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Metarrestin blocks metastasis by impairing a new function of EEF1A involved in modulation of ribosomal biogenesis

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In the last decade a number of studies have indicated the importance of ribosomal biogenesis as a fundamental process controlling epithelial to mesenchymal transition (EMT) both during embryogenesis and cancer development. Studies toward understanding the underlying mechanisms responsible of neurocristopathies and metastasis have shown that the up-regulation of ribosomal biogenesis is important for promoting efficient EMT, migration and invasion. One cellular marker of metastatic potential is the perinuclear compartment (PNC), a unique structure adjacent to the nucleolus which indicates an elevated state of transcription and assembly of ribosomal components, and correlates clinically with metastasis of solid tumors.Screening and optimizing for disassemblers of the PNC, we identified metarrestin, a well-tolerated orally-bioavailable small molecule able to block metastasis in three different mouse cancer xenograft models of breast, prostate and pancreatic human cancers. In vitro, Mearrestin blocks migration and invasion of metastatic tumoral cells at nontoxic doses. Pull down studies identified EEF1A (EEF1A1 and EEF1A2) as the main binding partner of metarrestin. We then sought to validate this target by through siRNA treatments, evaluation of the levels of nascent pre-rRNA, visualization of nucleolar structure changes by immunofluorescence of key proteins. The results indicated that metarrestin blocks a previously unknown function of EEF1Ainvolved inthe up-regulation of the transcriptional activity of RNA Polymerase I. Metarrestin's modulation of Pol I-EEF1A-dependent function impacts ribosome synthesis and nucleolar structure without affecting other classical functions of this protein such as its role in translation elongation and protein synthesis. Our studies represent a broad and novel way to block the progression of tumorgenesis toward metastasis and open the door to the development of a new generation of nontoxic anticancer agents specifically blocking metastasis.

Biography:

Dr. Juan Marugan has been involved for more than 20 years in translational sciences, with extensive experience as a team leader of programs at lead optimization stage, many of which have been licensed to pharmaceutical companies, producing also several molecules that advanced toward pre-clinical development and clinical trials. His job responsibilities include lead discovery and optimization with early ADME and pharmacokinetics profiling, managing internal and external resources, structure-activity relationship optimization, chiral separation, and *in vivo* studies. He is also very familiar in other areas of translation such as structure-based drug design, high-throughput screening, enzymatic and cell assays, and *in vivo*disease models.

Dr. Marugan serves since 2008 as team leader within the division of preclinical innovation of NCATS. Previously he held positions of increase responsibilities in several pharmaceutical companies from research scientist to head of pre-clinical drug research.