A Survey of siRNA Nanoscale Delivery Patents

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Abstract

Small interfering RNA ("siRNA") therapy uses small molecules designed to pair with the sequence of messenger RNA that encodes disease-related proteins. The biotechnology industry has applied for and received hundreds of U.S. patents related to the nanoscale technologies to help with effective siRNA delivery. For example, Tekmira Pharmaceuticals has a patent portfolio for its lipidoid nanoparticle siRNA delivery technology, while Arrowhead Research has obtained patents covering its RONDEL platform of self-assembled siRNA-containing nanoparticles. This article summarizes some of the most visible siRNA delivery technologies and their patents in the current landscape.

1. Introduction

In recent years, small interfering RNA ("siRNA") therapy has shown promise as a potential pathway for the treatment of human diseases caused by the expression of disease-related proteins. Such therapy works by introducing into cells molecules of siRNA that have been designed to pair with the sequence of the messenger RNA ("mRNA") that encodes the protein of interest. The pairing of siRNA with target mRNA results in enzymatic cleavage of the target mRNA by the intracellular multiprotein complex "RISC," thereby silencing expression of the disease-related protein.

One of the main obstacles to the successful implementation of siRNA therapy is the difficulty in delivering effective amounts of siRNA to relevant sites of action in the body. siRNAs are small molecules—on the order of only 21-23 nucleotides[1]—and are prone to elimination from the body

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[1] *See, e.g.*, U.S. Patent No. 7,799,565 (Tekmira) at Col 1, ll. 33-34.

by the kidney, degradation by endogenous enzymes such as nucleases and lysozymes, and attack by the immune system.

In response to these problems, the biotechnology industry has applied for and obtained hundreds of United States patents directed to nanoscale technologies for effective siRNA delivery. Most of these patents fall into a few broad categories, the most prevalent of which are siRNA nanoparticles comprising lipids that promote fusion with cell membranes and uptake of the siRNA into the cytoplasm; siRNA nanoparticles comprising positively or neutrally charged polymers to accomplish similar functions; and the use of conjugated antibodies, aptamers or other cell-specific ligands to direct siRNA nanoparticles or naked siRNA molecules to particular tissues or sites of action in the body.

This article discusses some of the most visible patents in the current landscape.[2]

2. Tekmira Pharmaceuticals Corporation's Technology

Tekmira Pharmaceuticals Corporation of Vancouver owns several patents directed to its "LNP" (lipidoid nanoparticle) siRNA delivery technology, which it has licensed to partners such as Alnylam and Merck. Although the efficacy of siRNA therapy can be highly sensitive to many conditions, including the choice of delivery vehicle, LNPs have been reported to successfully deliver effective siRNA payloads to a number of different cells such as liver cells, solid tumor cells and phagocytic cells.[3]

Tekmira's LNP patent portfolio includes U.S. Patent Nos. 7,745,651, 7,799,565, 8,058,069 and 7,901,708. The '651 patent describes and claims cationic nitrogen-containing lipids having one or two lineoyl groups that can be used to make siRNA liposome nanoparticles that purport to increase their "fusogenicity," or the ability of the nanoparticles to fuse with cell membranes, thereby increasing efficiency of delivery.

The '565 patent describes serum-stable nucleic acid-lipid particles ("SNALPs") that encapsulate interfering RNA and efficiently deliver it into cells. Each SNALP is comprised of an interfering RNA, a non-cationic lipid, a cationic nitrogen-containing lipid, and a bilayer-stabilizing component such as a conjugated lipid or a polyethylene glycol ("PEG")-lipid conjugate.

Similar to the '565 patent, the '069 patent describes and claims serum-stable nucleic acid-lipid particles. The '069 particles comprise a nucleic acid, a cationic lipid, a non-cationic lipid comprised of phospholipid and cholesterol or cholesterol derivatives, and a conjugated lipid. The '708 patent claims a process for producing lipid vesicles that encapsulate therapeutic agents by mixing an aqueous solution of nucleic acids from one reservoir with an organic lipid solution from a second reservoir to produce a lipid vesicle instantaneously.

[2] While this article reports on the general subject matter of these patents, it takes no position on their validity or on the scope of protection that they might provide.

[3] Tekmira Presents Preclinical Data Demonstrating LNP Technology Innovations at mRNA Health Conference (Oct. 25, 2013), http://www.azonano.com/news.aspx?newsID=28606.

