Design, synthesis and validation of nano-drug delivery systems in fluorescent cancer stem cell models

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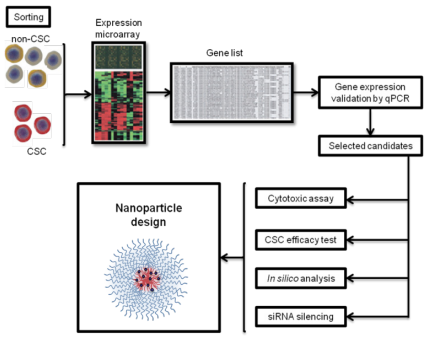
Metastatic spread to distal organs and progressive gain of chemo-resistance of advanced cancers are sustained by the presence of Cancer Stem Cells (CSCs) within the tumor. Therefore, many advanced therapies in development, aim to eliminate CSCs and thus prevent tumor growth and the appearance of metastases. Likewise, we developed polymeric nanoparticles loaded with ZileutonTM, a potent inhibitor of CSCs. ZileutonTM as anti-CSC drug was chosen based on specific target selection using various CSC fluorescent models, previously developed in our laboratory.

Drug delivery through nanoparticles has great potential to increase efficacy and reduce toxicity and adverse effects. In this context, ZileutonTM nanoparticles effectively target CSCs, block their ability to form mammospheres and to invade in vitro, and do not cause any toxicity in vivo, in healthy animals. Besides, our nanoparticles reduce number of CSCs within the tumor and effectively block the Circulating Tumor Cells (CTCs) in the blood stream.

However, therapies seeking for elimination of CSCs in order to prevent tumor growth and the appearance of metastases have an important limitation, because the eliminated CSCs are constantly replaced by new cells with "stem" phenotype, thanks to their considerable plasticity. Indeed, eliminated CSCs are being constantly replaced by a process of de-differentiation (reversion) of "bulk" tumor cells in order to ensure the propagation of the tumor after treatment. As a result, CSCs specific treatments have just limited clinical success. We have thus successfully evaluated, the combination of polymeric nanoparticles with ZileutonTM and the AbraxaneTM (Nab-PTX) nanoparticles used in clinic, that eliminate "bulk" tumor. This cocktail represents an ideal option to abrogate tumor and metastatic growth, avoiding CSC reversion (dynamic phenotype).



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