

# BRAIN METASTASIS JUNIOR GROUP

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## OVERVIEW

Brain metastasis is the most common neurological complication of cancer. When metastatic cells reach the brain, prognosis is poor given that local therapies (i.e., surgery and radiation) have limited benefit for patients, and the disease inevitably progresses. The rise in the number of patients with brain metastasis is partially due to the increasing number of systemic therapies that work extra-cranially but are unable to provide the same therapeutic benefit in the brain. Consequently, cancer cells present at this secondary site have additional time to evolve and to grow into clinically detectable lesions. In the laboratory, we study why and how cells from different cancer types (breast cancer, lung cancer and melanoma) are able to access the brain, survive and colonise this vital organ. We dissect the biology of these processes *in vivo* using experimental models and patient-derived material in order to challenge the current status of this unmet clinical need.

**“We reported the first strategy involving a liquid biopsy biomarker and a non-toxic radiosensitizer to personalise the use of radiotherapy in patients with brain metastasis.”**

Graduate Students  
Laura Adriana Álvaro, Ana de Pablos  
Aragoneses, Pedro García, Carolina  
Hernández, Irene Salgado

Technicians  
Patricia Baena, Virginia García-Calvo  
(since April), María Perea (until  
November), Diana Patricia Retana,  
Olivia Ana Sánchez

Lab Administrative Manager  
Jorge Guillermo Ortiz (since March)

Francisco de Vitoria, Madrid, Spain)

Visiting Student  
Irene Cornejo (June-December)  
(Summer Traineeship, *Universidad*

## RESEARCH HIGHLIGHTS

In 2022, we established a novel research line in Cancer Neuroscience, aiming to understand the biology underlying the neurocognitive impact of brain metastasis.

Among other activities, additional single cell approaches (i.e., spatial transcriptomics) were incorporated into our experimental pipeline.

We also consolidated research findings, with an impact on various aspects relevant for brain metastasis, such as novel strategies for immunotherapy, new cellular targets within the pro-metastatic microenvironment, and an unexpected avenue for preventing metastasis.

And, finally, we consolidated our scientific strategy as a productive source of findings to be translated from bench to bedside. The most recent examples are the clinical studies following from the discovery of a biomarker of radiosensitivity compatible with liquid biopsy (now part of a prospective observational multicentric clinical study) and the clinical trial combining a RAGE inhibitor and radiotherapy (now in phase I/II trial). ■



**FIGURE** (a) The microenvironment enhances the secretion of S100A9 from cancer cells that binds to RAGE, which could be targeted with a specific inhibitor. (b) Targeting of S100A9 blocks brain metastasis radioresistance. (c) S100A9 is a biomarker of radioresistance from liquid biopsy.

## PUBLICATIONS

Monteiro C\*\*, Miarka L\*\*, Perea-García M, Priego N, García-Gómez P, Álvaro-Espinosa L, de Pablos-Aragoneses A, Yebra N, Retana D, Baena P, Fustero-Torre C, Graña-Castro O, Troulé K, Caleiras E, Tezanos P, Muela P, Cintado E, Trejo JL, Sepúlveda JM, González-León P, Jiménez-Roldán L, Moreno LM, Esteban O, Pérez-Núñez Á, Hernández-Lain A, Mazarico Gallego J, Ferrer I, Suárez R, Garrido-Martín EM, Paz-Ares L, Dalmasso C, Cohen-Jonathan Moyal E, Siegfried A, Hegarty A, Keelan S, Varešlija D, Young LS, Mohme M, Goy Y, Wikman H, Fernández-Alén J, Blasco G, Alcázar L, Cabañuz C, Grivennikov SI, Ianus A, Shemesh N, Faria CC, Lee R, Lorigan P, Le Rhun E, Weller M, Soffiatti R, Bertero L, Ricardi U, Bosch-Barrera J, Sais E, Teixidor E, Hernández-Martínez A, Calvo A, Aristu J, Martín SM, Gonzalez A, Adler O, Erez N; RENACER, Valiente M\*. Stratification of radiosensitive brain metastases based on an actionable S100A9/RAGE resistance mechanism (2022). *Nat Med* 28, 752-756. (\*\* Shared authorship. (\*) Corresponding author.

- A prospective multicentric observational study will be initiated based on these results.
- A phase I/II clinical trial will be initiated based on these results combining a RAGE inhibitor with radiotherapy.

See also:

- *Nature Medicine*. DOI: 10.1038/s41591-022-01776-5 (11 April 2022).
- *Cancer Research*. DOI: 10.1158/0008-5472.CAN-82-11-BI (6 June 2022).

Zhu L, Retana D, García-Gómez P, Alvaro-Espinosa L, Priego N, Masmudi-Martín

## PATENT

M, Yebra N, Miarka L, Hernández-Encinas E, Blanco-Aparicio C, Martínez S, Sobrino C, Ajenjo N, Artiga MJ, Ortega-Paino E, Torres-Ruiz R, Rodríguez-Perales S; RENACER, Soffiatti R, Bertero L, Cassoni P, Weiss T, Muñoz J, Sepúlveda JM, González-León P, Jiménez-Roldán L, Moreno LM, Esteban O, Pérez-Núñez A, Hernández-Lain A, Toldos O, Ruano Y, Alcázar L, Blasco G, Fernández-Alén F, Caleiras E, Lafarga M, Megías D, Graña-Castro O, Nör C, Taylor MD, Young LS, Varešlija D, Cosgrove N, Couch FJ, Cussó L, Desco M, Mouron S, Quintela-Fandino M, Weller M, Pastor J and Valiente M\*. A clinically-compatible drug-screening platform based on organotypic cultures identifies vulnerabilities to prevent and treat brain metastasis (2022). *EMBO Mol Med* 14, E14552. (\*) Corresponding author.

## AWARDS AND RECOGNITION

- Manuel Valiente:
- Chair of the EANO Scientific Committee, the European Association of Neuro-Oncology.
  - Board Member-Elect of the Metastasis Research Society (MRS).
  - EACR Reviewers' Panel (panel member), the European Association for Cancer Research.