3. Silence Therapeutics' Technology

Silence Therapeutics, based in Germany, has a rival cationic lipid delivery technology called AtuPLEX. Silence Therapeutics owns a suite of patents including U.S. Patent No. 8,107,804, which describes and claims nitrogen-containing cationic lipids comprising lysyl, ornithyl, 2,4-diaminobutyryl, histidyl and certain acyl moieties, and U.S. Patent No. 8,357,722, directed to compositions comprising those same lipids.

The '722 patent additionally includes claims in which a "helper lipid" selected from the group of phospholipids and steroids may be present. The AtuPLEX technology is being used for Silence Therapeutics' own Atu027 antitumor siRNA therapy candidate, and has been licensed to Quark Pharmaceuticals and Pfizer in connection with PF-4523655, an siRNA therapy candidate for the treatment of age-related macular degeneration.[4]

4. Marina Biotech's Technology

Washington State's Marina Biotech is seeking to treat familial adenomatous polyposis and bladder and liver cancer by inhibiting therapeutic targets using two siRNA delivery systems: a dialkylated amino acid-based liposome (DiLA^2) delivery system, and an amphoteric-based liposomal delivery system (SMARTICLES), which it acquired from Novosom AG of Germany. Marina Biotech has non-exclusively licensed its siRNA delivery technology to Roche, its DiLA^2 system to Novartis,[5] and its SMARTICLES technology exclusively to ProNAi Therapeutics.[6]

Marina Biotech's large patent estate includes U.S. Patent Nos. 7,939,505, 8,192,753, 8,193,246, and 8,236,770. The '505 patent, directed to the DiLA^2 delivery system, describes methods of delivering therapies using lipophilic compounds with amino acid residues and one or more lipophilic tails. The claims recite DiLA^2 molecules and formulations, methods of delivering siRNA using those molecules and formulations, and methods for the treatment of diseases with DiLA^2

[4] Silence and InteRNA Partner to Develop AtuPlex-Formulated Anticancer miRNAs (Sept. 12, 2011), http://www.genengnews.com/gen-news-highlights/silence-and-interna-partner-to-develop-atuplex-formulated-anticancer-mirnas/81245659/.

[5] Technology Licenses, http://www.marinabio.com/technology_licensees.

[6] Marina Biotech and ProNAi Therapeutics Announce License Agreement for the Development of DNAi-Based Therapeutics (Mar. 14, 2012), http://www.marketwired.com/press-release/Marina-Biotech-ProNAi-Therapeutics-Announce-License-Agreement-Development-DNAi-Based-OTCQX-MRNA-1631505.htm.

formulations.[7] Marina has reported that the DiLA[2] technology has been successfully used to deliver Marina Biotech's Unlocked Nucleic Acid ("UNA") siRNAs in models of bladder and liver cancer.[8]

The '753 patent claims pH-sensitive, two-tailed cationic lipids that can create liposomes for use in both the DiLA[2] and SMARTICLES systems, as well as pharmaceutical compositions that include the claimed lipids, and kits for administering the resultant lipid formulations. The '246 and '770 patents are directed to lipids for use in the SMARTICLES delivery system, with the '246 patent being directed to sterol derivative compounds that enhance the fusogenicity of lipid assemblies, and the '770 to amphoteric lipid formulations consisting of both neutral and charged lipids to increase serum stability in comparison with mostly cationic lipid formulations. Marina Biotech's licensee of the SMARTICLES technology, ProNAi Therapeutics, has reported success in Phase I and II clinical trials using SMARTICLES to deliver PNT2258, an anti-Bcl-2 inhibitor and potential treatment for lymphoma.[9]

5. Dicerna Pharmaceuticals' Technology

Dicerna Pharmaceuticals, a Massachusetts company focusing on oncology and liver diseases, uses its EnCore Lipid Nanoparticles to deliver its proprietary Dicer Substrate RNAi ("DsiRNA") into cells. The EnCore nanoparticles consist of a core comprised of lipid and DsiRNA surrounded by a lipid mixture envelope.[10] Dicerna's DsiRNA molecules, at 25 or more base pairs, are somewhat larger than typical siRNAs, and have the ability to engage the Dicer enzyme,[11] which facilitates the formation of the RISC complex. Dicerna claims this engagement of RISC early in the gene silencing cascade allows its therapies to be potent even at low doses.[12] Dicerna reports that it hopes to begin clinical trials in 2014 for hepatocellular carcinoma patients using DCR-M1711, a DsiRNA formulated in EnCore nanoparticles.[13]

