Versatile Polypeptide-based Nanoconjugates for Multimodal Therapeutic Applications

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Polypeptides are already playing a major role on a number of different relevant areas such as nanomedicine[1]. The physico-chemical parameters of a polypeptide-conjugate, and hence its biological performance, are defined by an intricate interplay of multiple structural factors. This highlights the need for detailed structure-activity relationship studies to develop the hierarchical strategies of polypeptide conjugate design. However, structural complexity also represents a unique opportunity, since small changes at the structural level might endow nanomedicines with outstanding and unexpected biological performance[1].

In our group, we have overcome the main classical limitations for the synthesis of defined polypeptides using precise controlled reactions followed by an adequate characterization yielding to well-defined polypeptidic architectures by NCA polymerization techniques[2]. In addition, post-polymerization techniques allow us the introduction of a variety of functionalities yielding a set of orthogonal reactive attachment sides[1,3]. Using these techniques and following a bottom-up strategy we have been able to obtain star-based polypeptide architectures with the capacity to self-assemble yielding supramolecular nanostructures with interesting properties[4]. This strategy together with an adequate polymer-drug linker design[5] enabled in vitro and in vivo evaluation, revealing a lack of toxicity, an enhanced in vitro cell internalization rate and significantly greater terminal and accumulation half-life in vivo together with a significant lymph node accumulation[4]. These results allow us to envisage these systems as promising nanocarriers for therapeutic or diagnostic applications, especially in anti-cancer treatments including lymph node metastasis and cancer immunotherapy. Proof of Concept for metastatic breast cancer [5,6] including brain metastasis, prostate cancer and for immunotherapy design in melanoma and pancreatic tumors will be also shown as well as the use of this self-assembled architectures in regenerative medicine applications such as neurodegenerative disorders[7]. Further exploration with polypeptides with inherent imaging properties are also being explored[8].

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