PROJECT

Supervisor:	MARINA MACCHINI
Title:	Improving KRAS blockage-based treatments in Pancreatic Adenocarcinoma Models
Curriculum:	Cellular and Molecular Biology
Link to the personal page of the University or relevant hospital site website:	https://www.hsr.it/dottori/marina-macchini https://pancreascenterhsr.it/il-team/dr-ssa-marina-macchini

Description of the Project (max 3,000 characters including spaces)

Background/gap of knowledge

Pancreatic adenocarcinoma (PDAC) is a lethal malignancy with few therapeutics options and no targeted therapies approved so far. Despite the advances in chemotherapy, a minority of patients (pts) benefits from current treatments, with a 5-year overall survival of 13%. The identification of innovative treatments is urgently required to improve PDAC pts survival [1-4].

Rationale and hypothesis

KRAS mutation is the most common tumor-initiating event in PDAC, occurring in more than 90% of the pts [5]. The oncogenic point mutations, most frequently at codon G12, lead to KRAS constitutive activation [6]. A new family of PanKRAS inhibitors (KRASi) are currently in clinical development, showing encouraging preliminar results [ct.gov NCT05379985/NCT06625320]. A major concern for the long-term efficacy of these compounds is represented by the development of acquired genomic alterations in RAS signaling pathways inducing treatment resistance (RAS amplification, MAPK/PI3K alterations, feedback induced RTKs) [7], as well as the TME modifications potentially-induced by the treatment. KRASi may increase the number of CAFs in mouse models of PDAC [8], and among them EGFR-activated myCAF are known to sustain the metastasizing process [9]. The novel EGFRxHER3 ADC, composed by a tetravalent bispecific antibody conjugated to a topoisomerase I inhibitor, is able to dual target EGFR and HER3 in expressing cells [9-10]. The EGFR/HER3 pathway plays a crucial role in PDAC tumorigenesis [11-12], showing high level of ERBB3 expression in PDAC samples and cell lines according to TCGA and CCLE, with immunostaining reactivity in about 30% of resected pts. Moreover, high level of ERBB3 expression is related to poor prognosis [13]. As shown in other solid tumors and PDAC preclinical models [14-15] a vertical inhibition of RAS-related signaling, increases KRASi efficacy,

potentially stimulating the anti-tumorigenic TME function. In this light EGFRxHER3 ADC represent a new player able to target both cancer than stromal cells, enhancing the KRAS single target blockage, both improving its activity in HER3 expressing PDAC pts than overcoming resistance.

Objectives and specific aims

AIM1: To analyze an established cohort of multicellular patient-derived organoids (PDOs) as 2D/3D co-cultures of PDAC and stromal cells (PCSs/CAFs) to better recapitulate the human PDAC complexity in vitro. To generate PDAC PDOs-derived xenografts and PCSs co-cultured PDOs (PDX).

AIM2: To explore the mechanism of action of the EGFRxHER3 ADC and KRASi combination with/without additional selected drugs (chemotherapy, CDK4/6 inhibitors, DDR inhibitors) in PDAC cell line/PDAC PDOs/ PCSs co-cultured PDOs. To confirm the efficacy and test toxicity of the selected EGFRxHER3 ADC/ KRASi based- combinations in PDX mouse models.

Expected outcomes

To identify a subset of PDAC with specific vulnerabilities that may benefit from targeted-KRAS and EGFR/HER3 treatments, focusing on tumor-stroma crosstalk and potentially enhanced by rationally designed combinations, validating the translatability to human PDAC pts through animal models.

Skills that the student should acquire (max. **591/600** characters including spaces):

Student must develop skills for wet lab research, focusing on cells/PDOs culturing, flow-cytometry, western blotting, PCR analysis. Animal regulatory training must be completed according to IACUC, in order to get access to the animal facility to conduct mouse research. Candidate will be encouraged to independently set experimental plans, with proper timing and tools, improving troubleshooting. Student is expected to get a broad knowledge of the literature on PDAC field, developing a critical view. He/She will be encouraged in developing team-working skills but also leadership ability.

References (max. 15)

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8. Wa Mahadevan K, McAndrews K, LeBleu et al. KRASG12D inhibition reprograms the microenvironment of early and advanced pancreatic cancer to promote FAS-mediated killing by CD8+ T cells. Cancer Cell 2023; 41: 1606-20.
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14. Liaki V, Barrambana S, Kostopoulou M et al. A targeted combination therapy achieves effective pancreatic cancer regression and prevents tumor resistance an anti-EGFR therapy alone or with synergistic drugs could overcome KRAS-induced resistance. PNAS 2025; https://doi.org/10.1073/pnas.2523039122
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