



APV Focus Group Drug Delivery

Combining Science & Technology to Create Advanced Drug Delivery Systems

INTERNATIONAL ASSOCIATION FOR PHARMACEUTICAL TECHNOLOGY

NEWSLETTER | ISSUE 1/2008

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DRUG DELIVERY EVENTS

Provided by Christoph Blümer

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[Amorphous Materials, Challenge or Opportunity?](#)

Bath (UK), March, 18th - 19th 2008

[Details](#)

[APV: 6th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology](#)

Barcelona (Spain), April 7th - 8th 2008

[Details](#)

[Ophthalmic drug delivery: What is currently available and where are we going?](#)

London (UK), June, 30th 2008

[Details](#)

[Suggest a meeting to be announced!](#)

NEWS FROM FOCUS GROUP EVENTS

Provided by Carmen Lobback (Bayer Schering Pharma)

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[Looking back on the seminar "Novel excipients or novel use of known excipients from technical feasibility to registration" - Berlin, Germany, \(APV Course No. 6135\)](#)

On 11th to 12th December 2007 a seminar organized by the APV focus group "Drug Delivery" took place in Berlin dealing with challenging questions around novel excipients or novel use of known excipients in a new application from technical feasibility to registration. Course leader Stefan Bracht, PhD, Bayer Schering Pharma AG, was pleased to welcome more than 40 highly interested scientists and managers from different countries with diverse backgrounds ranging from Quality Control and Regulatory Affairs to pharmaceutical formulators, analytical scientists, manufacturers, suppliers and academia.

A comprehensive program with speakers from the pharmaceutical industry but also regulatory authorities like the BfArM was offered. Main topics were perspectives of formulators and manufacturers on pharmaceutical excipients regarding GMP and GDP, safety evaluation, but also regulatory requirements. Furthermore functionality, specifications and methods for analytical characterization were discussed. Besides requirements regarding excipients also challenges in the gastrointestinal tract were an aspect. Potential excipient interactions with in vivo drug performance were presented and discussed. Supplementary information material and databases were provided and in a concluding lively round table discussion one could seize the opportunity to address open questions and comments.

The main take home message of the course was that an early and close cooperation between suppliers/manufacturers of excipients, their pharmaceutical customers and regulatory agencies is essential in order to avoid surprises at late stages in drug development.



Abraxane™ Injectable Suspension (Abraxis BioScience Ltd)

Abraxane™ Injectable Suspension 5mg/ml is a novel formulation of the anti-tumour agent, paclitaxel, which exploits Abraxis Bioscience's nab™ technology. It was approved by the EMEA in Oct 2007 for the monotherapy of metastatic breast cancer in patients, for whom first-line therapy has failed and anthracycline-containing therapy is not indicated, and by the FDA in July 2005. Each vial contains 100 mg paclitaxel encapsulated in approximately 900mg human albumin nanoparticles (mean diameter around 130 nm) for reconstitution with 0.9% NaCl.

The use of albumin-based carriers overcomes the highly lipophilic paclitaxel's solubility issues and enables the creation of a solvent-free formulation. Furthermore, the delivery system passively targets the drug to the tumour, and concentrates it within the interstitium by virtue of its nanoparticulate size and the properties of albumin itself. The albumin carriers are thought to bind to gp60 receptors on the endothelial cells of the tumour's dense vasculature, triggering their transport into the interstitium via caveolae. Once there they bind to SPARC (Secreted Protein Acidic and Rich in Cysteine) which is over-expressed by many cancerous cells. Binding to SPARC helps anchor the carriers in close proximity to the tumour cell membranes, thus, facilitating release of paclitaxel close to its site of action.

