PROJECT

Supervisor:	Dr. Giovanni Sitia
Title:	Preserving IFNAR1 competence to improve perioperative IFNα therapy against liver micrometastatic disease in colorectal and pancreatic cancer
Curriculum:	Basic and Applied Immunology and Oncology
Link to the personal page of the University or relevant hospital site website:	https://research.hsr.it/en/divisions/immunology-transplantation-and-infectious-diseases/experimental-hepatology/giovanni-sitia.html

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

Background/gap of knowledge

Colorectal cancer (CRC) and pancreatic ductal adenocarcinoma (PDAC) frequently recur in the liver after apparently curative surgery, indicating persistence of occult micrometastatic disease. Perioperative type I interferon (IFNα) is an attractive strategy because it can act on tumor cells, the hepatic vascular niche, and antitumor immunity. However, its benefit is often limited and non-durable during sustained exposure. A major unresolved question is whether this loss of efficacy reflects progressive loss of IFNAR1 competence in tumor and immune compartments.

Rationale and hypothesis

Our preliminary data show that CRC and PDAC liver metastasis models display distinct endogenous IFN-I states, that IFNα monotherapy has limited durable benefit, and that pharmacologic IFNAR1 stabilization can preserve receptor expression, maintain CD8 T-cell fitness, and improve antimetastatic response. We hypothesize that sustained IFNα loses efficacy because IFNAR1 competence progressively declines, and that pharmacologic strategies preserving IFNAR1 will sustain productive IFN-I signaling, limit adaptive resistance, and improve control of liver micrometastatic disease.

Objectives and specific aims

Aim 1: define pharmacologic strategies that preserve productive IFN-I signaling in CRC and PDAC tumor cells and antigen-specific CD8 T cells exposed to sustained IFNα in vitro.

Aim 2: test whether the lead IFNAR1-stabilizing strategy improves durable control of liver micrometastatic disease during perioperative IFNα therapy in vivo, with analysis of metastatic burden, endogenous tumor-specific CD8 T-cell responses, and liver microenvironment remodeling.

Expected outcomes

The project will identify context-specific strategies that preserve IFNAR1 competence, clarify whether therapeutic benefit reflects tumor-intrinsic and/or T-cell-intrinsic effects, and determine whether IFNAR1 stabilization can convert transient IFNα activity into durable perioperative control of minimal residual disease. The work is expected to provide mechanistic insight and preclinical rationale for future perioperative immunotherapy approaches against liver metastatic recurrence.

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

The student will acquire expertise in tumor immunology, 2D/3D cell culture, retroviral engineering of tumor models, flow cytometry, IFN-signaling assays, qPCR/western blot, antigen-presentation and OT-I coculture assays, mouse liver metastasis models, mesenteric vein injection, osmotic pump implantation, MRI-based longitudinal monitoring, tissue processing, histology/immunofluorescence, experimental design, statistics, and scientific communication.

References (max. 15)

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9. Basavaraja, R., Zhang, H., Holczbauer, A., Lu, Z., Radaelli, E., Assenmacher, C.A., George, S.S., Nallamala, V.C., Beiting, D.P., Meyer-Ficca, M.L., et al. (2024). PARP11 inhibition inactivates tumor-infiltrating regulatory T cells and improves the efficacy of immunotherapies. Cell Rep Med 5, 101649. 10.1016/j.xcrm.2024.101649.

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11. Bresser, K., Dijkgraaf, F.E., Pritchard, C.E.J., Huijbers, I.J., Song, J.Y., Rohr, J.C., Scheeren, F.A., and Schumacher, T.N. (2020). A mouse model that is immunologically tolerant to reporter and modifier proteins. Commun Biol 3, 273. 10.1038/s42003-020-0979-0. expertise in tumor immunology, 2D/3D cell culture, retroviral engineering of tumor models, flow cytometry, IFN-signaling assays, qPCR/western blot, antigen-presentation and OT-I coculture assays, mouse liver metastasis models, mesenteric vein injection, osmotic pump implantation, MRI-based longitudinal monitoring, tissue processing, histology/immunofluorescence, experimental design, statistics, and scientific communication.