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## A Review on siRNA Therapeutics



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### ABSTRACT

The siRNA (small interfering Ribonucleic acid) is advanced therapeutics, which is used in various high-risk diseases such as cancer, viral infection, respiratory disorder and autoimmune-disorder. siRNA have great advantage due to its ability to silence the gene expression, those genes which are able to cause disease. siRNA therapeutics is used in treatment of wide range of diseases due to its specificity, adaptability and broad targeting capability. Due to lack of ability to cross cell membrane and stability in bloodstream, the siRNA formulated in the form of nanoparticles, liposomes, polymer lipid system and dendrimers to overcome this problem and utilise the potential of these therapeutic system. This review includes mechanism of action, barriers to siRNA therapeutics and strategies to overcome them and sources of precursor.



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## INTRODUCTION-

RNAi is an endogenous pathway, in that pathway, the double stranded RNA (dsRNA) triggers the silencing of the gene expression after the transcription by activating siRNAs can silencing any gene expression with higher specificity and efficiency. The siRNA therapeutics is used in the treatment of cancer, respiratory disorder, auto-immune disorder, viral infection and hereditary disorder. The siRNA based therapeutic is the need of effective and safe delivery of drug. The main problem with siRNA therapeutics is it does not readily cross the cell membrane and stability problem in bloodstream, to overcome this problem modification is needed in the dsRNA. Therefore siRNA therapeutics requires to chemical modification, to bring siRNA to its site of action without adverse effect. The siRNA drug delivery system having high affinity towards antibody or antibody fragment or receptor ligands to bind with surface receptor and mediate cell specific uptake. This is an overview targeted delivery of siRNA. In nontargeted delivery to tackle the problem of intracellular delivery and rapid excretion siRNA formulated in the form of lipid nanoparticles (LNPs) and these LNPs are small and homogeneous. In siRNA therapeutic system gene silencing is produced by introduction of synthetic RNA in to the siRNA to the target cell to elicit RNA interference that results into inhibition of specific mRNA expression. (1,2,7,9,10)

## DIFFERENCE BETWEEN siRNA and miRNA

siRNA	miRNA
<ol style="list-style-type: none"> <li>1. siRNA has important function is gene silencing.</li> <li>2. siRNA is full complementary for miRNA.</li> <li>3. Mean length of siRNA approx. 20 – 22nt.</li> <li>4. The action of siRNA is cleaving mRNA.</li> <li>5. siRNA is either a natural or a synthetic one.</li> <li>6. clinical application – Therapeutic agent</li> </ol>	<ol style="list-style-type: none"> <li>1. miRNA has play important role in Gene regulation.</li> <li>2. miRNA partial complementary to siRNA.</li> <li>3. Mean length of miRNA approx. 19 – 25 nt.</li> <li>4. Action is inhibiting or replaces translation of mRNA.</li> <li>5. miRNA is natural molecule.</li> <li>6. clinical applications – Drug target therapeutic agent Diagnostic and biomarker tool.</li> </ol>

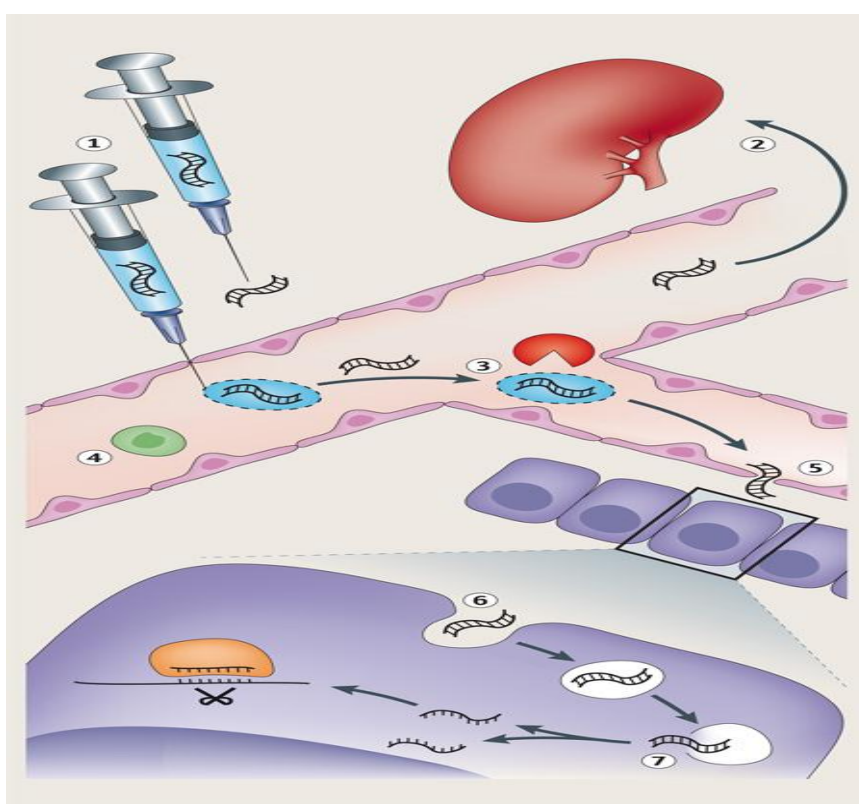
(5,6)