Abraxane™ has many clinical advantages over its competitors including a better safety profile and a much reduced risk of hypersensitivity reactions. Thus, it can be dosed at 260 mg/m² (instead of the typical 175 mg/m²) and without pre-medication with steroids or antihistamines. In addition, it results in linear paclitaxel pharmacokinetics and can be administered in 30 minutes as opposed to 3 hours. The higher dosing enabled by this formulation has resulted in improved efficacy with a reconciled target lesion response rate of 21.5% being achieved in a recent Phase 3 trial. This is compared to 11.1% for a solvent-containing comparator product.

Abraxane™ had \$134m of sales within the U.S. in its first year of launch.

Further information at <http://www.abraxisbio.com/> and N. Desai et al, Clin. Cancer Res., 12, (2006) 1317-1324.

Effentora™ (Cephalon)

Effentora™ was approved by the EMEA in January 2008 for the treatment of breakthrough pain in adults with cancer who are already receiving maintenance opioid therapy. This buccal tablet formulation of fentanyl citrate is already marketed in the US under the trade name, Fentora™ and is available in strengths ranging from 100 – 800 mcg (calculated as base). The formulation is based on the OraVescent™ drug delivery technology. The technology is believed to promote the delivery of fentanyl by generating CO₂ on contact with saliva, which transiently lowers the pH and enhances drug dissolution. The pH, however, rapidly returns to previous levels promoting absorption of the highly lipophilic fentanyl across the oral mucosa. The absolute bioavailability of fentanyl from the buccal formulation is 65 %. This is approximately 30 % -50% higher than that achieved from transmucosal formulations of fentanyl, such as the company's Actiq™ formula. The increase in bioavailability is thought to be due to the greater extent of buccal absorption from the Fentora™ product which is also reflected in an around 50 % decrease in Tmax.

Cephalon developed the buccal formulation as an improvement on its Actiq™ product, whose worldwide sales of around \$575 million (2006) are threatened by generic competition in the US. In addition, the company has recently submitted supplemental data to the FDA to support the use of Fentora™ for breakthrough pain in other types of chronic pain including that of neuropathic origin.

Further Information at <http://www.cephalon.com/> and <http://www.fentora.com/>

Evonik Röhm GmbH, Business Line Pharma Polymers

Röhm, part of Evonik Degussa GmbH, is manufacturing and supplying functional coatings for the pharmaceutical industry. Of these, EUDRAGIT® polymers are extensively used for Enteric Delivery, Controlled Release, and Protective Coatings.

Röhm has more than 50 years of experience in EUDRAGIT® polymer design and formulation know-how for pharmaceutical applications, and has developed intellectual property on advanced oral drug delivery technologies. Pharma Polymers business model for commercialization of these drug delivery technologies range from the development of customer-specific solutions to out-licensing strategies.

Evonik Röhm fact sheet:

Founded:	1897
Location:	Darmstadt, Germany
Ownership:	Röhm is a part of the new Evonik Degussa GmbH
Employees:	More than 35.000 in the whole Degussa group
Key technologies:	<p>EUDRAMODE® is a multiunit, pH independent releasing system, based on controlled ionic interactions, capable of giving a tailored drug delivery, eg. quick slow, zero order, accelerated or pulsed etc.. The system consists of pellets with a neutral polymer coated inner core of anions, layered with the drug and further coated with polymethacrylate polymer containing quaternary ammonium groups. The drug release is modulated by controlled ionic interactions and the rate of release can be steered by using different anion cores and change in the polymer coating film thickness. The concept has been confirmed in proof-of-concept studies and <i>ivivc</i> investigations.</p> <p>EUDRAPULSE™ is designed to give pulsatile release profile with various lag times. It is based on a core with a combination of drug with organic acids or salts from organic acids, top-coated with EUDRAGIT® RL/ RS polymers.</p> <p>The pulsatile drug delivery is achieved through an ionic interaction of the organic anion and the quaternary ammonium group of the polymethacrylate copolymer,</p> <p>EUDRACOL™ combines the function of an EUDRAGIT® FS 30 D layer dissolving above pH 7. and a the controlled release of a pellet system previously coated with EUDRAGIT® RL and/or RS layer for sustained release in the colon. This technology provides an oral drug delivery that could be more beneficial to treat the colonic diseases compared to the existing conventional therapies.</p> <p>For all technologies the final dosage form can either be a capsule or pellets compressed to disintegrating tablets.</p>
Website:	http://www.pharma-polymers.com
Contact:	Dr. Bianca Brögmann Global Technical Manager Drug Delivery Evonik Röhm GmbH Kirschenallee 45 D-64293 Darmstadt Phone: +49 6151 18-3519 or -4019 Fax: +49 6151 18-3520 e-mail: Bianca.Broegmann@evonik.de