Dicerna's nanoparticle delivery system and DsiRNAs are described in U.S. Patent Application U.S. 2013/0225663, which claims formulations comprising agents capable of inducing an immune response, such as double-stranded RNAs ("dsRNAs"), and one or more lipids capable of reducing or

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[7] Marina Biotech Announces Allowance of Patent Covering DiLA2 Delivery Platform From U.S. Patent Office (Jan. 3, 2011), http://www.marketwired.com/press-release/marina-biotech-announces-allowance-patent-covering-dila2-delivery-platform-from-us-patent-nasdaq-mrna-1374784.htm.

[8] *Id.*

[9] Marina Biotech Announces That Licensee ProNAi Therapeutics Reported Phase 1 Study Results Using SMARTICLES® Nucleic Acid Delivery Technology (Dec. 5, 2012), http://www.marketwired.com/press-release/-1733843.htm; ProNAi Therapeutics Reports Anti-Tumor Activity from Ongoing Phase II Clinical Study of PNT2258, a Novel BCL2-Inhibitor, at ASH Annual Meeting (Dec. 9, 2013), http://www.businesswire.com/news/rxtimes/20131209006427/en/ProNAi-Therapeutics-Reports-Anti-Tumor-Activity-Ongoing-Phase.

[10] Dicer Pharmaceuticals EnCore™ Lipid Nanoparticles, http://www.dicerna.com/approach-about-lnp.php.

[11] Dicerna Announces Additional Patent Claims Allowed, Broadening Coverage of Extended Dicer Substrate Therapeutic Structures (July 1, 2013), http://www.dicerna.com/pdf/dsHandleDicernaPatentPR_07.01.13.pdf.

[12] Therapeutic Approach, http://www.dicerna.com/approach.php.

[13] Dicerna Raises $60M in Series C, Aims for Clinical Trials in 2014 as it Weighs an IPO (Aug. 1, 2013), http://www.genomeweb.com/rnai/dicerna-raises-60m-series-c-aims-clinical-trials-2014-it-weighs-ipo.

preventing that immune response. The application additionally claims such a formulation combined with a lipid delivery moiety, and methods and kits for administering the formulations to reduce target gene expression.

6. Bioneer Corporation's Technology

Korean biotechnology company Bioneer Corporation, along with its California based subsidiary Bioneer Inc., have developed what it calls the SAMiRNA (Self-Assembled-Micelle-inhibitory-RNA) siRNA delivery system, comprised of serum-stable self-assembling nanoparticles of lipid/PEG bi-conjugated siRNAs and targeting moieties.[14] Bioneer is developing therapies for solid cancers, COPD and liver fibrosis, as well as antiviral treatments and, in a partnership with Sanofi, a treatment for liver cancer.[15] Bioneer's patents and patent applications for the SAMiRNA system include U.S. Patent No. 8,324,365 (claiming a oligonucleotide-hydrophilic polymer conjugate for gene transfer, self-assembling polyelectrolyte complex micelles comprising the conjugates and cationic polymers or peptides, and a method for preparing these micelles) and Application No. 11/651,011 (claiming siRNA-hydrophilic polymer conjugates, polyelectrolyte complex micelles comprised of the conjugates and cationic compounds, methods for preparing the conjugates and micelles, and methods of delivering siRNA using the micelles).

7. Alnylam Pharmaceuticals' Technology

Alnylam Pharmaceuticals of Massachusetts has a range of siRNA therapies in development, including ALN-TTR02 and ALN-TTRsc for amyloidosis, ALN-AT2 for hemophilia, and ALN-PCS for hypercholesterolemia.[16] The company has recently reported clinical success with ALN-PCS,[17] and plans to have at least five RNAi therapies in clinical development by the end of 2015.[18] Alnylam's early siRNA delivery efforts were focused on lipid-like nanoparticle technology, but the company has since shifted its focus to a delivery system that conjugates siRNA molecules directly to N-acetyl-galactosamine (GalNAc) sugar molecules, with the intention of promoting uptake by liver cells, or hepatocytes.[19] In addition to conducting its own research, Alnylam has numerous partnerships and licenses with companies such as Isis, Merck, Medtronic, Roche, and Genzyme.

[14] Platform Technology, http://us.bioneer.com/SAMiRNA/Platformtechnology.aspx.

