Identifying molecular signatures of tumor dormancy as a basis for the rational design of precision nanomedicines

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Tumor progression is dependent on a number of sequential steps, including initial tumor-vascular interactions and recruitment of blood vessels, as well as established interactions of tumor cells with their surrounding microenvironment and its different immune, endothelial and connective cellular and extra-cellular components. Failure of a microscopic tumor, either primary, recurrent or metastatic, to complete one or more of these early stages may lead to delayed clinical manifestation of the cancer. Micrometastasis, dormant tumors, and minimal residual disease, contribute to the occurrence of relapse, and constitute fundamental clinical manifestations of tumor dormancy that are responsible for the majority of cancer deaths. However, although the tumor dormancy phenomenon has critical implications for early detection and treatment of cancer, it is one of the most neglected areas in cancer research and its biological mechanisms are mostly unknown.

To that end, we created several models of patient-derived cancer models mimicking pairs of dormant *versus* fast-growing, primary *versus* metastatic and drug-sensitive *versus* drug-resistant cancers using cutting-edge techniques of patient-derived xenografts, 3D printing and genetically-modified mouse models. We investigated the molecular changes in tumor-host interactions that govern the escape from drormancy and contribute to tumor progression. Those led to the discovery of novel targets and provided important tools for the design of novel cancer nano-sized theranostics (***thera***peutics and diag***nostics***).[1] Our libraries of precision nanomedicines are synthesized as highly controlled micellar, nanogels, coiled or globular particulated supramolecular structures consisting of linear, hyperbranched and dendritic polymers based on polyglutamic acid, polyethyleneglycol, poly(N-(2-hydroxypropyl)methacrylamide), polyglycerol, and hybrid systems.[2-6] We hypothesize that the acquired knowledge from this multidisciplinary research strategy will revolutionize the way we diagnose and treat cancer.

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