Versatile Star-shaped Polypeptide Conjugates with Controlled Self-assembly as Single Agents and in Combination Therapy

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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 [2].

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 (including stars, graft and block-copolymers) by NCA polymerization techniques [3]. In addition, post-polymerization techniques allow us the introduction of a variety of functionalities yielding a set of orthogonal reactive attachment sides [4]. 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 [5].

Star-shaped polypeptides with different cores and varied length of arms have been studied. We observed two different mechanism that control the self-assembling behaviour of these polymers. For compounds with short arms we observed formation of supramolecular polymers driven by hydrophobic interactions and hydrogen bonding. For bigger polymers we observed core-independent self-assembly. Supramolecular polymers and polyions with transition state formed distinct morphological structures - fibrillar and spherical, respectively. Interestingly enough, for some molecules we also observed an intermediate mechanism. Many compounds were found to be ionic strength and temperature dependent that directly correlated with the reported mechanism of self-assembly.

This strategy 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 [5].

These results allow us to envisage these systems as promising nanocarriers for therapeutic or diagnostic applications, especially in anti-cancer treatments. Additionally, further studies to identify the mechanism for the significant accumulation found in the lymph nodes will open up a wide range of opportunities for the currently unsuccessful clinical approaches to target lymph node metastasis, imaging of sentinel lymph node and cancer immunotherapy.

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