Lipoid GmbH

Lipoid was founded in 1977 in Ludwigshafen, Germany, and focuses on the production of high quality lecithins and phospholipids for the pharmaceutical application in industrial scale.

Lipoid's unique product portfolio encompasses lecithins and phospholipids for all pharmaceutical applications: egg yolk and soybean derived lecithins and phospholipids, hydrogenated phospholipids, synthetic phospholipids and customized lipid based compounds. Thus, customers make individual choices for individual solutions of specific formulations. Frequently, products have been developed on customers demand and in close cooperation with customers.

More than 80% of the Lipoid products are used for pharmaceutical applications and are manufactured according to cGMP. For the parenteral products the entire production process is performed under controlled air conditions. At the final step the product is filtered through 0.2 µm into a clean room class ISO 5 (formerly class 100).

The products are mainly used for sophisticated drug delivery systems like emulsions, mixed micelles, liposomes and further systems.

Lipoid fact sheet:

Founded:	1977
Location:	Multiple sites in Germany, Switzerland, USA
Employees:	Approx. 250
Ownership:	Privately held
Key technologies:	Purified lecithins and natural, hydrogenated, and synthetic phospholipids.
Website:	http://www.lipoid.com
Contact:	Dr. Jürgen Zirkel Managing Director Lipoid GmbH Frigenstr. 4 D-67065 Ludwigshafen Phone: +49 621 538 190 Fax: +49 621 553 559 e-mail: info@lipoid.com

DRUG DELIVERY TERMINOLOGY

Provided by Dr. Karsten Cremer

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Nanoemulsion

A system with a liquid continuous phase in which at least one other liquid phase is dispersed as fine droplets having an average diameter of less than 1 micrometer. [Write a comment on this definition](#)

A nanoemulsion comprises at least two liquid phases which are not freely miscible. Often one of the phases is hydrophilic and the other hydrophobic; such emulsions are usually referred to as "water-in-oil" (w/o) or "oil-in-water" (o/w) emulsions, even if the respective phases do not, strictly speaking, consist of water and an oil. Other types of nanoemulsions contain two immiscible aqueous phases (w/w) or lipophilic phases (o/o). In the pharmaceutical field, o/w-nanoemulsions are used as infusions for parenteral nutrition. Experimental uses in drug delivery include the parenteral delivery of highly lipophilic drug substances such as diazepam, dexamethasone or flurbiprofene.

German: Nanoemulsion

French: [Provide a translation](#)

Spanish: [Provide a translation](#)

Microemulsion

A thermodynamically stable, clear, isotropic liquid system comprising a hydrophilic and a hydrophobic liquid, a surfactant and usually a co-surfactant. [Write a comment on this definition](#)

In a microemulsion, a liquid component is most often dispersed in a continuous liquid phase in the form of swollen micelles. Interestingly, the typical diameter of such colloidal structures is in the range of only 10 to 50 nanometres, so that the term "microemulsion" is - strictly speaking - a misnomer. In drug delivery, microemulsions are used for the oral administration of poorly water-soluble drug substances. Parenteral delivery is difficult due to their high surfactant content.

