Enzymatic Synthesis of Aptamer-Targeted Polynucleotide Drugs for Cancer Therapy

Cytostatic nucleosides are nucleoside analogs that are widely used in cancer treatment, however, a big challenge for these therapeutics is their targeted administration to malignant cells. Polymeric nanoparticles are one of the most common carriers that translate the potency of drugs into multifaceted delivery systems that target malignant cells and accumulate in tumors by taking advantage of the EPR effect. Here we present the proof-of-concept for a nucleic acid-based delivery system that consist of (i) cytostatic nucleotides as part of the delivery carrier, and (ii) aptamers that mediate targeted drug delivery. In this delivery system we exploit our recent discovery that terminal deoxynucleotidyl transferase (TdT), a template independent polymerase, can polymerize nucleotide triphosphate by a living chain-growth polycondensation mechanism, we term TdT catalyzed enzymatic polymerization (TcEP). TcEP allows for the manipulation of the molecular weight of the reaction products by the feed ratio of nucleotide (monomer) to oligonucleotide (initiator) and provides access to amphiphilic polynucleotide architectures that can self-assemble into multifunctional micellar structures. Building on this discovery, we use TcEP to grow a polynucleotide chain that consist of repeats of cytostatic nucleosides (e.g., FdUTP), from an initiator that consists of a DNA or RNA aptamer. This “one-pot” enzymatic polymerization strategy thus enables us (i) to maximize drug loading through direct polymerization of cytostatic nucleotides; i.e., the active drug is an integral, structural part of the delivery platform, and (ii) to streamline nanoparticle formation by using TcEP to append a hydrophobic domain to the 3’-end to drive micellar self-assembly in solution.

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Professor Zauscher is an expert in (bio)surface and interface science, where his research is broadly focused on studying the behaviors and properties of soft-wet materials on surfaces and interfaces. A large portion of Prof. Zauscher’s work is focused on fabrication and characterization of surface-confined biomolecular and polymeric micro- and nanostructures and the necessary methodologies to manipulate these structures at the nanoscale. Within this broad research scope, his research crosses disciplinary boundaries. Recent, translational research activities in his lab have also led to intellectual property and the founding of a startup company. This company develops microfluidic quartz crystal microbalance sensors that sense the presence, adsorbance, and binding of biological analytes in liquid environments with unprecedented sensitivity. Prof. Zauscher authored/co-authored over 150 publications, with ~8500 citations and a Google Scholar h-index of 42.