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Synthesis of DNA-Peptide-DNA Triblock Molecules

-Hybrid oligonucleotide-peptide compositions have many applications including DNA and RNA delivery, dynamic biomaterials, and hybrid self-assembling nanomaterials. The different components impart different activities; the peptide can be used for cell targeting, endosomal escape, cell surface receptor engagement, or enzymatic responsiveness, while the oligonucleotide component can be used for cargo attachment, dynamic exchange, or immobilization on a DNA nanostructure. The creation of such hybrid materials with orthogonal oligonucleotides on either side of the peptide, with site-specificity, is much less common and much more challenging. However, these types of triblock molecules can have their own unique applications, such as biosensors, reporters of protease activity, templates for protein synthesis, and more.

Researchers at the Biodesign institute of Arizona State University have developed a novel method for synthesizing DNA-peptide-DNA (DPD) triblock molecules as well as uses for such molecules. The method involves attaching oligonucleotide sequences on each side of a peptide that are partially complementary with each other. Because the two oligonucleotide regions are only partially complementary, a stable DPD hairpin can be created that is short enough to enable easy strand displacement.

This technology presents an easy and effective method for creating DPD triblock molecules that have a multitude of applications in drug delivery, novel nanostructures, constraining peptides to biologically active confirmations and more.

Potential Applications

- Biosensors
- Novel Peptide-DNA nanostructures

- Stimulus-responsive therapeutic carrier/delivery vehicle/nanostructures
- With DNA cleavage, the remaining peptides could serve as monomers for full-length protein synthesis
- Cleavable reporters of protease activity
- Latches for oligonucleotide nanostructures
- Logic-gated degradable crosslinks for hydrogels
- Used to constrain peptides into a loop structure or other biologically active conformation
- Folded copolymers with multiple peptide loops for multivalent target binding

Benefits and Advantages

- The partially complementary DNA strands keeps the hairpin stable but short enough to enable easy strand displacement
- These DPD molecules can be used for many different applications with modifications to the structures
- Can be used to create (DNA-peptide)n alternating copolymers
- May also be amenable to creating DNA-protein-DNA triblock molecules
- Better yield and greater simplicity

For more information about this opportunity, please see

MacCulloch et al - ChemComm - 2022

For more information about the inventor(s) and their research, please see

Dr. Stephanopoulos' Biodesign webpage

Dr. Stephanopoulos' laboratory webpage