German: Mikroemulsion

French: [Provide a translation](#)

Spanish: [Provide a translation](#)

[Suggest a term to be defined](#)
[Suggest a definition](#)

Lea Ann Dailey, a young upcoming scientist in the field of pulmonary drug delivery, started her scientific career in 1999 in the labs of Dr. Vincent H.L. Lee and Dr. Kwang-Jin Kim (Dept. of Pharmaceutics, University of Southern California, Los Angeles) where she spent half a year as an intern, working in the field of PepT2 mRNA identification in primary cultured rat alveolar epithelial cell monolayers.



Before, she studied pharmacy at the Philipps University Marburg, where she returned after her last pharmaceutical exam to prepare her PhD thesis in the research group of Prof. Thomas Kissel in the Institute of Pharmaceutics and Biopharmacy. There she continued to work on the pulmonary drug delivery field, in cooperation with the University of Giessen Lung Center. Within this highly interdisciplinary research team comprised of pharmaceutical scientists, aerosol physicists and research clinicians, she undertook to develop and evaluate polymer-based nanoparticles for the controlled delivery of drugs to the lung with applications in both conventional inhalation therapy and gene delivery.

After receiving her PhD, Lea Ann Dailey accepted a position as a postdoctoral researcher at Nektar Therapeutics in San Carlos, CA, USA, where she expanded from 2004 to 2005 her knowledge in the field of dry powder formulations for inhalation and aerosol medicines. Since 2005 she holds a Lectureship in Formulation Science and Drug Delivery at King's College London (KCL). Since taking up this position, she continued to pursue her interest in nanoparticulate drug delivery vehicles, by commencing work on nanoparticle drug delivery systems for the treatment of lung infection, with a special emphasis on tuberculosis. Additionally she began to broaden the scope of her research platform to include a more fundamental investigation into the role of nitric oxide in respiratory diseases such as asthma, infection, cystic fibrosis and pulmonary hypertension as well the study of methods to target the delivery of nitric oxide to the lung.

Lea Ann Dailey is author or co-author of actually more than 10 peer-reviewed articles, 2 book chapters (in preparation) and holds a patent on biodegradable colloidal particles for pulmonary applications. She is member of several major scientific societies. (More information on the [web page](#))

FEATURED ARTICLE

SILENCING – A REVOLUTION IN THERAPEUTICS?

By [Dr. Louise Rosenmayr-Templeton](#), [Tower Pharma Consulting](#), Auhofstr. 197/10, A-Vienna

1. Introduction

RNA interference (RNAi) is a mechanism by which small stretches of double-stranded RNA act to inhibit gene expression in a sequence-specific manner. The phenomenon was first reported in plants in 1990, but it was the discovery in 2001 that small pieces of double-stranded RNA could post-transcriptionally silence gene expression in mammalian cells, which sparked the current interest in silencing RNAs (siRNAs) (1). This article sets out to give a brief overview of siRNA, its potential as a therapeutic approach, the problems associated with its delivery and the ways that researchers are currently trying to overcome these.

2. Mechanism of Action

siRNAs cause the silencing of gene expression because they are recognised and processed by the same cell machinery that is involved in a naturally occurring form of RNA interference (reviewed in 2). This system, which is illustrated in Figure 1, is thought to form part of the body's defence system against viruses and the products of aberrant genes. It involves the production of microRNAs (miRNAs) by the action of the enzyme, Dicer, on longer double-stranded precursors. Like miRNAs, synthetic siRNAs typically are 21-23 nucleotides in length and have a characteristic 2 nucleotide 3' overhang. Hence, they both are recognised by the multi-protein RNA-Induced Silencing Complex (RISC) present in the cytoplasm and are loaded on to it. In the case of siRNA, both strands are initially loaded before one, the passenger or sense strand, is cleaved leaving the other attached to the RISC.

