Brief summary on the Research Work of the Applicant

Background: Mutant KRAS-induced tumorigenesis is prevalent in the lung, colon, and pancreatic ductal adenocarcinomas. For the past 3 decades, KRAS mutants seem undruggable due to their high-affinity GTP-binding pocket and smooth surface. Structure-based drug design helped in the design and development of first-in-class KRAS G12C inhibitor Sotorasib (AMG 510) which was then approved by the FDA. Recent reports state that the AMG 510 is becoming resistant in non–small-cell lung cancer (NSCLC), pancreatic ductal adenocarcinoma (PDAC), and lung adenocarcinoma patients and the crucial drivers involved in this resistance mechanism is unknown. **Methods:** In that study, Initially, the GSE dataset was retrieved from NCBI-GEO, pre-processed, and then subjected to differentially expressed genes (DEG) analysis using the limma package. Then the identified DEGs were subjected to protein-protein interaction (PPI), followed by cluster analysis and hub gene analysis, which resulted in the identification of probable markers. **Results:** Furthermore, the enrichment and survival analysis revealed that the small unit ribosomal protein (RPs) RPS3 is the crucial biomarkers of AMG 510 resistance in KRAS G12C mutant MIA-PaCa2 cells pancreatic ductal adenocarcinoma cells. **Conclusion:** Finally, he concluded that the RPS3 is a crucial biomarker in Sotorasib resistance which evades apoptosis by MDM2/4 interaction. he also suggests that the combinatorial treatment of Sotorasib and RNA polymerase I machinery inhibitors could be a possible strategy to overcome resistance and has to be studied in *In vitro* and *In vivo* in near future.

Overall, the applicant's research work identified the novel correlation between the Ribosomopathies and Sotorasib resistance in KRAS G12C mutated Pancreatic ductal adenocarcinoma.

Dean SBST

Dean
School of Bio Sciences & Technology (SBST)
Vellore Institute of Technology (VIT)
(Deemed to be University under section 3 of UGC Act, 1956)
Vellore – 632 014, Tamil Nadu, India