Engineering DNA Nanocrystals for Trigger-Responsive Drug Delivery: A Biocompatible Approach to Nanomedicine

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Cancer’s therapeutic landscape is significantly limited; chemotherapeutics indiscriminately target rapidly dividing cells, adversely affecting healthy tissues. While targeted nanomedicines are emerging, they rely on inorganic polymers and metal frameworks, introducing foreign materials into the body. Leveraging DNA’s universal biocompatibility, this study is the first to engineer programmable DNA nanostructures (pDn) to recognize the acidic tumor microenvironment for targeted drug delivery while also designing structures to selectively bind to lanthanides, which aggregate in tumor regions. After specifically designing a DNA triplex framework functionalized with the standard DNA I-motif for pH sensing, crystals were successfully purified and synthesized using hanging-drop purification, confirming design-assembly. To selectively bind lanthanide ions, the novel pDn was restructured, replacing the I-motif with modified DNA-based aptamers, and stabilized with double thymine tails. Crystals with the isolated hair-pin loop of uranyl-sensing aptamers (Kim, 2011) yielded peaks of 34.5 rfu, confirming selective pDn/metal-ion binding, establishing a baseline for lanthanide analysis. Synthesis of pDn with truncated lanthanide-sensing DNA aptamers (Andralojc, 2022) generated crystals with peak fluorescence at 5.1 rfu (excitation:500 nm, emission:595 nm), consistent with neodymium spectra. Additional UV-Vis absorption spectra yielded strong, standardized peaks for europium (415 nm) , gadolinium (615 nm), and neodymium (420 nm), further supporting pDns’ selective lanthanide-binding. Harnessing DNA's inherent biocompatibility and programmability successfully offers a groundbreaking solution to the long-standing challenges of targeted treatment and biomaterial incompatibility.

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