Prof. M. Angela Nieto
Instituto de Neurociencias
Consejo Superior de Investigaciones Científicas
Universidad Miguel Hernández

GROUP MEMBERS and GROUP ORGANIZATION

1.Principal Investigator

• **M. Angela Nieto** *(Profesor de investigación CSIC)*

2.Tenured scientist

• **Joan Galceran** *(Científico Titular CSIC)*

3.Postdocs

• **Nitin Narwade** *from May 2020 (Currently Postdoc MOMENTUM Program)*

• **Sonia Vega** *(CSIC permanent position)*

• **Jussep Salgado** *from January 2023 (U Castilla La Mancha, visiting professor)*

4. PhD students

• **Raul Jiménez Castaño** *from March 2021 (FPI – SO excellence grant contract)*

• **Angelita Costantino** from March 2023 (*FPI contract*)

• **Adrián Cuevas** *from September 2024 (PhD contract Generalitat Valenciana)*

6. Technicians & Lab administration

• **Cristina López Blau** (*AEI-MCIU National Plan grant contract)*

• **M Teresa Gómez** *(AEI-MCIU National Plan grant contract)*

• **Gema Osuna** *(Universidad Miguel Hernández)*

• **Daniel Vergara** *(Universidad Miguel Hernández)*

We are a stable research group since January 1993. We are working on different projects related to cell plasticity during embryonic development and in disease with particular emphasis on cancermevolution towards metastasis. Technicians are in charge of the mouse transgenic colonies and surgical procedures, and the fish facility, respectively. In addition to the PI, another scientist holding a CSIC permanent position (Joan Galcerán) contributes to the supervision of students and coordinates all the transgenic approaches, including CRISPR/Cas9 genome editing in mouse and fish. A senior scientist (holding a PhD and a permanent CSIC position), coordinates all Cell Biology experimental approaches. The overall project in the lab involves a horizontal conceptual knowledge and multiple experimental approaches (genetics, cell & molecular biology, single-cell omics including sequencing and spatial transcriptomics, animal models of disease, image analysis, histology, computational analysis and modelling, etc). We use the mouse, the chick and the zebrafish as experimental models as well as 2D and 3D cultures plus samples from patients affected with the pathologies we previously study in the animal models. This provides a pluridisciplinary training and background to the PhD students and postdocs. We dedicate particular efforts to make sure that they are exposed to all techniques and experimental systems during their time in the lab. They also usually travel for short stay visit in another lab, attend national meetings and several international meetings. In addition to individual and small groups meetings, we also gather every Wednesday for 4 hours where they present the progress of the work, we propose new ideas and discuss new findings

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published. This is crucial for students and postdocs, who get exposed to all the projects in the lab and improve their data presentation skills. All activities in the lab are in English, including conversations, all communications by email and meetings.

The Neurosciences Institute (IN) is a well renowned institution, particularly in the Neuroscience field but also in cancer. As such, Angela Nieto coordinates Cancer Connection, the recently created CSIC national cancer network, an initiative to give visibility to cancer research at CSIC and to promote collaborations and interactions with different institutions and stakeholders. In addition, research programmes have been established recently at the IN, of which that on "Cell Plasticity and brain repair" is coordinated by AN as well. The IN runs international Master and PhD programmes, and due to the scope in Neurosciences and Biomedicine, biologists, medical doctors, physiologists, and physicists work together in cooperative projects. The Institute runs a weekly series of seminars with international speakers. The Department also runs monthly seminars for PhD students and young scientists to present their data. The institute **holds the Severo Ochoa Institute of Excellence Award by the Spanish Government from 2014.** English is the official language for all Institute activities.

MAIN ACHIEVEMENTS of the group IN CANCER RESEARCH

- We found a relationship between embryonic development and cancer, describing EMT as a mechanism that regulates the spread of cancer cells from the primary tumour to form metastases (*Science 1994; Nature Cell Biology 2000; Genes and Dev 2004*), opening a new research field.
- We found that cell plasticity is behind metastatic potential, changing prevalent views (*Cancer Cell 2012*)
- We described a gene regulatory network operating both in development and cancer that drives different types of EMTs driven by antagonic EMT transcription factors (Snail and Prrx; *Nat Comm 2019*)
- We have unveiled distinct plasticity (EMT) programmes in tumour evolution in segregated cancer populations, adding an unexpected additional level of intratumour heterogeneity and providing new information to design better antimetastatic therapeutic approaches (*Nature Cancer, 2024*).
- The PI coordinates the National cancer CSIC research network, "Connexión Cáncer", with close to 600 scientists in 20 CSIC Institutes (www.conexion-cancer.csic.es)

Examples of international references to our work:

- Prof. N. Le Douarin in Curr Op Gen Dev 4, 685-695 (1994):

  "Since the paper by Nieto et al. in a recent issue of Science, definition of the neural crest has become much easier. … represents a remarkable discovery in the field of neural crest development, as it opens a new avenue toward the understanding of how

and why a subset of neuroepithelial cells starts its developmental program by becoming migratory before homing to various and definite embryonic areas".

