

**Title : Bifunctional Nanoparticles: pros and cons for the definition of
theranostic anticancer agents**

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Cancer targeted therapy aims at reducing unwelcomed effects on healthy tissues and at enhancing drug accumulation at the lesion site. The nature of delivery system (targeting strategy) and use of adapted drug combinations (therapeutic strategy) are of the outmost importance and it is tempting to develop multifunctional targeted and therapeutic particles that targets tumor cells but also induce curing effects. Integrins and Neuropilin-1 (Nrp1) are over-expressed in the tumor vasculature and tumor cells, and their expression has been correlated with angiogenesis and progression. Importantly, integrins and NRP1 can interact physically and functionally. In this study, we generated 15 batches of bifunctional [anti integrin] / [anti NRP1] NPs, that target integrin and NRP1 simultaneously. We introduced different ratio of [anti integrin] and [anti NRP1] targeting ligands (100/0, 25/75, 50/50, 75/25 or 0/100 % [anti integrin] / [anti NRP1] respectively) and increasing amount of total ligands/NP on the surface of silica-based NP. Our in vitro results demonstrate that NP with the highest number of ligands present the strongest binding efficiency in the selected integrins and Nrp1 higher expression cells, In particular, this leads to important and rapid internalization of receptors with a powerful inhibition of associated kinase activity. Unexpectedly, cell survival associated signaling pathway can be activated by indicated NPs independently of their blocking effect on upstream kinase activity. Interestingly, the activation of core survival signaling cascades varies according to the ratio of ligands and, more importantly to the amount of NP.

In conclusion, our study suggests that bifunctional [anti integrin] / [anti NRP1] NPs would be of great potential for cancer targeted drug delivery and therapy, but that their composition should be carefully selected. Importantly, their biological effect could vary according to their local concentration.