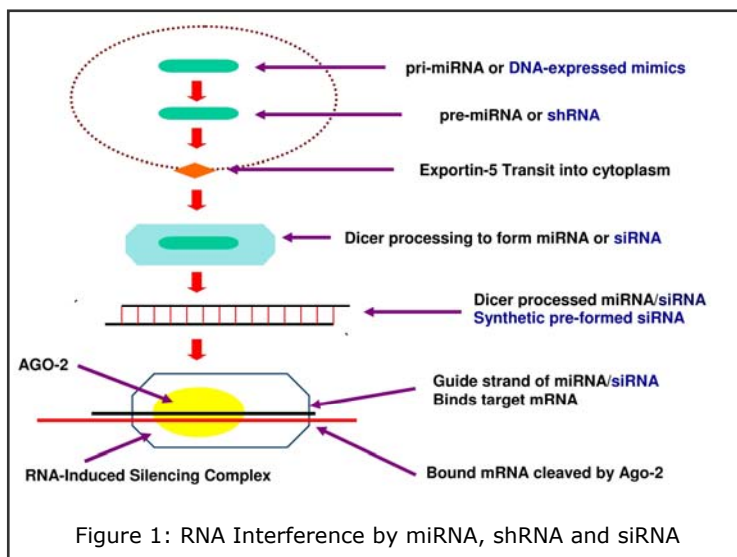


Figure 1: RNA Interference by miRNA, shRNA and siRNA

The attached strand acts as a guide to bind messenger RNA (mRNA) with complimentary or near complimentary sequences according to Watson-Crick base-pairing rules. This binding facilitates mRNA cleavage by the enzyme, Argonaute 2 (Ago-2), present in the complex. The cleaved mRNA is then further broken down by nucleases in the cytoplasm, thus, preventing its translation into protein.

siRNA can either be delivered as pre-formed 21 base duplexes that interact with RISC or as DNA-based expression cassettes that encode for miRNA-type hairpin precursors. These precursors are most commonly in the form of short hairpin RNA (shRNA) (see Figure 1) which are exported out of the nucleus by the Exportin-5 transport system. Following export, the hairpins are cleaved by Dicer to form siRNAs which are passed to RISC like their synthetic pre-formed counterparts (2). In general, the shRNA route produces silencing of greater duration than the typical 3-7 days in rapidly dividing cells, and 3 weeks in non-dividing ones, achieved by the pre-formed duplexes (3). However, saturation of the Exportin-5 system has been observed following shRNA administration, resulting in toxicity (reviewed in 2).

3. Therapeutic and Scientific Promise

siRNAs open up the possibility of treating a wide range of diseases as they potentially could be tailor-made to be selective for any known mRNA. Potential therapeutic areas include cancer, age-related macular degeneration (AMD), viral infections, dominant genetic diseases e.g. Huntington's and autoimmune diseases. In addition, these oligonucleotide duplexes are active at nanomolar concentrations making them far more potent than other expression inhibitors with similar applicability such as antisense oligodeoxyribonucleotides (4). Furthermore, RNA interference can occur without invoking an interferon or other immune response, provided the strands are kept short (typically less than 23 base pairs) and do not contain motifs, e.g. GU-rich regions, known to activate toll-like receptors (reviewed in 2). These properties have resulted in the rapid establishment of siRNAs as a genetic tool in the fields of functional genomics, therapeutic target identification and validation. However, before they can make their mark as a major class of therapeutic compounds, a number of challenges must be overcome with respect to their delivery and duration of action.

4. Hurdles to Delivery

The delivery challenges facing scientists developing siRNA therapeutics can be grouped into the following categories:

In vivo Half-life - In order for a siRNA *in vivo* strategy to be successful, the oligonucleotide duplex must be delivered intact into the cytoplasm where it can bind to RISC. However, siRNA is susceptible to nucleases, making its half-life unacceptably short. In addition, if delivered systemically, siRNA is rapidly excreted by the kidney. Thus, for a delivery system to be effective, it must protect the strands from enzymatic attack and, if required, prolong the duplex's time in the circulation.

