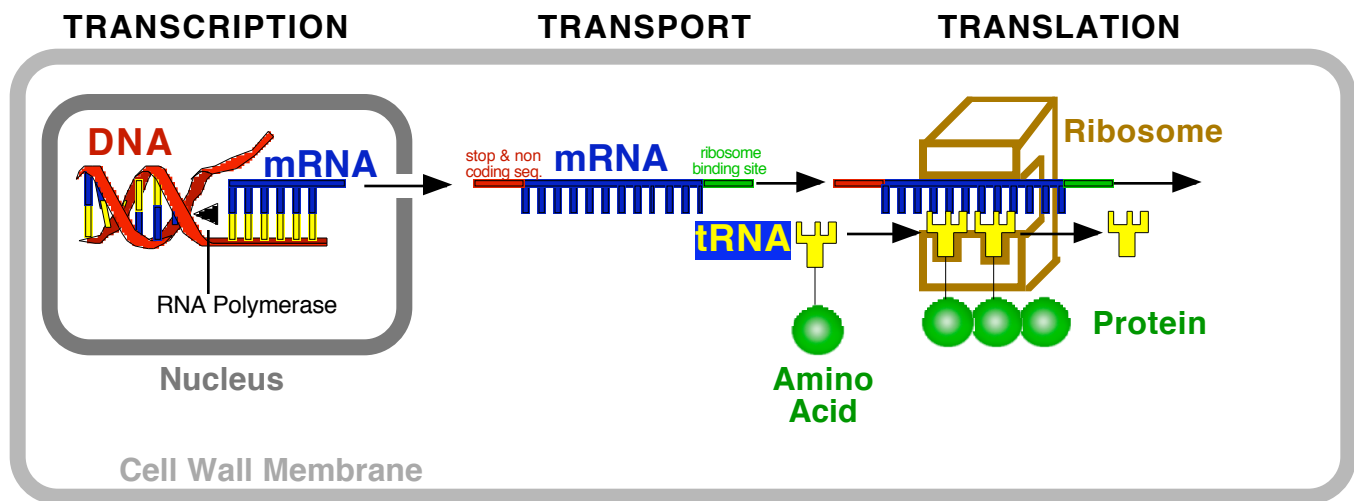


Comparison of Three Types of RNAi: Antisense RNA, siRNA, and TTRI

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Background:

Synthesis of proteins is achieved by a process that involves 1) Transcription of DNA into mRNA in the nucleus, 2) Transport of the mRNA strand to the ribosome (mostly rRNA), and 3) complimentary base pair binding of tRNA with an attached amino acid, whereby the mRNA strand is translated into a protein:



Any compound that functions to interfere with or inhibit RNA (mRNA, rRNA, or tRNA) at any point in the process (transcription, transport, or translation) functions to interfere with or inhibit protein synthesis.

Normal non proliferating, non secretory, cells have a low level of ongoing protein synthesis to replace degraded proteins. In 1988 Okazaki et. al. at the Kochi Medical School in Japan demonstrated that normal cells (human epidermoid, *ex vivo*) could withstand continuous, full spectrum, inhibition of translation of RNA into proteins for three days, with no reduction in cell viability.

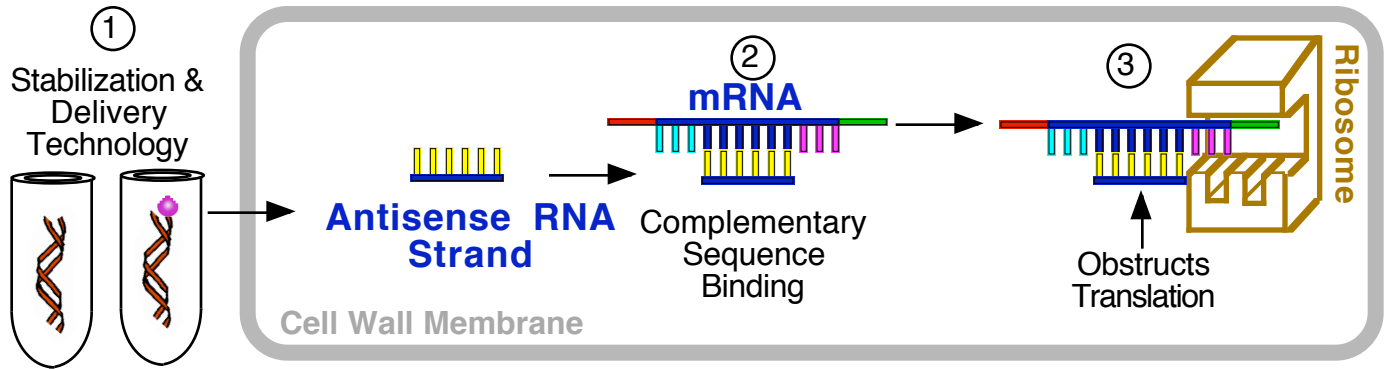
Synthesis of a single aberrant protein, or overexpression of a single normal protein, is at the root of certain disease conditions. Hyperactive synthesis of a large spectrum of proteins is also involved in many disease conditions such as Cell Hyperproliferation, Inflammation, and Viral Infections.

