REPORT
25th SOCIAL RETURN OF THE RESEARCH
CANCER

PERSONALISED IMMUNOTHERAPY FOR ENDOMETRIAL CANCER

Dr Alena Gros Vidal
VHIO Vall d'Hebron Institut d'Investigació Oncològica
Dr Xavier Matias-Guiu Guia
IRBLl Institut de Recerca Biomèdica de Lleida
Dr Ignacio Melero Bermejo
CIMA Universidad de Navarra - FIMA Fundación para la Investigación Médica Aplicada Navarra
Dr José Maria Piulats Rodríguez
Institut Català d'Oncologia - IDIBELL Institut d'Investigació Biomèdica de Bellvitge

1. Summary of the project

The aim of this project was to better understand the immune infiltrate of endometrial cancer in order to personalize its treatment with immunotherapy. To achieve this goal we aimed to perform a detailed phenotypic analysis of the immune infiltrate in endometrial cancer and its correlation with prognosis, develop personalized T cell-based therapies to treat endometrial cancer, and establish human mouse models to guide the rational design and application of immunotherapies in patients with endometrial cancer.

2. What has it discovered?

Our results demonstrate that endometrial cancer is frequently infiltrated by tumor-reactive intraepithelial lymphocytes (TILs), and that the expression of specific cell surface receptors (PD-1hi and CD39 or PD-1hi) can be used to select and expand CD8+ and CD4+ tumor-reactive TILs, respectively. Furthermore, biomarkers preferentially expressed on tumor-reactive TILs, but not the frequency of CD3+, CD8+ or CD4+ lymphocytes, have prognostic value suggesting their protective role in antitumor immunity.

We have shown that the characteristics of immune infiltration in a primary tumor resection studied with multiplexed immunofluorescence (PD-L1, PD-1, CD8, CD68, FOXP3 and CK) can reliably predict recurrence in patients with primary stage low-grade endometrial cancer, over and above molecular subtypes.

Moreover, the study of POLE-mutated tumors has identified a gene, WNK2, which can be inactivated by promoter hypermethylation, and this is associated with a decreased immune response.

3. What practical application will this result have?

Our results indicate that immune infiltrate and biomarkers preferentially expressed by tumor-reactive T lymphocyte-specific are associated with a better prognosis in

endometrial cancer patients and this could be used to improve the therapeutic management of patients. Moreover, since tumor infiltrating and reactive lymphocytes are observed in a large proportion of endometrial tumors, we propose to treat patients with tumor-specific lymphocytes selected using the described biomarkers, to establish new therapeutic strategies with cell therapy. During the project multiple PDX models have been established that will enable us to test the efficacy of these therapies in order to translate these cell therapies to patients.

4. Bibliography generated

Lozano-Rabella M, Garcia-Garijo A, Palomero J, Yuste-Estevanez A, Erhard F, Farriol-Duran R, Martín-Liberal J, Ochoa-de-Olza M, Matos I, Gartner JJ, Ghosh M, Canals F, Vidal A, Piulats JM, Matías-Guiu X, Brana I, Muñoz-Couselo E, Garralda E, Schlosser A, Gros A. Exploring the Immunogenicity of Noncanonical HLA-I Tumor Ligands Identified through Proteogenomics. Clin Cancer Res. 2023 Jun 13;29(12):2250-2265. doi: 10.1158/1078-0432.CCR-22-3298. PMID: 36749875; PMCID: PMC10261919.
Palomero J, Panisello C, Lozano-Rabella M, Tirtakasuma R, Díaz-Gómez J, Grases D, Pasamar H, Arregui L, DorcaDuch E, Guerra Fernández E, Vivancos A, de Andrea CE, Melero I, Ponce J, Vidal A, Piulats JM, Matias-Guiu X, Gros A. Biomarkers of tumor-reactive $CD4^+$ and $CD8^+$ TILs associate with improved prognosis in endometrial cancer. J Immunother Cancer. 2022 Dec;10(12):e005443. doi: 10.1136/jitc-2022-005443. PMID: 36581331; PMCID: PMC9806064.

Devis-Jauregui L, Vidal A, Plata-Peña L, Santacana M, García-Mulero S, Bonifaci N, Noguera-Delgado E, Ruiz N, Gil M, Dorca E, Llobet FJ, Coll-Iglesias L, Gassner K, Martinez-Iniesta M, Rodriguez-Barrueco R, Barahona M, Marti L, Viñals F, Ponce J, Sanz-Pamplona R, Piulats JM, Vivancos A, Matias-Guiu X, Villanueva A, Llobet-Navas D. Generation and Integrated Analysis of Advanced Patient-Derived Orthoxenograft Models (PDOX) for the Rational Assessment of Targeted Therapies in Endometrial Cancer.AdvSci (Weinh). 2022 Nov 14;10(1):e2204211. doi: 10.1002/advs.202204211. Epub ahead of print. PMID: 36373729; PMCID: PMC9811454.

Jiménez-Sánchez D, Ariz M, Chang H, Matias-Guiu X, de Andrea CE, Ortiz-de-Solórzano C. NaroNet: Discovery of tumor microenvironment elements from highly multiplexed

images. Med Image Anal. 2022 May;78:102384. doi: 10.1016/j.media.2022.102384. Epub 2022 Feb 14. PMID: 35217454; PMCID: PMC9972483.

Esteve-Puig R, Bonifaci N, Dorca E, Royo R, Dueso A, Gatius S, Santacana M, Pedrosa A, Gut M, Tomaselli M, Rodríguez A, Arribas C, Barrero P, Piñeyro D, Vidal A, Esteller M, Torrents D, Piulats JM, Matias-Guiu X, Llobet-Navas D
Genome-wide analysis of epigenetic intratumor heterogeneity in POLE-mutated tumors uncovers predictive biomarkers of immunotherapy response in poorly immunogenic endometrial carcinoma.