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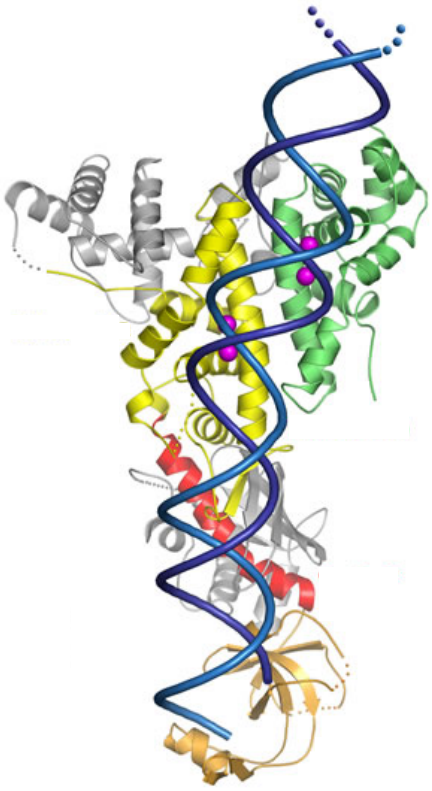
City of Hope
NATIONAL MEDICAL CENTER AND
BECKMAN RESEARCH INSTITUTE

Signal Activated RNA Interference



DESCRIPTION

RNAi therapy, the process of using a short sequence of siRNA to silence a gene, is currently limited by an inability to completely avoid non-specific distribution of siRNA once introduced to the body; siRNA could potentially enter healthy cells and alter normal gene expression. This limits RNAi therapy targets to genes that are not expressed in normal cells or to isolated tissues, such as the eye, that are directly accessible. This joint City of Hope and Caltech technology greatly expands the possibilities for RNAi therapy by targeting cells with a specified genetic profile and, in those cells only, activating siRNAs that need not be inherently cell-specific.

By carefully designing a construct with overlapping sequences, siRNA is packaged into a larger pseudoknot structure that is unrecognizable to cellular enzymes and renders the siRNA inactive. If a cell expresses a specific gene, part of the pseudoknot binds to that mRNA, and the structure unfolds. Once unfolded, RNAse H and Dicer enzymes can cleave the pseudoknot RNA and release the disguised siRNA to silence its targeted gene. For example, constructs could be designed such that anti-HIV siRNAs are only activated when HIV is present, creating a negative feedback mechanism to control virus replication. Alternatively, the technology could be used in concurrence with other therapies; for example, a construct could be designed to inhibit P-glycoprotein production, a protein associated with multi-drug resistance, when activated by genes expressed in cancer cells. This would restore drug susceptibility to tumors without silencing the same gene in other cells such as hepatocytes, hematopoietic stem cells, or the blood-brain barrier where expression is vital to tissue function.

KEY ASPECTS

- Allows cell-selective RNAi therapies that are activated by specific gene expression
- Applications in gene therapy,antiviral therapeutics, and cancer therapeutics

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Title	US Application Number	Filed
Pseudoknot constructs for signal activated RNA interference	61/613,617	3/21/2012

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