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Systemic Delivery Remains a Major Challenge for Oligonucleoide-based Therapeutics?

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There is an increasing interest in development of technologies employing synthetic oligonucleotides for manipulating gene expression. The interest in oligonucleotides arose because of the pioneering work of Paterson et al. [1], who showed that exogenous nucleic acids modify gene expression, and Stephenson and Zamecnik [2], who demonstrated that a short oligodeoxyoligonucleotide (13-mer) antisense to Rous Sarcoma Virus (RSV) inhibits viral replication in cell culture. Further studies revealed that these antisense oligonucleotides block gene expression by either sterically obstructing ribosome necessary for transcription or forming a RNA-DNA duplex, which becomes substrate for RNase H enzyme that cleaves the RNA strand of RNA-DNA complex [3]. Another promising mechanism by which oligonucletides inhibit gene expression is RNA interference (RNAi) or posttranscriptional gene silencing mechanism, where a double-stranded small interfering RNA (siRNA) targets mRNA for cleavage in a sequence-specific manner [3]. Aptamers are also oligonucleotide-based product but, unlike antisense and siRNA, selectively bind to target molecules, ranging from small molecules to proteins. When bound to target proteins, aptamers are able to interfere with their biological activity [3].

The researchers were quick to realize the immense potential of oligonucleotides in treating viral diseases and cancer. However, the potential could not be immediately realized because of some inherent drawbacks associated with oligonucleotide-based therapeutics-chemical synthesis, degradation by nucleases in circulation, and poor systemic delivery. Thanks to tremendous efforts of Khorana, Letsinger, and Caruthers [4], solid-phase synthesis of oligonucleotides has now become routine, similar to peptides. The problem of poor stability in blood plasma has been addressed by incorporating chemical modifications in oligonucleotide structure (e.g. phosphorothioate oligonucleotide, 2'-O-methyl oligonucleotide, morpholino oligonucleotide, locked nucleic acid, etc).

In spite of above developments, the full therapeutic potential of oligonucleotides has not been fully realized. So far only two products, fomivirsen (withdrawn due to poor demand) and pegaptanib, have been approved for clinical use and it is intriguing to note that both approved therapies are administered locally (intravitreally). The major hurdle impeding the path of oligonucleotide-based therapeutics is their poor systemic delivery. Several approaches are being explored to address the issue of poor system delivery but each has its own limitations. The viral vectors are efficient but there are safety concerns associated with them. Liposomes are great alternatives but there are concern about their loading, stability, and storage. The cationic peptides and polymers are also being investigated but they show poor efficiency. Recently developed Stable Nucleic Acid Particle (SNALP) for siRNA delivery appears to be a promising alternative. However, we are still far away from a major breakthrough that will fully address the issue of poor systemic delivery associated with oligonucleotide-based therapeutics.

References

1. Paterson BM, Roberts BE, Kuff EL (1977) Structural gene identification and mapping by DNA-mRNA hybrid-arrested cell-free translation. Proc Natl Acad Sci USA 74: 4370-4374.

2. Stephenson ML, Zamecnik PC (1978) Inhibition of Rous sarcoma viral RNA translation by a specific oligodeoxyribonucleotide. Proc Natl Acad Sci USA 75: 285-288.

3. Opalinska JB, Gewirtz AM (2002) Nucleic-acid therapeutics: basic principles and recent applications. Nat Rev Drug Discov 1: 503-514.

4. http://www.trilinkbiotech.com/tech/oligo_history.asp

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