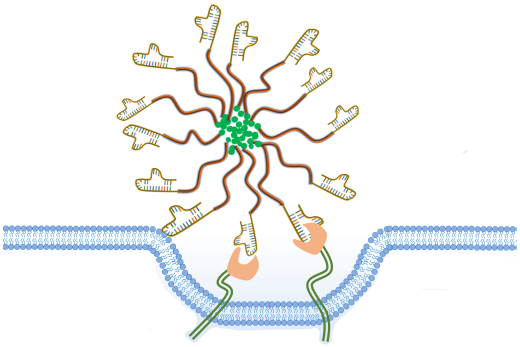
Enzymatic synthesis of aptamer-targeted polynucleotide drug delivery platforms for cancer therapy

Duke LICENSING & VENTURES



Unmet Need

In the United States alone, over 1.8 million new patients were diagnosed with cancer in 2021, and over 600,000 patients died from the disease. Cytostatic nucleotides, such as gemcitabine and 5-fluorouracil, have been used for the treatment of multiple cancers – however, current delivery methods for these drugs are inefficient resulting in poor pharmacokinetics and pharmacodynamics, as well as systemic off-target toxicity. These issues can lead to drug resistance and tumor recurrence in patients. Nanoparticles, which can be naturally derived, chemically synthesized, or made up of hybrid materials, have been developed to address these therapeutic issues – however the design of these nanoparticles is highly complex and involves multi-step chemical conjugation processes to generate. There is a need for a nanoparticle-based delivery method that would increase therapeutic efficacy, improve target specificity and enhance bioavailability of cytostatic nucleotides as well as simplify the design to allow for improved structure and architecture.

Technology

Duke inventors have developed a delivery method for non-natural therapeutic nucleotides for the treatment of diseases such as cancer. This is intended to be used for patients whose tumors over-express cell surface receptors, such as nucleolin or interleukin-6, that can be targeted with an aptamer. Specifically, this nucleic acid-based delivery platform consists of the targeting moieties as aptamers, polymerized cytostatic nucleotides, and non-natural nucleotides that can self-assemble into nanoparticles. Self-assembly leads to simplified generation of nanoparticles thus addressing a key current limitation of other nanoparticle delivery systems. Additionally, these nanoparticles display high avidity to malignant cells and thus enhanced delivery of chemotherapeutic nucleotides, thereby decreasing off-target toxicity. Duke inventors have successfully synthetized amphiphilic polynucleotides that self-assemble into micellar nanoparticles and are stable for 24 hours. This has been demonstrated using an aptamer targeting prostate-specific membrane antigen and a derivative of the approved cancer drug 5-fluorouracil.

Duke File (IDF)

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Inventor(s)

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- Zauscher, Stefan

Links

- From the lab of Dr. Ashutosh Chilkoti
- High-Molecular-Weight Polynucleotides by Transferase-Catalyzed Living Chain-Growth Polycondensation (Angewandte Chemie, 2017)
- Enzymatic synthesis and modification of high molecular weight DNA using terminal deoxynucleotidyl transferase (Methods Enzymol, 2019)
- Enzymatic Synthesis of Nucleobase-Modified Single-Stranded DNA Offers Tunable Resistance to Nuclease Degradation (Biomacromolecules, 2018)

Other Applications

This technology could also be used to deliver nucleotide analogs that would be used for the treatment of viral diseases such as SARS-CoV-2.

Advantages

- Drastically simplified route for synthesis of “all nucleotide” drug delivery platform
- Improved target specificity compared to current nucleoside analog delivery systems
- Enhanced bioavailability leading to lower dosing requirements and superior clinical efficacy

Publications

- Concentration-independent multivalent targeting of cancer cells by genetically encoded core-crosslinked elastin/resilin-like polypeptide micelles. (Biomacromolecules, 2021)
- U.S. Patent Application (US16/927,982)

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