tumors to directly suppress T cell activity. Monoclonal antibody-based checkpoint inhibitor blockade (CIB) therapeutics (including anti-PD1 and anti-CTL4 therapies alone or in combination) have revolutionized the treatment of non-small cell lung cancer (NSCLC) and are now used as front-line therapy. However, only ~20% of all NSCLCs benefit from checkpoint blockade. Therefore, it is imperative to understand the mechanisms regulating immune checkpoints in lung cancer.

We used Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)- based screening to identify regulators of PD-L1 in human lung cancer cells. *Uroporphyrinogen Decarboxylase* (*UROD*), a key enzyme in the heme biosynthesis pathway, was identified as a potent PD-L1 negative regulator. We show that impairment of heme production, which activates the Integrated Stress Response (ISR), results in enhanced *PD-L1* translation. *PD-L1* translation is repressed by non-canonical upstream open reading frames in its 5′ UTR, which are bypassed by ISR pathway activation, leading to suppression of anti-tumor immunity. We demonstrate that ISR-dependent translation of PD-L1 requires the translation initiation factor EIF5B. EIF5B overexpression, which is observed in human lung cancers and associated with poor prognosis, is sufficient to induce PD-L1. These findings uncover a new mechanism of immune surveillance regulation and suggest novel targets for therapeutic intervention.