Size and Anionic Nature of siRNA itself - The second issue concerns the inability of the large (molecular weight approx. 13 kDaltons) and highly negatively charged siRNAs to pass through the cell membrane by passive diffusion. Therefore, for the oligonucleotides to reach their site of action, any delivery system must open up pores or tight junctions and/or promote cell entry via endosomes.

Endosomal Escape - The third hurdle relates to the endosomal route of cell entry, and concerns the need for the siRNA to escape from the vesicles following uptake in order to bind to RISC.

Non-specific Delivery and Off-Target Effects - Unless targeted, siRNA duplexes can be potentially taken up by any cell. This not only increases the dose required to achieve silencing due to drug "wastage," but also increases the possibility of off-target effects. These are due to siRNA binding to mRNAs whose sequence is not 100 % complimentary. Knowledge about the exact influence of siRNA structure, chemistry and formulation on off-target effects has grown over recent years but is still evolving (2, 5). However, if siRNA can be targeted to a particular cell type, this would both minimise the potential for side-effects and the dose required.

Transitory Nature of the Silencing Effect - The fifth big issue with siRNA delivery is the transient nature of its inhibitory effect on protein translation which necessitates multiple dosing. The use of DNA cassettes, as described in Section 2, can result in a longer duration of action. However, DNA is just as big a delivery challenge as RNA and, to date, shRNA has been mainly delivered via viral vectors (see 2 for review).

5. Strategies Used to Improve the Delivery of siRNA

5.1. Modifications to the Structure of siRNA Itself

Researchers have focussed on three main areas: stability, optimisation of potency and specificity. For example, the serum stability of siRNA has been improved by including F or OMe groups at 2' position (6), or by the use of locked nucleic acids (7). In another approach RXi Pharmaceuticals (<http://www.rxipharma.com/>) are developing siRNAs with blunt ends (as opposed to overhangs) that are nuclease resistant. With respect to potency and specificity, a great deal of work is currently being carried out to elucidate which parts of a sequence are critical for target mRNA binding and guide strand loading, and which motifs can trigger immune responses (2, 6-7 and 8).

5.2. Cationic Lipids and Liposomes (reviewed in 9 and 10)

The complexation of siRNA with cationic lipids or its encapsulation in liposomes helps mask its anionic charge and promotes its uptake by the endosomal route, while protecting it from enzymatic attack. Examples of cationic lipids/liposome systems used in siRNA delivery include Lipofectamine 2000, which is commonly used for *in vitro* studies, N¹-cholesteryloxy carbonyl-3,7-diazanonane-1,9-diamine/DOPE combinations and cardiolipin. In such approaches the lipid to RNA ratio should be optimised to ensure the complexes are below the 150 nm limit for uptake into clathrin-coated pits, and that the stability of the oligonucleotides is maximised. The conjugation of RNA to lipids such as derivatives of lauric acid or cholesterol has also been shown to improve delivery of siRNA to cells (11).

Often fusogenic lipids, such as L- α dioleoyl phosphatidyl ethanolamine (DOPE), or pH-sensitive peptides, e.g. polyhistidine lysine, are included in the formulation to destabilise the endosomal membranes and release the siRNA into the cytoplasm. For example, Silence Therapeutics (<http://www.silence-therapeutics.com/>) has developed a siRNA lipoplex formulation containing cationic and fusogenic components for anti-angiogenic therapy. However, despite some improvements in delivery, many cationic lipids are toxic and may in themselves alter gene expression (5). There is therefore a need to develop lipids with high transfection activity but low toxicity for siRNA delivery.

5.3. Cationic Polymers and Nanoparticles (reviewed in 9-10, 12)

A number of polymers have been used to complex and/or encapsulate siRNA. The rationale for their use is similar to that for the lipid complexes/liposomes described in Section 5.2. In addition, some have the potential to cause endosomal rupture due to their high charge densities and/or swelling effects which result in an influx of water and protons.

