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Development

Can RNAi Deliver?

RNAi has great promise as a therapeutic but biological hurdles must be overcome before the dream is realized.

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Andrew Fire's and Craig Mello's Nobel Prize-winning discovery that genes could be "silenced" as a result of the exogenous administration of double-stranded RNA molecules into the cell served as the firing of the starter's pistol in the race to develop RNA interference (RNAi) therapeutics. In the years that have followed that initial discovery, drug researchers have embraced the promise of RNAi-based products and have worked aggressively toward the goal of developing the first RNAi therapeutic capable of treating human disease.

Today, the RNAi therapeutic space is crowded, with several companies claiming success in the development of small interfering RNA (siRNA) molecules that could potentially silence disease genes. Yet, despite some significant progress, companies in this field have yet to overcome the major hurdle in the advancement of RNAi therapeutics—the sustained systemic delivery of siRNA to the target tissue. Without a means to selectively and effectively achieve targeted tissue and intracellular delivery of siRNA molecules, it will be impossible to unlock the full potential of this exciting new class of therapeutics.

Characteristics of RNAi delivery systems

Characteristic	Local Administration	Chemical Modification	Synthetic Vector: Liposomal	Synthetic Vector: Polymer Nanoparticles	Viral Vectors
Systemic Delivery	No	Yes	Yes	Yes	Yes
Protect & Sequester Active siRNA	No	Yes: However, only protects against degradation	Yes	Yes	Yes
Targeted Tissue Binding and Intracellular Uptake	Targeted by virtue of local delivery	Usually not targeted	Possible but predominant distribution to liver	Possible	Possible
Active siRNA Release	Possible	Possible	Possible	Possible	Possible
Other	Limited applications	May alter potency and safety	Tendency to target liver tissue (suitable for metabolic and hepatic viral applications)	Broad applications based on polymer and targeting moieties	More sustained delivery but potential for long-term complications

Over the last few years, researchers have observed that siRNA molecules, when administered systemically with available delivery technologies, are largely unable to reach their intended destination—the cytoplasm within the cell of targeted tissue. Numerous biological barriers prevent the siRNA molecule's ability to reach the cytoplasm, hence prohibiting its effectiveness. Such barriers include:

- Rapid urinary excretion due to the molecule's small size
- Enzymatic degradation/serum instability
- Non specific tissue distribution
- Difficulty binding to target tissue
- Challenges of intracellular uptake and incorporation into RNA-induced Silencing Complex (RISC)

To overcome these problems, researchers in the RNAi field are actively pursuing a number of novel delivery technologies.

Delivery Systems: Problems and Solutions

While several companies are currently employing local administration techniques, the effectiveness of such delivery is limited to those conditions that are presently treated locally (e.g., inhalation therapy for respiratory conditions, ocular injections for diseases of the eye, etc.). Alternatively, systemic delivery, if accurately targeted to a specific tissue, can potentially address a much broader scope of indications. Other factors that make systemic delivery more attractive may include increased accessibility and improved patient compliance. Most siRNA delivery solutions currently being developed are designed to enable systemic administration. These include chemical modification, as well as synthetic and viral vectors.

In order to avoid the potential

of siRNA delivery is the ability to recognize and bind directly to the target tissue. Without such targeting, the molecules are distributed non specifically, resulting in the need for considerably higher dosing and the related side-effects. Several synthetic vector technologies currently in development have demonstrated the ability to bind guiding ligands to liposomal and polymer nanoparticles. Such ligands direct the molecules to receptors expressed in the specifically targeted tissue. Such binding of the ligand further allows receptor-mediated uptake of the siRNA payload by the specific cells of interest, further enabling the effectiveness of the molecule. The choice of those binding ligands and their successful integration in any siRNA-carrying nanoparticle system will define the targeted therapeutic areas for the different synthetic vector carriers.

Without a means to selectively and effectively achieve targeted tissue and intracellular delivery of siRNA molecules, it will be impossible to unlock the full potential of this exciting new class of therapeutics.

These platforms range from local delivery to chemical modification of siRNA to the use of synthetic (both polymer nanoparticles and liposomes) and non-synthetic (viral/DNA) vectors for systemic delivery. While each of these modalities offers an interesting approach to solving the delivery problem, none has demonstrated the ability to address the multiple biological obstacles that currently inhibit siRNA delivery.


In contemplating the optimal delivery system, it is important to clearly identify each characteristic required to combat the considerable barriers to siRNA delivery. These include:

- systemic administration
- protecting and preserving the active siRNA molecule until delivered to the target tissue
- direct binding of the siRNA molecule to the target tissue
- effective release of the siRNA molecule into the cytoplasm of the target tissue cell

degradation and renal elimination of the siRNA payload, it is critical that the siRNA molecules be sequestered and protected between the time of administration and payload delivery. Some chemical modifications have demonstrated the ability to increase molecule stability in serum. However, such modification may alter the fundamental characteristics of the siRNA molecule resulting in unwanted side effects. In addition, making siRNA molecules drug-like requires significant time and resources similar to drug discovery efforts for small molecules or antibodies. This negates one of the inherent advantages of RNAi therapeutics: the rapid identification of unmodified siRNAs for target genes. Alternatively, synthetic vectors, both liposomal and polymer nanoparticles, can directly utilize unmodified siRNAs, protecting them through encapsulation.

Another critical requirement

Should the siRNA remain intact and successfully bind to the targeted tissue cell, there remains yet another barrier to successful delivery—release of the active siRNA into the cell's cytoplasm and its successful integration into the RISC complex. Any siRNA-carrying particle system must demonstrate the ability to do both.

We are at a critical juncture in the development of effective RNAi therapeutics. In order to realize the tremendous promise of this unique approach to treating disease, a safe and effective platform for delivering siRNA molecules must be developed and validated. This achievement will resonate throughout the RNAi industry and clearly benefit all those working so diligently to make RNAi "gene silencing" therapeutics a reality. 

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