Engineering Fructose-Based Single-Chain Nanoparticles: Modulating Cellular Uptake and Biodistribution

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Single-chain nanoparticles (SCNPs) are a class of ultra-small, intramolecularly crosslinked polymeric nanostructures, offering unique physicochemical properties and high tunability for biomedical applications.[1] In particular, SCNPs derived from fructose-containing polymers have emerged as promising candidates for targeted cancer therapy, owing to their specific interactions with fructose transporters (GLUT5) that are overexpressed in many tumor cells.[2,3] These sugar-based SCNPs demonstrate advantageous bio-interface characteristics, including enhanced cellular uptake, favorable pharmacokinetics, and improved tumor penetration.[4-6]

Despite their promise, the translation of SCNPs into clinically viable nanomedicines remains limited by several key challenges, such as insufficient *in vivo* stability,[7] suboptimal biodistribution,[8] and inconsistent cellular internalization across different cell types.[9] Moreover, systematic investigations into how chemical design affects biological fate—including circulation profiles, tissue accumulation, and cellular uptake efficiency—are still lacking.

To address these limitations, we have developed a library of fructose-based SCNPs engineered with two distinct strategies: (1) PEGylation, to improve colloidal stability and extend systemic circulation time; and (2) precise functionalization, by introducing a range of chemical moieties to modulate their interactions with cellular membranes and biological environments. These SCNPs were rigorously characterized and evaluated both *in vitro* and *in vivo* to dissect how structural variations impact biological performance.

Our findings reveal clear structure–activity relationships that highlight the role of surface chemistry and hydrodynamic size in determining uptake efficiency, circulation time, and organ distribution. This work provides fundamental insights into the rational design of SCNPs for improved performance in nanomedicine, paving the way for the development of next-generation targeted delivery systems.

References:

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