One example of an endosomal rupturing polymer is Polyethylenimine (PEI). Studies in mammalian cell lines show that low molecular weight PEI (< 25 kDaltons) forms siRNA complexes with greater silencing efficacy and lower toxicity than its longer chain counterparts. Furthermore, PEI has been successfully used to deliver siRNA in mice and guinea-pig models of ovarian cancer and Ebola virus respectively. However, despite these successes, PEI is not an ideal siRNA carrier as it causes a certain degree of toxicity including effects on multiple genes and stimulation of the immune system (5).

Chitosan complexes and nanoparticles have also been used to deliver siRNA. For example, siRNA, encapsulated in chitosan nanoparticles, reduced the expression of enhanced green fluorescent protein (EGFP) by up to 80 % over controls when administered intranasally to transgenic EGFP mice. The extent of inhibition depended on the molecular weight of the polymer and its degree of deacetylation (reviewed in 9).

Calando Pharmaceuticals (<http://www.calandopharma.com/>) have developed linear cyclodextrin-based polymers, surface modified with adamantane groups linked to PEG 5000 and a targeting ligand, which form complexes with siRNA in the 50 nm size range. The company is, at present, developing a siRNA product using transferrin as the targeting agent against the M2 subunit of ribonucleotide reductase for the treatment of cancer.

Many other polymers have been used to complex and encapsulate siRNA (see 9-10, 12 for further examples). These include poly(lactide-co-glycolide) which offers the possibility of sustained release, protamine, which was incorporated into antibody conjugates for *in vivo* targeting to tumours, atelocollagen and block co-polymers of cationic polymers with poly(ethylene glycol) e.g. PEG-poly-(3-(3[(3-amino-propyl)amino]propyl)aspartamide).

5.4. Cell-penetrating peptides (reviewed in 13)

These are short cationic peptide chains, less than 30 amino acids in length, which can penetrate cell membranes and transport other molecules with them. Examples include derivatives of the HIV-1 Tat protein and poly-arginine peptides. They all share a high cationic charge density that facilitates their association with cell surfaces and promotes internalisation. They have been formulated with siRNAs either as complexes, or as conjugates where they are bound through disulphide bond formation. One issue for both approaches is that association of siRNA with the peptides can neutralise the positive charge necessary for their activity. At present, this appears to be less of an issue with complexes than with conjugates as it is easier to manipulate the ratio of peptide:siRNA they contain.

5.5. Surface Modification with Targeting Agents and/or Poly(ethylene)-glycol

Ideally, siRNA should be targeted to specific cells in order to minimise the dose required and the risk of off-target effects. Examples of targeting agents that have been used for *in vitro* and/or *in vivo* studies include transferrin, antibodies to cell surface receptors, RGD peptide (targets integrin receptors) and folate. (reviewed in 10 and 14). The first actively targeted siRNA therapeutic from Calando Pharmaceuticals will enter Phase 1 trials in the near future.

Poly(ethylene glycol) is often an integral part of siRNA lipid, polymer and conjugate systems due to its ability to reduce their uptake by the 333333-endothelial system and, thus, facilitate passive targeting to tumour and inflamed tissues. It can be either incorporated as PEGylated lipids/polymers within the formulation or through formation of block co-polymers with other polymers (see 9-10 and 12 for examples). Alternatively, siRNA has been conjugated to PEG and, for example, used to form mixed micelles with the cationic polymer, poly(lysine) (15). However, although in general, PEGylation improves colloidal stability, reduces toxicity and prolongs circulation, its presence can reduce transfection efficiency (16).

5.6. Local Delivery as a Strategy

Given the challenges associated with siRNA, it makes sense to reduce the number of barriers to delivery by targeting diseases that can be treated locally. This explains why diseases, where local delivery is possible such as wet AMD and Respiratory Syncytial Virus (RSV) infections, have become popular targets for companies developing siRNA therapies (see Section 6). In addition to direct delivery to the eye and lung, a number of other approaches are being explored. These include electroporation for delivery of siRNA to muscle and intratumoural and intrathecal injections for the treatment of cancer and brain disease respectively (reviewed in 10).

