doi: http://dx.doi.org/10.7124/bc.0009C9

Selective inhibition of me*tastasi*s in vivo, partly through disruption of nucleoli

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Identification and development of effective anti-cancer drugs using PNC as a phenotypic marker for metastatic potential of cancer cells. Methods: To identify compounds selectively targeting the metastatic state, we used the perinuclear compartment (PNC), a complex nuclear structure associated with metastatic behaviors of cancer cells, as a phenotypic marker for a high-content screen of over 140,000 structurally diverse compounds. Extensive medicinal chemical optimization of a screening hit yielded metarrestin, which has been evaluated for *in vitro* and *in vivo* efficacy against xenograft tumor growth and metastasis from three type's human cancers in animal models. Biochemical and cellular characterizations have identified some of the modes of action for metarrestin. Results: Metarrestin disassembles PNCs in multiple cancer cell lines, inhibits invasion *in vitro*, blocks metastatic development in three mouse models of human cancer, and extends survival of mice in a metastatic pancreatic cancer xenograft model even when macrometastasis have developed. Metarrestin induces little toxicity or discernable adverse effects in animals when treated daily up to 4 months. Metarrestin selectively disrupts the nucleolar structure and inhibits RNA polymerase (Pol) I transcription in cancer cells, at least in part by interacting with the translation elongation factor eEF1A2. Thus, metarrestin represents a potential therapeutic approach for the treatment of metastatic cancer. Conclusion: PNC and nucleoli may play roles in metastatic cancer development.

doi: http://dx.doi.org/10.7124/bc.0009CA

The systematic study on the epigenomics of mei-Cohesins in the norm and as Cancer-Testis proteins

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