[15] Programs and Pipeline, http://us.bioneer.com/SAMiRNA/ProgramsandPipeline.aspx.

[16] Alnylam Overview, http://www.alnylam.com/About-Alnylam/index.php.

[17] Alnylam and Collaborators Publish Clinical Trial Results with ALN-PCS, an RNAi Therapeutic Targeting PCSK9 for the Treatment of Hypercholesterolemia, in The Lancet (Oct. 3, 2013), http://www.marketwatch.com/story/alnylam-and-collaborators-publish-clinical-trial-results-with-aln-pcs-an-rnai-therapeutic-targeting-pcsk9-for-the-treatment-of-hypercholesterolemia-in-the-lancet-2013-10-03.

[18] Alnylam Overview, http://www.alnylam.com/About-Alnylam/index.php.

[19] Delivering RNAi Therapeutics, http://www.alnylam.com/Programs-and-Pipeline/Delivery.php.

Alnylam has an estate of over 700 issued siRNA-related patents, including delivery patents. Its lipid-based delivery patents include U.S. Patent Nos. 6,858,225 (claiming methods of preparing lipid-nucleic acid compositions by mixing modified lipids with protonatable or deprotonatable lipids that are charged at one pH and neutral at another pH to encapsulate and protect charged therapeutic agents) and 8,158,601 (claiming cationic lipid formulas, lipid formulations using the claimed cationic lipids along with neutral lipid, sterol, PEG or PEG-modified lipid, and optionally a therapeutic agent or targeting lipid, and methods for preparing the lipid formulations and introducing therapeutic agents into a cell using the lipid formulations). Alnylam's patent estate also contains patents directed to various serum-stable lipid-nucleic acid complexes formed using detergent dialysis or organic solvent methods and methods for introducing these complexes into cells, including U.S. Patent Nos. 5,976,567 (neutrally charged lipid particles), 6,534,484 (nuclease-resistant lipid particles comprised of cationic and non-cationic lipids), 6,586,410 (methods of introducing lipid-nucleic acid complexes made of cationic and conjugated lipids into cells), and 6,815,432 (nucleic acid-lipid particles comprised of cationic and non-cationic lipids, PEG-lipid conjugate, and nucleic acid, and methods for introducing nucleic acid into a cell using these lipid particles).

The patents related to Alnylam's more recently developed GalNAc delivery technology include U.S. Patent Nos. 5,859,221, 6,153,737, 6,476,205, and 8,450,467. The '221 patent claims a nuclease-resistant oligonucleotide compound that hybridizes with DNA or RNA that has at least one nucleoside with a modified deoxyfuranosyl. The '737 patent, which Alnylam has licensed from Isis, describes linked nucleosides that have increased cellular uptake due to nucleoside functionalization at the 2' position with a substituent connected by a linking group. Various substituents can be used, such as steroids, lipophilic molecules, or proteins. The '205 patent claims nuclease-resistant oligonucleotides that have been modified with substituents at their 2' position. The resulting oligomers are capable of drug delivery or can interfere with nucleic acid activity. Alnylam's recently issued '467 patent describes processes of making carbohydrate ligands that are conjugated with iRNA agents. The iRNA agents can include N-Acetyl-Galactosamine (GalNAc), galactose, lactose, N-Ac-Glucosamine, or mannose. Carbohydrate ligands such as these can be used to target liver cells, which reportedly makes them potentially useful in targeting nucleic acids expressed by viruses that cause hepatitis.

8. Arrowhead Research Corporation's Technology

Arrowhead Research Corporation is a biopharmaceutical company focused on treatments for obesity, chronic hepatitis B virus infection, and oncology. Through a number of licenses and acquisitions, Arrowhead has obtained rights to five different RNAi delivery systems,[20] including the nanoparticle-based RONDEL and the Dynamic Polyconjugate ("DPC") systems.

