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Series Introduction: Emerging clinical applications of nucleic acids

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Perspective

Attempts to employ nucleic acids in gene therapy have become commonplace in recent years, but efficient gene transfer methods have proved unexpectedly difficult to devise, and safety concerns linger. At the same time, however, the study of nucleic acids has revealed remarkable properties of DNA and RNA molecules that could make them attractive therapeutic agents, independent of their well-known ability to encode biologically active proteins. Now would seem to be a good time to consider alternative uses of nucleic acids that do not rely on virus-based vectors or even on gene transfer. Accordingly, the strategies explored in this Perspective series exploit a number of different facets of RNA and DNA biochemistry. Certain nucleic acid molecules can bind to and inhibit the function of target proteins, while others provide a source of tumor antigens, and still others can perform catalysis. Recently, therapies that employ nucleic acids in some of these novel ways have passed the stage of in vitro and animal tests and have begun to be evaluated in clinical trials for treating a variety of disorders. This Perspective series offers an update on the progress in this field. Nucleic acids that bind to target molecules The concept of using nucleic acids to bind to and inhibit the activities of target proteins grew out of early HIV gene therapy studies that […]

SERIES INTRODUCTION

Emerging clinical applications of nucleic acids

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Attempts to employ nucleic acids in gene therapy have become commonplace in recent years, but efficient gene transfer methods have proved unexpectedly difficult to devise, and safety concerns linger. At the same time, however, the study of nucleic acids has revealed remarkable properties of DNA and RNA molecules that could make them attractive therapeutic agents, independent of their well-known ability to encode biologically active proteins. Now would seem to be a good time to consider alternative uses of nucleic acids that do not rely on virus-based vectors or even on gene transfer.

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Nucleic acids that bind to target molecules

The concept of using nucleic acids to bind to and inhibit the activities of target proteins grew out of early HIV gene therapy studies that employed RNA ligands, termed decoys, to competitively inhibit the activities of essential HIV proteins and in the process block viral replication (1). TAR and RRE decoys were expressed in cells to bind and squelch the activities of the HIV RNA-binding proteins tat and rev. Similarly, double-stranded DNA decoys have been employed to squelch the activities of a variety of transcription factors (2). The use of combinatorial libraries of nucleic acids and in vitro selection methods, termed SELEX, allow nucleic acid–based ligands (aptamers) to be developed as specific, high-affinity antagonists to virtually any target protein (3, 4). The ability to modify nucleic acids to enhance the stability and bioavailability of decoys and aptamers should allow these nucleic acid–based therapeutics to be administered in a manner more like traditional drug delivery than like gene therapy.

Three papers in this series describe the development of therapeutic decoys and aptamers. Hicke and Stephens discuss the potential utility of aptamers as imaging reagents, and White, Sullenger, and Rusconi review the development of therapeutic aptamers. Finally, Mann and Dzau provide the reader with an overview of the transcription factor decoy approach and discuss results from early clinical trials using this therapeutic strategy.

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Nucleic acids that encode tumor antigens

The field of cancer immunotherapy has recently undergone a revolution with the discovery that vaccination with tumor antigen–loaded dendritic cells can elicit protective immunity in animals challenged with tumors (5). This observation has led many investigators to attempt to define the most effective tumor antigens for immunotherapy. Mitchell and Nair describe recent efforts to employ total tumor RNA as the source of antigen for such vaccination strategies. As the authors argue, one potential advantage of this approach is that such antigens can be obtained from even a few tumor cells taken from a patient, because standard molecular techniques allow RNA isolated from these cells to be amplified without limit. The authors also discuss the future clinical prospects for this new nucleic acid–based vaccination strategy.

Nucleic acids that perform catalysis

The discovery by Cech and Altman that certain RNAs can perform catalysis dramatically changed how scientists viewed the role of nucleic acids in nature (6, 7). The observation that certain catalytic RNAs, termed ribozymes, can be made to specifically cleave (8, 9) or splice (10) target RNAs has engendered much excitement about the potential therapeutic utility of these molecules. Much of this effort originally focused upon the use of ribozymes in gene therapy strategies. More recently however, much progress has been made in the development of synthetic nuclease-resistant ribozymes for therapeutic applications. In addition, through the use of in vitro evolution techniques, DNA-based enzymes have also been obtained that cleave target RNAs (11). In this Perspective series, Usman and Blatt describe recent advances in the use of synthetic ribozymes in animals and the clinic, and Khachigian discusses the potential utility of DNA enzymes as therapeutic agents.

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