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Editorial Open Access

Gene Silencing by Catalytic DNAzymes – Potential Future Therapeutics

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Editorial

The discovery of DNA polymerases, Restriction enzymes and Reverse transcriptase has revolutionized Gene Technology in the last four decades. Progress in these areas was augmented by the development of various techniques to synthesize nucleotide substrates with various modifications. Rapid advances were made in gene sequencing which paved the way for sequencing of many genomes across different phyla. All these contributed immensely to the design and development of nucleic acid therapeutics for various diseases. Antisense oligonucleotides were the first one to be tested by Zamecnik's group in 1978 to inhibit retrovirus replication. Since then many antisense oligonucleotides targeting specific messenger RNAs (antisense approach), triplex or quadruplex-forming oligonucleotides targeting various genes (antigene approach), siRNAs targeting various transcripts, and finally DNAzymes targeting specific gene transcripts have come into vogue.

Antisense drugs to treat a variety of diseases including cancers, diabetes, infectious, and inflammatory diseases are being researched [1] and as of 2014 only two antisense drugs, Vitravene and Kynamro, have been approved by the US Food and Drug Administration for the treatment of cytomegalovirus retinitis and for homozygous familial hypercholesterolemia, respectively. Given the length of time, effort and money spent on these antisense drugs it is somewhat disappointing to find that this approach has not been successful due to inherent problems in targeting specific gene transcripts whose expression level and half-life vary from gene to gene.

The recently discovered siRNA appears to be a better approach due to selectively silencing the endogenous regulatory pathway of RNA. However, there are serious limitations in this approach because of the vulnerability of RNA molecules to ribonucleases in the intracellular milieu, activation of innate immune response, and non-specific side reactions [2,3]. Nevertheless the optimism persists that these can be developed as potential therapeutics; the fact that more than 20 to 25 siRNA drugs, targeting various RNAs, are in clinical trials vouch for their potential.

Selection of the target and the design of proper drug are the critical barriers in developing therapeutics. Considering the problems associated with antisense drugs, siRNAs, RNA cleaving-DNA enzyme (DNAzyme) technology is a better and novel therapeutic approach to control tumor growth. DNAzymes are single-stranded catalytic DNA molecules that can bind to and specifically cleave targeted mRNA with a catalytic efficiency of greater than 10^9 $M^{-1}min^{-1}$, higher than any known nucleic acid enzyme. DNAzymes are stable in serum and contrary to siRNA, can be distributed to all major organs including brain, when systemically administered, without a need for retroviral vector or lipid base vehicle. They are also more stable than siRNA drugs and their synthesis is easy and inexpensive. Intensive research led to the identification of an extremely potent DNAzyme referred to as '10-23' cleaving DNA enzyme where, the central catalytic motif is flanked by two arms of complementary sequence to the target RNA. This approach is highly specific and has enormous potential for applications in all types of cancers, diabetes, viral diseases, etc. Preclinical studies indicated that DNAzymes targeting c-jun is safe, well tolerated, and inhibited the growth of two major skin tumor types in animal models [4]. Phase 1 clinical trial has also shown that the DNAzymes are safe and well tolerated. DNAzyme targeting c-jun and EBV-LMP1 protein in nasopharyngeal carcinoma are in phase I/II clinical trials [5,6]. Many others including programmable DNAzymes [7] will enter into clinical studies in near future. Since DNAzymes are catalytic molecules in many instances a single injection appears to be sufficient to have a sustained inhibition of the target mRNA silencing. This is one major advantage in this approach. We think that if we can identify the key regulatory molecules in various diseases, it would be possible to develop DNAzymes as the most effective anti-therapeutic drugs.

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