In general, siRNA is ideally suited for treatment of conditions involving synthesis of a single protein and TTRI (Targeted Transient Ribosomal Inhibition) is ideally suited for treatment of conditions involving hyperactive synthesis of a large spectrum of proteins.

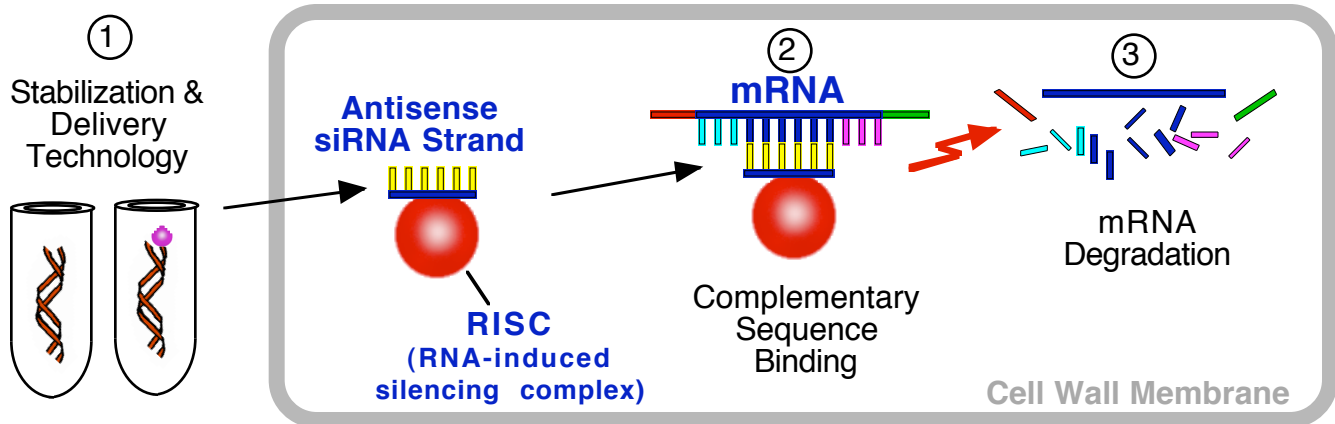
Summary of RNAi Technologies:

The three major RNAi (RNA interference) technologies are Antisense RNA, siRNA (Short Interfering RNA), and TTRI (Targeted Transient Ribosomal Inhibition). All 3 function to inhibit translation of RNA into proteins. However the Mechanisms of Action (MOAs) vary, the spectrum of protein synthesis inhibition varies, and the ability to delivery the drug into a target cell population varies.

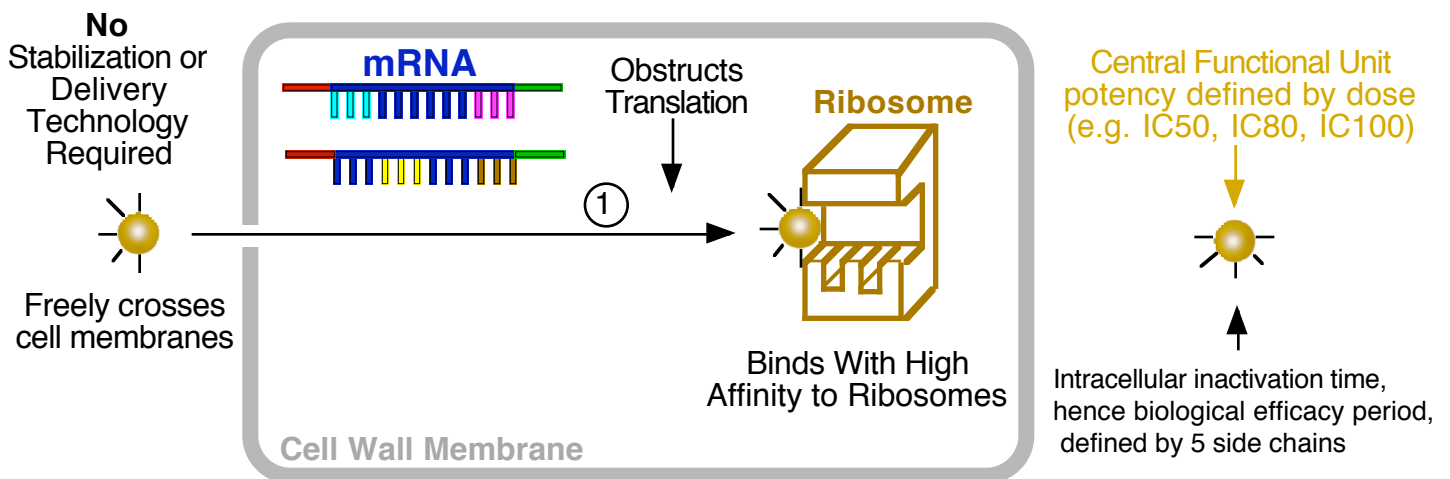
Antisense RNA: Antisense RNA is a nucleotide strand that uses complementary sequence binding (Antisense) to mRNA to obstruct its translation into proteins at the ribosome. Stabilization technology is required to prevent enzymatic degradation and includes use of double stranded molecules. Delivery technology includes addition of a lipophilic group to facilitate entry into a cell:



siRNA: siRNA uses Antisense technology. After cell entry, the double strand attaches to an aggregate of proteins called the RNA-inducing silencing complex (RISC), which unwinds the siRNA into a single strand, which then binds to and degrades the targeted mRNA:



TTRI: TTRI uses a compound that readily crosses cell membranes and binds with high affinity to ribosomes, preventing translation of mRNA into proteins:



Comparison of RNAi Pharmacokinetics (PK):

A 2004 Scientific American article succinctly summarized the paramount importance of PK: “The success or failure of RNAi as a therapeutic will hinge on getting the drug into target cells without its being chopped up by enzymes. The drug must then persist in the cell long enough to carry out its job of binding to and inhibiting specific messenger RNAs. The challenge of delivery and stabilization has also posed a significant hurdle for the success of antisense.”

Antisense RNA based technologies are basically like building a park bench that needs to be delivered to the moon. Building the park bench is easy. Delivering it to the moon (across a cell membrane, to a target cell population) is the difficult task.

The TTRI technology does not require any delivery or stabilization technology. TTRI is a non systemic treatment that is administered by topical, inhalable, or transdermal delivery, with the drug being retained where applied and kept out of circulation because of its blood insolubility. It delivers itself (readily crosses cell membranes and binds with high affinity to ribosomes) and can be delivered only to the cells where it is needed by use of appropriate administration method.

Comparison of RNAi Pharmacodynamics (PD):

Antisense RNA targets a single sequence of nucleotides hence inhibits synthesis of a single protein.

siRNA uses Antisense technology but has the potential to be a 100 fold or more potent than Antisense RNA, as the siRNA strand does not disrupt only a single mRNA strand, but keeps doing the same job over and over. Conditions currently being targeted for treatment by siRNA include macular degeneration, diabetic retinopathy, cancer, hepatitis c, obesity, type 2 diabetes, Parkinson's, and amyotrophic lateral sclerosis.

TTRI is orders of magnitude more potent than either siRNA or Antibody technologies from a therapeutic standpoint. TTRI silences expression of every protein underlying the etiology and pathology of a disease condition in the tissue mass to which it is applied. As an example, in a herpes lesion, topical application of TTRI inhibits synthesis of all 80+ herpes viral proteins (etiology) plus the full spectrum of inflammatory proteins causing the redness, pain, and swelling (pathology). For influenza, inhaled TTRI silences expression of all 10 viral proteins (etiology) plus prevents de novo synthesis of cytokines and leukotrienes (pathology) associated with mortality. TTRI is viral mutation or alteration insensitive, and can arrest any flu stain, including any variant of H5N1. TTRI primary indications include:

Disease	US Cases	Therapeutic Advantage
Psoriasis	7,500,000	Targeted Anti-Inflammatory, Antiproliferative
Herpes Oral/yr.	40,000,000	Targeted Antiviral, Anti-Inflammatory
Herpes Genital/yr.	80,000,000	Targeted Antiviral, Anti-Inflammatory
Age Spots		Targeted Apoptosis (Ablative Regimen)
Acne	17,000,000	Targeted Antiproliferative, Anti-Inflammatory
COPD - Chr. Bron.	9,800,000	Targeted Anti-Inflammatory, Antiproliferative
Asthma	16,400,000	Targeted Anti-Inflammatory
Influenza / Pandemic		Targeted Antiviral, Anti-Inflammatory
Rheum. Arthritis	2,500,000	Targeted Anti-Inflammatory, Antiproliferative

Detailed human safety data and efficacy data for TTRI is available for download at <http://www.nexgen.biz/rnaipsrdata.pdf>