

# MICROENVIRONMENT & METASTASIS JUNIOR GROUP

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## OVERVIEW

In the Microenvironment and Metastasis laboratory, we are interested in understanding the crosstalk between tumour and stromal cells along metastatic progression. We are interested in how tumour cells can extrinsically influence the evolution of cancer during metastatic spread. For this purpose, we are analysing 1) the role of small extracellular vesicles (sEVs) in primary tumour evolution and pre-metastatic niche formation in melanoma, prostate and pancreatic cancer, and 2) the influence of obesity in breast cancer metastasis, as well as defining 3) the relevance of nerve growth factor receptor (NGFR) in melanoma, oral squamous cell carcinoma, and bladder cancer metastasis, aiming to develop new targeted therapies.

“We analyse the intrinsic and extrinsic mechanisms involved in metastatic dissemination, aiming to develop novel therapeutic targets.”

Graduate Students  
Enrique Bastón, Elena Castellano (until December), Juan García-Agulló, Teresa González (until March), Alberto Hernández

Technicians  
Sara Sánchez-Redondo, Vanesa Santos

Students in Practice  
Eduardo Garvín (until Feb.) (Univ.

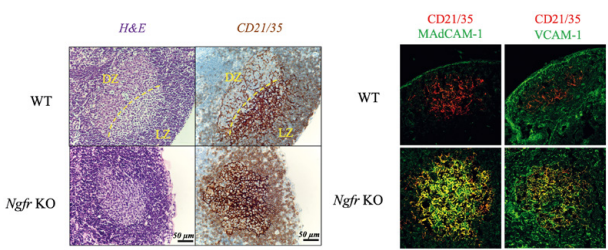
Francisco de Vitoria, Madrid, Spain), Sandra López (March-July) (Bachelor's Degree Final Project Student, Univ. Francisco de Vitoria, Madrid, Spain)

Visiting Scientist  
Marion Pascale (January-June) (Instituto de Oncología Vall D'Hebron, Barcelona, Spain)

## RESEARCH HIGHLIGHTS

**Relevance of extracellular vesicles in tumour cell evolution and metastasis.** Extracellular vesicles (EVs) contain different biomolecules including DNA and RNA. However, the importance of nucleic acids in EVs and the consequences of its transfer to the tumour microenvironment are poorly understood. We are exploring the influence of tumour-shed EVs in surrounding tumour cells, stroma, and healthy tissue during tumour progression. In addition, we are analysing EV-associated nucleic acids as surrogate markers of tumour progression, developing highly-sensitive methods for detecting minimal residual disease and metastatic risk. Moreover, we are currently investigating the role of extracellular vesicles in prostate cancer premetastatic niche formation through the analysis of their molecular cargo and their influence in the lymph node microenvironment. We aim to define novel biomarkers of early dissemination by liquid biopsy and potentially new anti-metastatic therapies.

**Understanding the link between obesity and breast cancer metastasis.** Since obesity is linked to hypercoagulability and increased risk of breast cancer, we are evaluating if high-fat diet (HFD) influences breast cancer metastasis. We observed that HFD increases tumour-platelet-endothelial cell interaction favouring tumour cell homing and metastasis. Importantly, our data support that anti-platelet therapies reduce tumour cell homing and metastasis in HFD-fed mice, supporting the observation that anticoagulant agents or caloric intake reduction could modify premetastatic niche formation, decreasing metastasis in obesity models of triple-negative breast cancer (TNBC).



**FIGURE 1** *Ngfr* loss leads to lymph node germinal center (GC) hyperproliferation, aberrant structure, and loss of polarisation. Representative H&E and CD21/35 IHC staining (left panels) and immunofluorescence (right panels) of the indicated markers. Immunised wt mice and *Ngfr* KO germinal centres are shown in left panels. Yellow dashed lines divide GC dark zone (DZ) and light zone (LZ). Wt and KO *Ngfr* KO GCs are shown in right panels analysing the expression of the follicular dendritic cell activation markers CD21/35 (red), MadCAM1 or VCAM1 (green); co-expression of markers is shown in yellow. Observe the lack of polarisation and structure in *Ngfr* KO GCs.

**Defining the role of NGFR in tumour progression, lymphoproliferative diseases, and autoimmunity.** NGFR is emerging as a key gene for metastatic spread and therapy resistance in several tumour types. We are analysing the role of NGFR in tumour metastasis and developing new therapies targeting NGFR to improve immunotherapy treatment in metastatic melanoma and other tumours such as oral squamous cell carcinomas (OSCC) and bladder carcinomas. Moreover, our data support a novel role for NGFR regulating immunity and cell proliferation in lymph nodes, suggesting an important role in follicular lymphoma or autoimmune disorders (FIGURE 1). ■

### PUBLICATIONS

- Carretero-González A, Hergueta-Redondo M, Sánchez-Redondo S, Jiménez-Embún P, Manso Sánchez L, Gil EC, Castellano D, de Velasco G, Peinado H (2022). Characterization of plasma circulating small extracellular vesicles in patients with metastatic solid tumors and newly diagnosed brain metastasis. *Oncoimmunology* 11, 2067944.
- González-Muñoz T, Kim A, Ratner N, Peinado H (2022). The need for new treatments targeting MPNST: the potential of strategies combining MEK inhibitors with antiangiogenic agents. *Clin Cancer Res* 28, 3185-3195.
- Leary N, Walser S, He Y, Cousin N, Pereira P, Gallo A, et al. (incl. Peinado H) (2022). Melanoma-derived extracellular vesicles mediate lymphatic remodelling and impair tumour immunity in draining lymph nodes. *J Extracell Vesicles* 11, e12197.
- Almansa D, Peinado H, García-Rodríguez R, Casadomé-Perales Á, Dotti CG, Guix FX (2022). Extracellular vesicles derived from young neural cultures attenuate astrocytic reactivity in vitro. *Int J Mol Sci* 23, 1371.
- Cardeños B, Clares I, Bezos T, Toribio V, López-Martín S, Rocha A, Peinado H,

- Yáñez-Mó M, Cabañas C (2022). ALCAM/CD166 is involved in the binding and uptake of cancer-derived extracellular vesicles. *Int J Mol Sci* 23, 5753.
- Santos-Coquillat A, González MI, Clemente-Moragón A, González-Arjona M, Albaladejo-García V, Peinado H et al. (2022). Goat milk exosomes as natural nanoparticles for detecting inflammatory processes by optical imaging. *Small* 18, e2105421.

### PATENT

- Peinado Selgas H, Saragovi HU, García Silva S, Nogués Vera L, Hernández Bar-

- ranco A. THX-B for treating and preventing cancer and metastasis. PCT Application (2022). *PCT/EP2022/070597. WO2023 002008A1*.

### AWARDS AND RECOGNITION

- Héctor Peinado:
- XII National Cancer Research Award “Doctores Diz Pintado”, Spain.
- Listed in the “World Ranking Top 2% Scientists”, 2022 edition of the Stanford University list of World Top 2% scientists.