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DESIGN AND DEVELOPMENT OF A PROTECTIVE DNA NANO-TUBE USING DNA ORIGAMI FOR ENHANCED CANCER GENE THERAPY*

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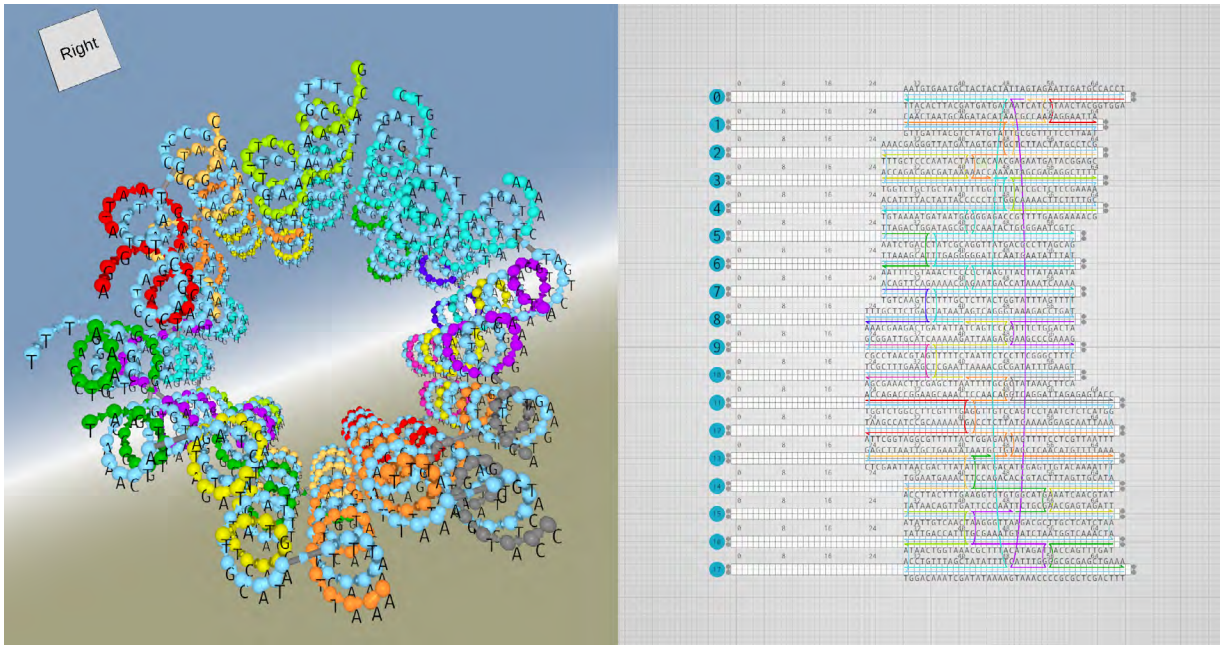
Abstract

In this study, we used DNA origami designing methods to develop a cost-effective DNA nano-tube, serving as a protective scaffold for incorporated therapeutic nucleic acids (TNAs). Our mini DNA origami construct is designed to provide protection from intracellular nucleases and to allow cancer markers entry for the selective release of TNAs.

Gene interference strategies based on therapeutic nucleic acids (TNAs), including, antisense oligonucleotides (ASO), RNA interference, ribozymes, and DNAzymes, provide promising pathways for treating human diseases [1]. However, each strategy comes with its own set of benefits and limitations that hinder the clinical use of these agents. Major challenges include low stability, difficulties in targeting specific molecules, and inefficient intracellular delivery, leading to poor selectivity, suboptimal efficiency, and off-target effects [2].

Introduced by Paul W.K. Rothemund in 2006, DNA origami allows for the precise folding of DNA into specific structures. This groundbreaking technique has expanded possibilities for biomedical applications, inspiring the development of novel, marker-activated nanomachines for targeted gene therapy [3, 4].

Through careful design, modification, and evaluation of stable DNA origami structures, this research seeks to develop a highly selective and effective approach for tumor therapy. The initial nano-tube design, created using caDNAno software, features 18 dsDNA helices formed by a 700-nucleotide-long scaffold and 24 staples ranging from 18 to 38 nucleotides. This design was further optimized with the ENSnano software, ensuring the scaffold's position minimizes anti-patterns in the staple sequences (see Figure). Remarkably, this nano-tube requires only a few amount of staples and a relatively short scaffold, eliminating the need for the traditional 7249-nucleotide M13mp8 genome and hundreds of staples used in DNA origami constructs [3],



DNA nano-tube design on ENSnano without staples overhangs

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thus proving its cost-efficiency. Additionally, overhangs were designed as additions to the generated staples to incorporate TNAs designed for cancer gene therapy. The nano-tube's pore allows small-sized nucleic acid cancer markers to enter and interact with the TNAs, ensuring their selective release within cancer cells. This nano-tube holds promise to facilitate gene silencing, offering a powerful method to combat cancer progression.

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