

## MICROENVIRONMENT & METASTASIS JUNIOR GROUP

Héctor Peinado  
Junior Group Leader

Staff Scientist  
Susana García

Post-Doctoral Fellows  
Marta Hergueta, Laura Nogués



### OVERVIEW

In the Microenvironment and Metastasis laboratory, we are interested in understanding the crosstalk between tumour and stromal cells along metastatic progression. We are especially interested in analysing the role of small extracellular vesicles (sEVs) in premetastatic niche formation in melanoma, pancreatic and prostate cancer. These particles reinforce tumour cell homing and metastasis in organs. Besides the role of sEVs, we are interested in understanding the influence of obesity and platelets in triple negative breast cancer and tumour metastasis in rare diseases such as follicular lymphoma and malignant peripheral nerve sheath tumours. Finally, we are defining new approaches to use circulating sEVs in liquid biopsies, analysing the use of mutations as indicators of minimal residual disease in melanoma and breast cancer.

**“Our Group aims to understand the extrinsic mechanisms influencing metastatic dissemination.”**

Graduate Students  
Elena Castellano, Juan García-Agulló (since November), Teresa González, Alberto Hernández

Technicians  
Enrique Bastón (since September), Sara Sánchez-Redondo, Vanesa Santos

Students in Practice  
Eduardo Garvín (since September) (*Universidad Francisco de Vitoria*, Madrid, Spain), Ane Rubio (until July) (*Universidad Complutense de Madrid*, Madrid, Spain)

Visiting Scientist  
Alberto Carretero (until September) (*Hospital Universitario 12 de Octubre*, Madrid, Spain)

### RESEARCH HIGHLIGHTS

**Development of EV-based liquid biopsy tests.** We are developing state-of-the-art technologies to implement EV-based tests in the prognosis of patients with melanoma and breast cancer. We are working on developing a new method for residual disease detection based on the combination of circulating nucleic acids and EVs that will facilitate the stratification of patients for the use of adjuvant therapies after surgery.

**Novel mechanisms driving local and distal metastasis in melanoma and prostate cancer.** We have discovered that nerve growth factor receptor (NGFR) is shuttled in sEVs, reinforcing lymph node pre-metastatic niche formation and metastasis. NGFR is secreted in sEVs, orchestrating the activation of lymphatic endothelial cells, which favours lymph node metastasis. Moreover, we have found that therapeutic targeting of NGFR reduces both local and distal metastasis and can be efficiently combined with immunotherapy. We are currently developing the use of NGFR inhibitors as novel anti-metastatic agents in melanoma and other cancer types. In addition, we aim to understand how sEVs influence lymph node metastasis in prostate cancer (PCa) and are analysing the proteomic signatures in PCa-secreted sEVs in order to define novel biomarkers of early dissemination.

**Obesity and breast cancer metastasis: the tumour-platelet connection.** In this project, we hypothesised that obesity influences systemic changes that pre-condition future organs of metastasis, generating a specialised microenvironment that we have termed “obese premetastatic niche”. We found that obesity reshapes metastatic organ composition, enhancing platelet activation, tumour cell homing and metastasis. Importantly, we identified that anti-platelet therapies reduced tumour cell homing and metastasis in obese mice, supporting the hypothesis that anti-coagulant agents could be used as anti-metastatic therapy in obesity models of breast cancer.

**Relevance of tumour microenvironment in metastasis.** In order to understand the relevance of the microenvironment in metastatic progression of rare cancers, we are analysing 1) the role of NGFR in follicular lymphoma progression, and 2) therapeutic strategies against Endoglin and MEK inhibitors in malignant peripheral nerve sheath tumours (MPNSTs). ■

#### SELECTED PUBLICATIONS\*

- García-Silva S, Benito-Martín A, Nogués L, Hernández-Barranco A, Mazariegos MS, Santos V, Hergueta-Redondo M, Ximénez-Embún P, Kataru RP, Lopez AA, Merino C, Sánchez-Redondo S, Graña-Castro O, Matei I, Nicolás-Avila JA, Torres-Ruiz R, Rodríguez-Perales S, Martínez L, Pérez-Martínez M, Mata G, Szumera-Cieckiewicz A, Kalinowska I, Saltari A, Martínez-Gómez JM, Hogan SA, Saragovi HU, Ortega S, García-Martín C, Boskovic J, Levesque MP, Rutkowski P, Hidalgo A, Muñoz J, Megias D, Mehrara BJ, Lyden D, Peinado H (2021). Melanoma-derived small extracellular vesicles induce lymphangiogenesis and metastasis through an NGFR-dependent mechanism. *Nat Cancer* 2, 1387-1405.
- Verweij FJ *et al.* (incl. Peinado H) (2021). The power of imaging to understand ex-

tracellular vesicle biology in vivo. *Nat Methods* 18, 1013-1026.

- Olmeda D, Cerezo-Wallis D, Castellano-Sanz E, García-Silva S, Peinado H, Soengas MS (2021). Physiological models for in vivo imaging and targeting the lymphatic system: nanoparticles and extracellular vesicles. *Adv Drug Deliv Rev* 175, 113833.
- Saltari A *et al.* (incl. Peinado H) (2021). Specific activation of the CD271 intracellular domain in combination with chemotherapy or targeted therapy inhibits melanoma progression. *Cancer Res* 81, 6044-6057.
- Hernández-Barranco A, Nogués L, Peinado H (2021). Could extracellular vesicles contribute to generation or awakening of “sleepy” metastatic niches? *Front Cell Dev Biol* 9, 625221.
- García-Silva S, Gallardo M, Peinado H (2021). DNA-loaded extracellular vesicles

in liquid biopsy: tiny players with big potential? *Front Cell Dev Biol* 8, 622579.

- Senís E *et al.* (incl. Peinado H). TUNAR lncRNA encodes a microprotein that regulates neural differentiation and neurite formation by modulating calcium dynamics (2021). *Front Cell Dev Biol* 9, 747667.
- Amor López A, Mazariegos MS, Capuano A, Ximénez-Embún P, Hergueta-Redondo M, Recio JA, Muñoz E, Al-Shahrour F, Muñoz J, Megias D, Doliana R, Spessotto P, Peinado H (2021). Inactivation of EMI-LIN-1 by proteolysis and secretion in small extracellular vesicles favors melanoma progression and metastasis. *Int J Mol Sci* 22, 7406.
- González Muñoz T, Amaral AT, Puerto-Camacho P, Peinado H, de Álava E (2021). Endoglin in the spotlight to treat cancer. *Int J Mol Sci* 22, 3186.
- García-Silva S, Ximénez-Embún P, Muñoz J, Peinado H (2021). Postlymphadenec-

tomy analysis of exosomes from lymphatic exudate/exudative seroma of melanoma patients. *Methods Mol Biol* 2265, 345-359.

\* Please see the Group's web site for a list of all publications (19 publications in 2021).

#### PATENT

- Peinado Selgas H, Saragovi HU, García Silva S, Nogués Vera L, Hernández Barranco A (2021). THX-B for treating and preventing cancer and metastasis. *EP21382669*.

#### AWARDS AND RECOGNITION

- Hector Peinado was awarded the *Leonardo Grant* by the *BBVA* Foundation for Researchers and Cultural Creators in 2021, Spain.