**MECHANISM OF ACTION-** There are two main stages for the mechanism of siRNA mediated gene silencing mainly post-transcriptional (PPGS). The PPGS can be further classified into the mechanism called the direct sequence-specific cleavage leading to translation repression and consequent degradation and transcriptional gene silencing (TGS). Both of each have specific repression effect. The ribonuclease protein called Diser which identified and cleaves the endogenous dsRNA in to the small double stranded fragments of 21 to 23 base pair in length with 2- nucleotide overhangs at the 3' end. This is called as siRNA to the RNA inducing silencing complex (RISC) passenger strand and guide strand connected to each other, after binding to RISC the guide strand target to mRNA argonaute-2 which cleaves mRNA in to small pieces between bases 10 and 11 to the 5' end of siRNA guide strand so the process of mRNA translation can be interrupted by siRNA. The mRNA mediate pathway gene silencing mechanism involves affecting the mRNA stability by inhibiting protein translation or by mediating its degradation or by inhibiting protein translation or interfering with the polypeptide through complementary binding to 3' UTR of specifically targeted mRNAs. (1,3,4,5,9)

**Table No. 1: Different used siRNA therapeutics (5,7,9)**

Sr. No.	Disease	Targeted Gene	Route of Administration	Targeted Organ
1.	Asthma	IL-13	Intravenous	Lung
2.	Breast cancer	C-X-C Chemokine receptor type 4	Intravenous	Lung metastatis
3.	Colorectal cancer	XIAT	Intratumoral	Colon
4.	Colon cancer	$\beta$ -Catenin	Intraperitoneal	Subcutaneous, Liver metastatis
5.	Ewingh Sarcoma	Vascular endothelial growth factor	Intrathecal	Subcutaneous
6.	Fibrosarcoma	Vascular endothelial growth factor	Intraperitoneal. Intravenous, subcutaneous, Intrathecal	Subcutaneous
7.	Glioblastoma	Urokinase-type plasminogen activator receptor + Urokinase plasminogen activator	Intraperitoneal	Brain
8.	Hepatitis C Virus	Hepatitis B Virus/ miR-122	Intravenous	Liver
9.	Lung cancer	STAT3	Intrathecal	Lung
10.	Meningloma	Urokinase	Intrathecal	Brain osmotic

		plasminogen activator receptor + Matrix metalloproteinase 9		pump
11.	Myocardial Infarction	RAGE	Intramyocardial	Heart
12.	Prostate cancer	Vascular endothelial growth factor	Intrathecal	Subcutaneous
13.	Sarcoma joint inflammation	VEGS, Fc $\delta$ RIII	Intratumoral, intraperitoneal	Joint
14.	Subcutaneous tumour	RRM2	Intravenous	Tissue
15.	Wound healing	T53 and Smad3	Intravenous	Cell of skin



**Figure No. 1: BARRIERS TO SIRNA THERAPEUTICS AND STRATEGIES TO OVERCOME THEM**

### 1) INTER CIRCULATION OR TARGET TISSUE

In the siRNA therapeutics administration the problem of maintaining stability and permeability so overcome the problem administration of siRNA therapeutics via parenteral subcutaneous and topical route. Lipid nanoparticles and other nanoparticles are administrated through iv route to tackle the problem of GalNAc they administrated via lymphatic to its target tissue. The topical administration used for targeting skin, eye and mucosa.

## 2) **AVOID EXCRETION –**

Another barrier for siRNA therapeutics is unwanted excretion to avoid this problem conjugation is used in PEGylating. Molecular weight of siRNA is increased to avoid renal excretion. Cholesterol conjugated siRNA binds to lipoprotein particles.

## 3) **AVOID NUCLEASE DEGRADATION-**

Nuclease is the strong problem of siRNA therapeutics modification are done in the siRNA therapeutics to overcome this barrier. Deoxynucleotide, phosphorothioate linkage that are backbone modification to overcome this problem, siRNA therapeutics formulated in the form of nanoparticle to overcome this barrier.

## 4) **AVOID IMMUNE RECOGNITION-**

It is avoided by modification of backbone i.e. 2'-o-methyl and 2'-fluoro that are incorporate. Introduction of surface charges minimise the effect of that barrier i.e. PEGylation.

5) **EXTRAVASATION-** Target endothelial or blood cells in that no need to exit the vasculature.

6) **CELLULAR UPTAKE-** Ligand conjugate with siRNA therapeutics for the cell specific uptake. Endogenous ligand used for uptake in hepatocytes i.e. cholesterol conjugated siRNA and LNPs.

7) **ENDOSOMAL RELEASE-** Low endosomal pH activated bilayer disrupting lipid that can stop the endosomal release. Another approach is used for membrane destabilising peptides and polymers. Increase endosomal accumulation. (3,6,8)

**SOURCES OF siRNA PRECURSORS-** The properties required for RNA Precursor is linear, long, perfectly base paired dsRNA and it directly incorporated in to the cytoplasm or taken up from environment. The activated protein Dicer which is processed with dsRNA and form siRNAs that direct silencing the affected gene. SiRNA plays important role in genome defence, it observed during Trans-gene and virus induced silencing in plant. After 2002 and 2003 in plants researcher have found transacting siRNA (Ta- siRNA) which is dised form specific gene and regulate the sets of target gene. After few days' endogenous siRNA (endo-siRNAs) have been found in plants. In that miRNA transcripts and other natural sense-

antisense pair, duplexes involving pseudogene-derived antisense transcripts and the sense mRNA from their cognate gene and hairpin RNAs (hpRNAs). From the above information it is clearly indicated that siRNA is not entirely a foreign nucleic acid product but it arises from the endogenous genome and they differ from exogenous siRNA. (4)

## CONCLUSION

siRNA is a nucleic acid-based therapeutic which has an ability to silence the gene expression by interfering with mRNA before its translation. siRNA therapeutics is an effective delivery for the treatment of cancer or autoimmune disorders. Primary success of siRNA therapeutics totally depends upon the suitable vector to deliver the gene at a desired site of action. Nanostructured lipid carriers play an important role in the delivery of siRNA at the desired site with desired stability of siRNA.

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