Arrowhead's subsidiary, Calando Pharmaceuticals, Inc., controls the RONDEL platform, which is comprised of self-assembled siRNA-containing nanoparticles. RONDEL nanoparticles have three components: (1) a linear polymer with positively-charged groups alternating with cyclodextrin

[20] Arrowhead Research Corporation Acquires Roche RNA Assets and Site (Oct. 24, 2011), http://www.arrowheadresearch.com/press-releases/arrowhead-research-corporation-acquires-roche-rna-assets-and-site

sugar molecules, (2) adamantane, and (3) PEG.[21] The positively-charged cyclodextrin molecules associate with the backbones of the negatively charged siRNA molecules in the core of the nanoparticle.[22] The hydrophobic adamantane, which is covalently bound to PEG, associates with the hydrophobic cores of the cyclodextrin to form a nanoparticle coated with PEG.[23] Cell-targeting molecules are further bound to the PEG-stabilized nanoparticle to direct it to the targeted cell.[24] Calando's patents include U.S. Patent Nos. 7,018,609 (claiming methods of preparing compositions that contain a therapeutic agent along with cyclodextrin-containing polymer and a complexing agent with at least one functional group, which together form an "inclusion complex"), 7,270,808 (claiming general formulas in which a polymer is joined by linking groups to a cyclodextrin moiety, a targeting ligand and a therapeutic agent), 8,110,179 (claiming various cyclodextrin-containing polymer formulations that bind to therapeutics and act as carriers for therapeutic delivery, and methods of making the polymers), and 8,404,662 (claiming polymeric compounds of cyclodextrin and comonomers that are bound to therapeutic agents to stabilize them for delivery, then are cleaved to release the therapeutic agent).

Unlike lipid-based systems that completely encapsulate the siRNA molecule for delivery, Arrowhead's DPC system uses an amphipathic polymer backbone that protects the siRNA molecule, which can be attached to or co-administered with the polymer.[25] The small DPC nanoparticles also have shielding agents such as PEG and targeting ligands attached to protect the nanoparticle and direct the siRNA to the correct cell.[26] The polymer backbone has the ability to lyse endosomal membranes so the siRNA can be released into the cell.[27] According to Arrowhead, this lytic ability can be masked using its proprietary chemistry in order to reduce the nanoparticle's toxicity and interaction with blood components and non-target cells.[28] Arrowhead also claims that the smaller 5-20 nanometer size of DPCs allows them to be more efficiently distributed from the vasculature to target cells than larger lipid nanoparticles, and that DPCs can target specific cells better than lipid systems through the use of targeting ligands.[29] Arrowhead recently reported positive results from a trial in a chimpanzee using its ARC-520 hepatitis B therapeutic, administered using the DPC system.[30]

Arrowhead's patent portfolio includes U.S. Patent Nos. 8,313,772, 8,426,554, and 8,501,930. The '772 patent describes compositions and delivery and manufacturing methods for DPCs that target liver cells, in which an siRNA attached to a carbohydrate or lipophilic targeting moiety can be co-administered with the DPC. Arrowhead's '554 patent describes reversibly modified DPCs covalently linked to a targeted RNAi or co-administered with an RNAi-targeting molecule conjugate. The '930 patent claims the use of targeted melittin or melittin-like peptides to deliver siRNA to liver

[21] RONDEL™ Technology, http://www.arrowheadresearch.com/technology/rondel

[22] *Id.di*

[23] *Id.*

[24] *Id.*

[25] Dynamic Polyconjugates, http://www.arrowheadresearch.com/technology/dynamic-polyconjugates

[26] *Id.*

[27] *Id.*

[28] *Id.*

[29] *Id.*

[30] Arrowhead Presents Data Suggesting ARC-520 Induces Therapeutic Flare in Chronic Hepatitis B (Nov. 4, 2013), http://www.arrowheadresearch.com/press-releases/arrowhead-presents-data-suggesting-arc-520-induces-therapeutic-flare-chronic

cells. The siRNA is conjugated to a hydrophobic group or galactose cluster and is co-administered with the reversibly masked melittin delivery peptide.

9. RXi Pharmaceuticals Corporation's Technology

Massachusetts-based RXi Pharmaceuticals Corporation conducts research on neurodegenerative diseases, oncology, type 2 diabetes, and obesity. Its siRNA delivery technology, the "sd-rxRNA" platform, is reportedly capable of delivering double-stranded siRNA molecules without the need for a separate delivery vehicle. According to RXi, the potential benefits of such self-delivery technology include reduced costs, patient-friendly subcutaneous administration, reduced side effects, and increased ability to target certain tissues.[31] RXi recently reported positive results in Phase I clinical trials for RXI-109, a self-delivering RNAi that reduces dermal scarring from surgeries.[32]

siRNA is double-stranded, rigid and negatively charged, making it difficult for it to pass through cell membranes. Rather than address this problem by encapsulating RNA in lipid nanoparticles, the sd-rxRNA technology attempts to do so by modifying the RNA molecule itself to have minimal double-stranded regions in addition to single-stranded regions. Further modifications to the RNA, such as phosphorylation, phosphorothioation, or methylation, are made to protect the RNA from enzymatic degradation before reaching the target cell, and to improve cell uptake. RXi has rights to several patents and patent applications in this area, including patents acquired from Advirna LLC.

