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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.

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

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Meiotic cohesin subunits are frequently expressed in cancers as Cancer-Testis (CT) Genes, and are potentially linked to the onset and proliferation of tumor cells. However, the roles of CT genes, and mei-Cohesin components in particular, in cancer were not studied in depth. In order to address this gap in research we took two approaches : the epigenomics of mei-Cohesin in normal primate testis and the reconstitution of mei-Cohesin complexes in somatic cell lines, both normal and transformed. Applying a novel ChIP-ChEP-seq method in Macaca fascicularis testis, we elucidated the overlapping pattern of mei-Cohesin binding to germline chromosome arms and centromeric repeats for SMC1b, STAG3, RAD21L and REC8 subunits. We also uncovered the rules guiding the cohabitation of mei-Cohesins with BORIS/CTCFL and CTCF-containing regulatory sites controlling gene expression and 3D chromatin structure during the spermatogenesis. Finally, by reconstituting REC8 and RAD21L based mei-Cohesin complexes in human somatic cell lines, we discovered the governing principles for mei-Cohesin binding to chromatin. The introduction of particular combinations of mei-Cohesin subunits into such a system was setting up a potential competition with somatic cohesin complex based on RAD21, resulting in chromosome instability phenotype. As a result of this work, we elucidated the potential biological roles of mei-Cohesin expressed as CT genes in cancer cells.

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Life span-resolved nanotoxicology identifies nuclear amyloid, altered metabolism and neurodegenerative processes in the *nematode Caenorhabditis elegans*

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Along with the expanding application of engineered nanomaterials (ENMs), there is a growing concern over their adverse toxicological effects on human health and the environment upon release and exposure. ENMs are increasingly used in consumer products, as food additives and in drug delivery. To keep up with the fast pace of ENM development, medium to high throughput methodology is required to understand the bioavailability and long-term effects related to ENMs. For the analysis of ENM-long-term effects, we use the invertebrate Caenorhabditis elegans which lives for only 3-4 weeks and is a realistic target organism of ENMs in the environment as well as a top animal model in the laboratory. We exposed adult worms with environmentally relevant ENMs such as silver, silica, ZnO, CeO2 and polystyrene (nano plastics) in liquid media with bacteria in 96-well microtiter plates. The microhabitat in 96-well microtiter plates apparently excluded cultivation stress and thus, enabled analyses