6. SiRNA Therapies in the Clinic

A number of siRNA therapeutics are currently in clinical development. One of the most advanced is besivasiranib from Acuity Pharmaceuticals (now the Opko Corporation), a siRNA against vascular endothelial growth factor (VEGF) for the treatment of wet age-related macular degeneration and diabetic macular edema, which has recently successfully completed Phase 2 trials. In addition, Silence Therapeutics and Sirna Therapeutics (<http://www.sirna.com/>) also have candidates for AMD in clinical development. With respect to viral infections, Sirna and Alnylam Pharmaceuticals (<http://www.alnylam.com/>) are currently developing products for hepatitis C virus and Respiratory Syncytial Virus (RSV) infection respectively, with the latter being in Phase 2. In addition to siRNA clinical candidates, many more siRNA therapeutics are at the preclinical stage with cancer, diabetes and genetic diseases, such as Huntingdon's, being popular targets.

7. Concluding Remarks

As can be seen from this article, RNAi therapeutics using siRNA is a rapidly evolving field with the potential to treat a large number of diseases, provided the issues with stability, delivery and sustained activity can be addressed. Its importance is highlighted by the number of strategic alliances formed between Big Pharma and the smaller specialist siRNA companies and the recent takeover of Sirna Therapeutics by Merck. However, despite the progress made, a number of key biological questions are yet to be fully answered. These include the potential of siRNA therapeutics to compete with endogenous miRNA production and the biological impact of this competition, and the possibility and impact of off-target effects and/or immune stimulation. These questions will continue to challenge scientists, clinicians and regulators alike as this class of molecules progresses from bench to clinic.

8. Further Reading

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The APV Drug Delivery Focus Group (APV DD) is a section of the APV (Arbeitsgemeinschaft für Pharmazeutische Verfahrenstechnik e.V. / International Association for Pharmaceutical Technology), a major European society for those sharing a professional interest in pharmaceutical sciences. The Focus Group was established in 2003 in response to the increasing importance of drug delivery within modern pharmaceuticals. [Read more...](#) [Contact us...](#)

COMBINING SCIENCE AND TECHNOLOGY TO CREATE ADVANCED DRUG DELIVERY SYSTEMS

OUR MISSION STATEMENT:

Modern drug delivery research and development is a truly multidisciplinary approach and must combine all relevant scientific, technical, medical and regulatory aspects required for the design, preparation, testing, manufacturing and registration of drug delivery systems and their components. It is the mission of the APV Drug Delivery Working Group to foster and promote all aspects of research and development required to transform drug molecules into safe, applicable and acceptable drug delivery systems, which provide therapeutic benefit, convenience to the patient and improve patient compliance.

Our mission includes in particular the following tasks:

- Thoroughly understanding the physical-chemical and biopharmaceutical properties of the drug substance to be delivered and the components of the drug delivery system
- Understanding the biological barriers and the interactions of the drug molecule and its delivery system with the biological environment and the biological target including PK/PD and PK/safety relationships
- Research on excipients, materials and technologies required for the design, preparation and manufacturing of drug delivery systems for a selected route of administration
- Development and understanding of methods for in vitro and in vivo evaluation of drug delivery systems and their components
- Knowledge of regulatory requirements for clinical testing, manufacturing and registration of drug delivery systems

All disciplines relevant to the above mentioned areas of drug delivery R&D are invited to contribute to the APV Drug Delivery Group:

Pharmaceutics, Biopharmaceutics, Analytics, Biology, Physical Chemistry, Biochemistry, Physics, Engineering Sciences, Nano Technology, Material Sciences, Polymer Science, Toxicology, Drug Safety, Clinical Research, Drug Regulatory Affairs, etc.

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