RXi's patent applications include U.S. Patent Application Nos. 2011/0263680, 2012/0040459, and 2012/0065243. The '680 application claims and describes modified nucleic acid molecules of varying lengths used to reduce gene expression and methods of modulating gene expression. The nucleic acid molecules consist of a guide strand and a shorter passenger strand, which creates a double-stranded region and a single stranded region on the 3' end. Various modifications can be made to the nucleotides and/or to the phosphate backbone, and the 3' end can be attached to a lipophilic group such as a sterol. The '459 application similarly describes modified nucleic acid molecules with single- and double-stranded regions, and additionally claims nucleic acid molecules with modified polynucleotides with sequences complementary to target genes, and modified single stranded polynucleotides capable of entering RISC. The '243 application also describes RNAi constructs with a guide and passenger strand that can have modified nucleotides. This application explains that one of the nucleotide strands is connected to a single stranded region of phosphorothoiate-modified nucleotides by a cleavable linker. All three of the patent applications include claims for inhibiting gene expression using the claimed nucleic acid molecules.

[31] RXi Pharmaceuticals Acquires Exclusive License to Proprietary, Potentially Paradigm-Changing RNAi Delivery Technology from Advirna LLC (July 27, 2009), http://www.biomedreports.com/200907272455/rxi-pharmaceuticals-acquires-exclusive-license-to-proprietary-potentially-paradigm-changing-rnai-delivery-technology-from-advirna-llc.html

[32] RXi Pharmaceuticals' Additional Results Show Up to 50% Knockdown (Dec. 5, 2013), http://secfilings.com/News.aspx?title=rxi_pharmaceuticals%27_additional_results_show_up_to_50%_knockdown&naid=617; RXi Pharmaceuticals' Valuation Moves from Product to Platform (Nov. 12, 2013), http://secfilings.com/News.aspx?title=rxi_pharmaceuticals%27_valuation_moves_from_product_to_platform&naid=592

10. Conclusion: Patent Litigation?

As the above examples show, a great many siRNA delivery patents have issued in the United States. It remains to be seen, however, which ones will present the greatest licensing opportunities and litigation risks. By its nature, siRNA therapy is specialized to particular proteins, cells and tissues, and in view of that fact, a one-size-fits-all siRNA delivery technology covered by broad patent claims seems unlikely to emerge. Moreover, the fact that the FDA still appears to be several years away from approving any siRNA or nanoparticle-based therapy—combined with the considerable bureaucratic uncertainties inherent in the FDA approval process—would appear to reduce the present risk of significant patent litigation over siRNA delivery technology.

Put simply, there does not yet seem to be much money at stake. Additionally, so long as the ongoing development and optimization of siRNA delivery technologies continues to be done largely in secret, trade secrets remain a viable—and potentially preferable—form of IP protection. It is not difficult to imagine that most technologists working in this field would prefer to keep any breakthroughs to themselves rather than patent those breakthroughs, thereby disclosing them to competitors and tolling the term of patent protection before they are ripe for commercialization. Indeed, the recently settled skirmish between Tekmira and Alnylam over the former's alleged siRNA delivery trade secrets may be evidence of this preference.

That being said, there appears to be considerable overlap in the siRNA delivery research among the companies discussed above that could lead to either collaboration or conflict. For instance, Alnylam and Arrowhead are both working on GalNAc-siRNA technologies, as described in Alnylam's 8,450,467 patent and Arrowhead's 2012/0157509 patent application.[33]

And, as siRNA therapies approach that point in their development where FDA approval becomes a realistic possibility, their corporate backers may take a financially conservative, risk-averse approach to selecting suitable accompanying delivery technologies, which could lead them to implement relatively mature, proven solutions that may be the subject of existing patents. Under those circumstances, significant patent disputes over siRNA delivery technologies could arise.

[33] Arrowhead Research Patent Application Shows Ample Experience with Triantennary GalNAc-siRNAs (Nov. 15, 2013), http://rnaitherapeutics.blogspot.com/2013/11/arrowhead-research-patent-application.html