

## **Biosketch Darío Lupiáñez**

My research focuses on the mechanisms controlling 3D gene regulation and their influence on developmental phenotypes. I did my PhD at the University of Granada (Rafael Jiménez-Miguel Burgos group), investigating the development of ovotestes in female moles. We established the mole as a research model and discovered molecular events associated to the sexual features of this species. We found that female moles display an extreme heterochrony in female meiosis (Zurita et al., *Sex Dev*, 2007). We also discovered that mole ovotestes develop a profuse vascular system that facilitate the export of androgens to the body (Lupiáñez et al., *J Exp Zool Part B*, 2012). Further, we identified that mole ovotestis development is associated to alterations on the spatiotemporal expression pattern of key sex determining factors (Carmona et al., *Int J Dev Biol*, 2009 and *J Exp Zool Part B*, 2009).

Then, I performed a postdoc at the Max Planck Institute for Molecular Genetics in Berlin (Stefan Mundlos group). We developed a novel method to model large structural variants in transgenic mice (Kraft et al., *Cell Reports*, 2015). Using this methodology, we were first to report that disruptions on 3D chromatin organization can cause congenital disease (Lupiáñez et al., *Cell*, 2015; Will et al., *Nat Genet*, 2017; Kragesteen et al., *Nat Genet*, 2018). We established a conceptual framework for interpreting the effects of structural variants on 3D gene regulation (Lupiáñez et al., *Trends Genet*, 2016; Spielmann et al., *Nat Rev Genet*, 2018), as well as developing predictive computational approaches (Bianco et al., *Nat Genet*, 2018).

In 2017, I started my laboratory at the Berlin Institute for Medical Systems Biology / Max Delbrück Center for Molecular Medicine (BIMSB-MDC). There, I studied how alterations in 3D gene regulation may underlie the emergence of phenotypical traits during *evolution*. An example is our study on the mole genome and on the molecular causes of intersexuality (Real et al., *Science*, 2020). We developed a phylogenomic analytical framework to identify species-specific structural variants affecting 3D chromatin organization. We subsequently identified mole-specific variants associated to ovotestis development and validated them in transgenic mice. We also applied this approach to investigate the molecular origin of wing-like fins in skates, revealing an involvement of the PCP pathway in anterior fin elongation (Marlétaz et al., *Nature*, 2023). We also explored the molecular mechanisms that drive 3D chromatin organization in vivo. One example is our molecular characterization of TAD boundary elements, revealing their cooperative nature (Anania et al., *Nat Genet*, 2022).

Since mid 2023, I am a tenured scientist position (científico titular CSIC) at the Centro Andaluz de Biología del Desarrollo (CABD-CSIC/UPO/JA) in Seville. We combine approaches to map 3D chromatin structures and regulatory elements, as well as cutting-edge genome editing technologies. With a particular interest in studying sex determination, we have recently reconstructed gene regulatory networks (Mota-Gomez et al., *BioRxiv* 2022) or identified new players involved in this process (Hurtado et al., *Nat Comms*, 2024)

I have received several fellowships and awards, including an ERC Consolidator Grant, the EMBO Young Investigator or the ESHG Young Investigator Award. I have 33 publications and 2 preprints, including first or senior author in high-impact journals like *Cell*, *Science* or *Nature* with a total of 4,782 citations (Google Scholar). I have been

invited lecturer at more than 80 international research centers and conferences. I have been main organiser of several international conferences (8 in total), including 2 editions of the EMBO workshop “The evolution of animal genomes”. I have supervised 24 students (9 PhD). I review for several funding agencies, including the European Research Consortium (ERC), and journals including *Science*, *Cell* or *Nature*. I am associated editor of *Science Advances* since 2020, member of the editorial board of “Nucleus” since 2022 and part of the board of directors of the Spanish Society of Genetics (SEG) since 2023 and of the Spanish Society of Developmental Biology (SEBD) since 2024.