- Extract from Prof. R. Weinberg letter en 2021 (codiscoverer fof the first oncogene and first tumor supproesor gene, MIT):

  "I am familiar with the work because it provided a solid and highly useful foundation for the currently thriving field of metastasis research (including research in my own laboratory beginning in 2004). The work (of her group) anticipated the findings of many other research groups, including my own, often by a decade. It was a visionary in predicting correctly that the EMT program lies at the heart of malignant progression, thereby establishing the conceptual paradigm that a cell-biological program that plays a critical part in normal embryonic development is subverted and exploited by cancer cells. Indeed, the metastases created by the EMT program that she has studied in such depth are responsible for possibly 90% of cancer-associated mortality".

- Mention of our work published in 2000 in Nature Cell Biology by the journal in its 25th anniversary (January 2024)

  Historical News & Views: Cancer. A milestone in epithelial–mesenchymal transition (2024). "Epithelial–mesenchymal transition (EMT) is crucial in embryogenesis and can be exploited by cancer cells to gain metastatic abilities. A hallmark of EMT is E-cadherin loss. In 2000, Snail was reported as the first E-cadherin repressor identified in the context of EMT, advancing our understanding of embryonic development and cancer progression". https://doi.org/10.1038/s41556-023-01228-3

- Publications of the group have gathered over 55000 citations (see http://scholar.google.es/citations?user=hVJw0GEAAAAJ&hl=es).

Top 10 publications

1. Youssef, K.K., Narwade, N., Arcas, A., Marquez-Galera, A., Jiménez, R., Lopez-Blau, C., Fazilaty, H., García-Gutierrez, D., Cano, A., Galcerán, J., Moreno-Bueno, G., Lopez-Atalaya, J.P. and Nieto, M.A.* (2024). Two distinct Epithelial to Mesenchymal Transition Programmes Control Invasion and Inflammation in Segregated Tumour Cell Populations. **Nature Cancer** 5, 1660-1680 DOI: 10.1038/s43018-024-00839-5 *Corresponding author

2. Youssef, K.K. and Nieto, M.A. (2024). The epithelial-mesenchymal transition in tissue repair and degeneration. **Nat. Rev. Mol. Cell. Biol.** 25, 720-739. DOI: 10.1038/s41580-024-00733-z *Corresponding author

3. Castroviejo, N., Ocaña, O.H., Rago. L., Coskun, H., Arcas, A., Galceran, J. and Nieto, M.A.* (2020). Reply to: Zebrafish prrx1 mutants have normal hearts. **Nature** 585, E17–E19. DOI: 10.1038/s41586-020-2675-0 *Corresponding author

4. Fazilaty, H., Rago, L., Youssef, K.K., Ocaña, O.H., Garcia-Asencio, F., Arcas, A., Galcerán, J. and Nieto, M.A.* (2019). A Gene Regulatory Network to Control EMT Programs in Development and Disease. **Nat. Comm.** DOI: 10.1038/s41467-019-13091-8 *Corresponding author

5. Ocaña, O.H., Coskun, H., Minguillón, C., Murawala, P., Tanaka, E.M., Galcerán, J., Muñoz-Chapuli, R. and Nieto, M.A.* (2017). A right-handed signalling pathway drives heart looping in vertebrates. **Nature** 549, 86-90. DOI: 10.1038/nature23454 *Corresponding author

6.- Nieto, M.A.*, Huang RY-J, Jackson, RA & Thiery, JP. EMT: 2016. **Cell** 166, 21-45 DOI: 10.1016/j.cell.2016.06.028 *Corresponding author

7.- Grande, M.T., Sanchez-Laorden, B.L., Lopez-Blau, C., De Frutos, C.A., Boutet, A., Rowe, G., Weiss, S. J., Arévalo, Lopez-Nova, J.M. and Nieto, M.A.* (2015). Snail1-induces partial epithelial-to-mesenchymal transition drives renal fibrosis in mice and can be targeted to reverse established disease. **Nature Med.** 21, 989-997. DOI: 10.1038/nm.3901 *Corresponding author

8.- Nieto, M.A*. (2013). Epithelial plasticity: a common theme in embryonic and cancer cells. **Science**, 342, 1234850. DOI: 10.1126/science.1234850 *Corresponding author

9.- Ocaña, O.H., Córcoles, R., Fabra, A., Moreno-Bueno, G., Acloque, H., Vega, S., Barrallo-Gimeno, A., Cano, A. and Nieto, M.A.* (2012). Metastatic colonization requires the repression of the epithelial-mesenchymal transition inducer Prrx1. **Cancer Cell** 22, 709-724. DOI: 10.1016/j.ccr.2012.10.012 *Corresponding author

