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Metarrestin effectively disassembles PNCs and inhibits metastasis

Chen Wang[c], Kevin Frankowski[a], Teper Yaroslav[d], SamarjitPatnaik[b], Frank Schoenen[a], Steve Titus[b], Lesley Griner[b], Noel Southall[b], Christopher Dextras[b], Jamey Sultan[b], IrawatiKandela[e], MarzenaLewandowska[c], Yi-ping Wen[c], John Norton[c], Wei Sun[b], Andrew Mazar[e], Jeffrey Aubé[a], Wei Zheng[b], Marc Ferrer[b], Udo Rudloff[d],Juan Jose Marugan[b] and **Sui Huang[c*]**

[a]Specialized Chemistry Center, The University of Kansas, USA
[b]NIH Chemical Genomics Center, National Center for Advancing Translational Sciences, NIH, USA
[c]Department of Cell and Molecular Biology, Northwestern University, Feinberg School of Medicine, USA
[d]Thoracic and GI Oncology Branch, Center for Cancer Research, NCI, USA
[e]Developmental Therapeutics Core facility, Northwestern University and the Robert Lurie Comprehensive Cancer Center, USA

Metastasis is the leading cause of cancer mortality. However, the development of effective anti-cancer drugs able to specifically block metastasis has been hampered by the complexity and poor understanding of the cellular mechanisms that regulate this process. To identify small molecules that selectively target metastatic development, a large diverse chemical library was screened searching for compounds able to eliminate the perinucleolar compartment (PNC). The PNC is a subnuclear structure, whose formation positively correlates with the metastatic potential of cancer cells. PNC prevalence in several cancers inversely correlates with clinical outcome. Metarrestin, a compound obtained through medicinal chemistry optimization of a hit from the screen, disassembles PNCs in cancer cells at submicromolar concentrations and inhibits cancer cell migration and invasion *in vitro*. *In vivo,* metarrestin effectively inhibits metastatic growth in murine xenograft models of metastatic disease using human pancreatic, prostate, and breast cancer cells. At doses able to disassemble PNCs, metarrestin selectively disrupts nucleolar structure and inhibits Pol I transcription without affecting Pol II transcription or protein translation and without eliciting DNA damage-repair and apoptotic responses. Affinity purification using a biotin-conjugated analog of metarrestin identified eEF1A as a binding partner. Manipulation of EEF1A levels by overexpression significantly enhance PNCs. Metarrestin is a well-tolerated molecule with a desirable pharmacokinetic profile and a novel mode of action, representing a new therapeutic approach to the treatment of metastatic cancer.