Targeting Tumor Microenvironment with Rationally Designed Polypeptide-based Conjugates

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The intrinsic characteristics of the tumor microenvironment (TME), including acidic pH and overexpression of hydrolytic enzymes, offer an exciting opportunity for the rational design of TME-drug delivery systems (DDS).

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 therapeutics with outstanding and unexpected biological performance [1,2].

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]. 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].

In order to target TME with the developed carriers, we synthesized and characterized pH-responsive biodegradable poly-L-glutamic acid (PGA)-based combination conjugates with the aim of optimizing anticancer effects. Different hydrazone pH sensitive linkers that can promote the specific release of the drug from the polymeric backbone within the TME have been implemented, together with a range of drug loading in order to achieve optimal effects on primary tumor growth, lung metastasis (~90% reduction), and toxicological profile in a preclinical metastatic triple-negative breast cancer (TNBC) murine model. The use of transcriptomic analysis helped us to identify the molecular mechanisms responsible for such results including a differential immunomodulation and cell death pathways among the conjugates. This data highlights the advantages of targeting the TME, the therapeutic value of polymer-based combination approaches, and the utility of –omics-based analysis to accelerate anticancer DDS [6].

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