Building Safe Therapeutic Carriers from DNA: A Comprehensive Evaluation of DNA Nanostructure Biocompatibility

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The rapid advancement of DNA nanotechnology has enabled the precise design of nanostructures with diverse architectures and functionalities. These DNA-based assemblies hold great promise as vehicles for targeted drug delivery; however, their biological safety and immunocompatibility still remain insufficiently characterized. A major challenge lies in the potential recognition of DNA nanostructures as foreign entities by the immune system, which may lead to rapid clearance or inflammatory responses.

In this study, we conducted a comprehensive evaluation of the biocompatibility of five distinct DNA nanostructures: Y-shaped (Y), tetrahedron (Td), nanohydrogel (NHG), and two DNA origami designs—a flat, two-layer square (ORI) and its extension-bearing variant (ORIext). These structures were examined across multiple biological systems to assess their compatibility with key cellular and immune components. Specifically, their effects were tested on peripheral blood mononuclear cells (PBMCs), neutrophils, red blood cells, endothelial cells (HUVECs), and hepatocytes (HepG2). Cell viability, functionality, and activation were evaluated, and proinflammatory signaling was assessed using HEK-Blue™ reporter cells overexpressing Toll-like receptors (TLRs). Endotoxin contamination was determined via the Limulus Amebocyte Lysate (LAL) assay.

Our results demonstrated high biocompatibility of all tested DNA nanostructures, with no evidence of cytotoxicity, hemolytic activity, or immune activation. Moreover, our research addresses the need for a detailed analysis of the biocompatibility of DNA nanostructures, considering their potential as delivery systems for modern, advanced therapeutics. A comprehensive approach to biocompatibility assessments that exceeds standard viability tests will improve the safety of DNS and support the successful translation of DNA-based nanomaterials from basic research to clinical use.

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References

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Figures

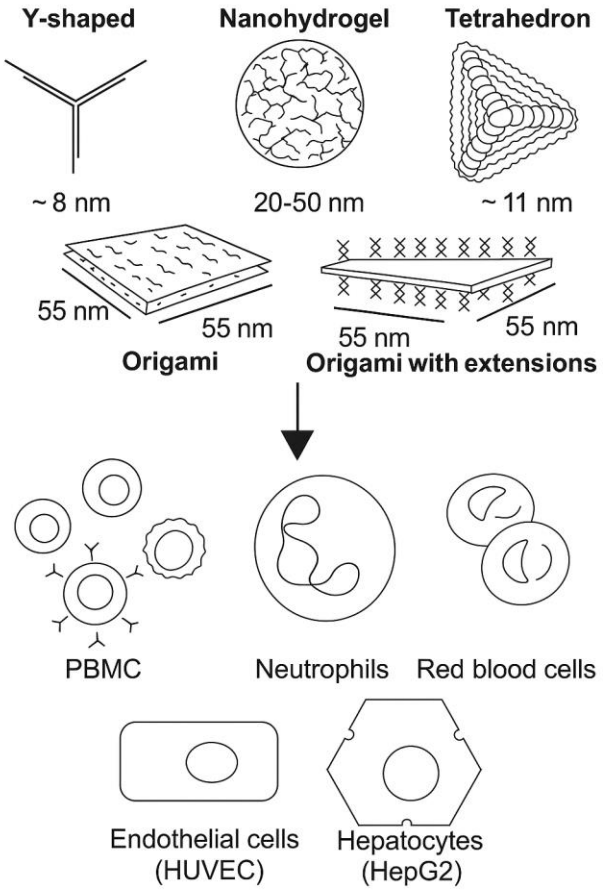

Figure 1. Schematic representation of the analyzed DNA nanostructures and the cells used for their biocompatibility evaluation.