10.- Cano, A., Pérez, M. A., Rodrigo, I., Locascio, A., Blanco, M. J., Del Barrio, M. G., Portillo, F. and Nieto, M. A.* (2000). The transcription factor Snail controls epithelial-mesenchymal transitions by repressing E-cadherin expression. **Nature Cell Biol**. 2, 76-83. DOI: 10.1038/35000025 *Corresponding author

Top 5 funding grants

- EMTASY. ERC Advanced grant. AdG322694. May 2013- December 2018. 2.460.000 €. P.I.: M. Angela Nieto
- The complexity of epithelial plasticity: implications in Physiology, Pathology and therapeutic Approaches. Spanish Ministry MCIU-RTI2018-096501-B-I0. 2019-2021. 605.000 €. P.I.: M. Angela Nieto
- Microenvironmental regulators of organ-specific metastatic colonization as therapeutic targets. AECC Foundation. December 2019- July 2023. 300.000 €. PI: M. Angela Nieto.
- NEUcrest— Horizon 2020- ITN--Training European Experts in Multiscale Studies of Neural Crest Development and Disorders: from Patient to Model Systems and Back again. H2020-MSCA-ITN-2019860635. October 2019- April 2024. PI: Anne-Helene Monsoro-Burq, Paris; M. Angela Nieto (PI subproject 501.000 €).

- Cell plasticity trajectories in development, cancer and fibrosis. CELLTRACK. Spanish Ministry of Science and innovation. PID2021-125682NB-I00. 2022-2025. 502.150 €. P.I.: M. Angela Nieto

THESIS DEFENDED IN THE LAST 5 YEARS (and current positions) AND THESIS IN PROGRESS:

- ***2021: Ainara González Iglesias.*** *"The Role of Scratch and Prrx1 Transcription Factors in Adult Neurogenesis". Universidad Miguel Hernández.Calif: Sobresaliente Cum Laude.* Now manager of "Conexión Cáncer" CSIC.
- ***2021: Francisco García-Asencio.*** *"The role of Prrx1 in mouse development and vascular biology" Universidad Miguel Hernández. Calif.: Sobresaliente Cum Laude.* Now Molecular Biologist at Oncobit AG, Zurich, Switzerland
- ***2022: Noemí Castroviejo Jiménez.*** "*TITULO: Genetic robustness: Cooperation of EMT-TFs in zebrafish heart laterality". Universidad Miguel Hernández. Calif.: Sobresaliente Cum Laude.* Currently working at Imaging Core Facilities at ZEISS.
- **2024: *Nitin Narwade:*** "*Spatiotemporal EMT-TFs gene regulatory landscape in development and disease". Universidad Miguel Hernández,. Calif.: Sobresaliente Cum Laude.* Now postdoc in the lab.
- ***In progress: Raúl Jiménez Castaño.*** "*Impact of intratumoural EMT heterogeneity on breast cancer progression" Universidad Miguel Hernández. Expected in 2025*
- ***In progress: Angelita Costantino:*** *"Regulators of metastatic colonisation as therapeutic targets". Universidad Miguel Hernández. Expected in 2026*
- ***In progress: Adrian Cuevas:*** *"Cancer cell – vasculature interactome in breast cancer evolution". Universidad Miguel Hernández. Expected in 2027*

CURRENT POSITIONS FOR POSTDOCS IN THE LAB THAT MOVE FORWARD IN THE LAST 5 YEARS

- ***Hakan Coskun***. Thesis and Postdoc, both in the lab. Now postdoc at Harvard University
- ***Oscar Ocaña***. Now Professor (Contratado Doctor) at Universidad de Jaén
- ***Aida Arcas.*** Now Research Scientist (Bioinformatician) at Clarivate.
- ***Luciano Rago.*** Now Research Scientist at EVOTEC, Toulouse, France.
- ***Melisa López-Antón.*** Now at Technology Transfer Office. Yale University, US.
- ***Alberto Cañibano.*** Now Postdoc at Universidad Pablo Olavide. Sevilla, Spain.
- ***Ismael Moreno.*** Now postdoc at CABD. Sevilla, Spain.

ADDITIONAL PI ACTIVITIES:

Invited conferences

Meetings: From 2020 invited to speak 48 meetings (30 international and 10 Spanish) of which 11 were Plenary/Keynote Lectures. Examples: Closing lecture XX International Course Developmental Biology, Chile 2025; II European Developmental Biology Congress, University of Oxford, 2023; Hegra Conference of Nobel Laureates and Friends. Saudi Arabia 2022; Opening lecture at SEBC Congress Madrid 2021; Keynote at VisegradSDB 2021 Szeged (Hungary); Keystone e-Symposium on “Plasticity” 2020; Closing lecture XX International Course Developmental Biology, Chile 2020.

Seminars: from 2020 invited to give 35 seminars including University of Heidelberg 2023; Kumammoto University Japan, 2023; University of Nebraska Medical Centre (UNMC) 2022; Induction Ceremony French Academy of Sciences, 2022; London Institute of Medical Sciences (LMS-MRC), 2021; University of Zurich, 2021; Induction ceremony Royal Academy of Sciences Spain 2020.