Pancreatic cancer is an aggressive malignancy and is the fourth cause of death by cancer with a 5 years survival rate of only 8%. Effective targeted therapies to treat Pancreatic Ductal AdenoCarcinoma (PDAC) patients are still awaiting clinical validation. Activating mutation of the KRAS oncogene occur in 90-95% of PDAC and is an initiating genetic event in PDAC. Although KRAS could represent an important therapeutic target, there is a lack of effective KRAS inhibitors. The analysis of KRAS-associated gene signatures in pancreatic cancer cell lines has revealed the presence of subtypes of PDAC tumors cells whose survival exhibit a strong dependency on KRAS.

Drug repositioning (i.e., the use of old drugs for a novel therapeutic indication) is a cost-effective approach to rapidly offer new therapeutic opportunities in the clinic. The repositioning of U.S. Food and Drug Administration (FDA)-approved drugs to target oncogenic pathways that still lack effective inhibitors, such as K-RAS, would be a relevant pharmacologic approach to inhibit oncogene-dependent tumor growth. Using a specific K-RAS-dependent gene signature, we implemented a computer-assisted inspection of a drug-gene network to in silico repurpose drugs that work like inhibitors of oncogenic K-RAS. We identified and validated decitabine - a FDA-approved drug - as a potent inhibitor of growth in pancreatic cancer cells and patient-derived xenograft models that showed K-RAS dependency. Mechanistically, decitabine efficacy was linked to K-RAS-driven dependency on nucleotide metabolism and its ability to specifically impair pyrimidine biosynthesis in K-RAS-dependent tumors cells and induce DNA damage. Preliminary data suggested that DEC could sensitize PDAC cells to drugs inhibiting DNA repair, such as the PARP inhibitor OLAPARIB, in selected PDACs.

Based on these findings, the ongoing project, developed through the strong clinical collaboration with the National Cancer Institute Regina Elena (Rome, Italy), together with other national and international cancer centres, will layout the basis for the repurposing of DEC in selected PDAC through the following research lines: 1) To understand the molecular mechanism of the cytotoxicity of DEC in KRAS-dependent PDAC tumor; 2) To investigate the pre-clinical efficacy of DEC or DEC plus OLAPARIB combined treatment by using Patient-Derived Xenograft (PDX)-PDAC models, orthotopic, and immunocompetent mice models of PDAC; 3) To analyze the
frequency of KRAS-dependent tumors in PDAC cohorts and the prognostic value of the KRAS dependency scores.

Overall, our research aims to extensively investigate the preclinical efficacy of a tailored drug repositioning in PDAC. If the preclinical efficacy is confirmed, results from this project will promote a phase II clinical trial of decitabine in selected PDAC patients.

References:

Keywords: pancreatic cancer, functional genomics, cell death and senescence, drug targets, oncoprotein, small molecule agents, oncogenes, cancer metabolism, pyrimidine biosynthesis, drug discovery technologies, in silico evaluation of drug repurposing.

Contacts: luca.cardone@cnr.it; luca.cardone@ifo.gov.it

Website(s): ND