A NOVEL SOLID SUPPORT FOR EFFICIENT REDUCTION OF PROCESS-RELATED IMPURITIES IN SYNTHETIC NUCLEIC ACID SEQUENCES

Technology Summary

The purity of synthetic nucleic acid sequences is essential to produce safe and efficacious nucleic acid-based drugs intended for antisense or RNA interference therapies. The use of antisense DNA (asDNA) sequences or small interfering RNA (SiRNA) duplexes have been demonstrated to be highly potent at silencing the expression of disease-causing proteins *in vitro*. However, the clinical applications to treat human diseases have been hindered by a number of fundamental issues including: (i) instability in biological media; (ii) poor delivery to target cells; (iii) poor uptake by target cells; and (iv) dose related toxicities (severe thrombocytopenic and/or peripheral neuropathy). One of the causes for these issues is the contamination with process-related impurities which consist of partially protected and/or 5'-uncapped DNA/RNA sequences that lead to the production of unwanted products.

To address this issue, FDA investigators have developed an improved solid support system that reduces impurities during the production of synthetic nucleic acid sequences. The solid support system consists of a 3-hydroxypropylated controlled-pore glass (CPG) support that has been prepared and functionalized with multiple hexaethylene spacers. The key difference in the CPG support is the transfer of the attachment site of the leader nucleoside further from the core of the solid support. This action facilitates the diffusion of the reagents and solvents to the lead nucleoside of the DNA/RNA sequence. Proof-of-concept studies show a reduction of process-related impurities in the nucleic sequences to an extent of <50%, when compared to that of the current commercially available, state-of-the-art long-chain alkylamine controlled pore glass (LCAA-CPG) supports.

Potential Commercial Applications

- Purification of synthetic nucleic acid sequences

Competitive Advantages

- Attachment site of the leader nucleoside moved to allow increased diffusion of reagents and solvents
- Reduction in contaminants during solid-phase synthesis

Development Stage:

- Proof of Concept system
- Development of automated, high-throughput system

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Publications:

- Grajkowski, A., et. al. An Improved PEG-Linked Solid Support for Minimizing Process-Related Impurities During Solid-Phase Synthesis of DNA and RNA Sequences. Curr Protoc. 2021 May;1(5):e108. PMID: 33945676

Product Area: CPG support, nucleic acid-based drugs, solid-phase DNA/RNA synthesis

FDA Reference No: E-2020-015

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