APV FOCUS GROUP DRUG DELIVERY

COMBINING SCIENCE & TECHNOLOGY TO CREATE ADVANCED DRUG DELIVERY SYSTEMS

INTERNATIONAL ASSOCIATION FOR PHARMACEUTICAL TECHNOLOGY

NEWSLETTER ISSUE 1/2017 - June

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DRUG DELIVERY EVENTS

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2017 Annual Meeting, Controlled Release Society
July 16-19, Boston, MA, USA — Details

\+ **APV / IPEC Europe Excipient Conference 2017 | KN 3177**
September 19-20, 2017, Berlin, DE — Details

\+ **9th conference of the European Paediatric Formulation Initiative | KN 6696**
September 19-21, 2017, Warsaw, PL — Details

\+ **APV Medicines for Older Adults | KN 6704**
November 07-11, 2017, Graz, AT — Details

Suggest a meeting to be announced!

DRUG DELIVERY PRODUCTS

Provided by Dr. Louise Rosenmayr-Templeton

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ARYMO™ ER

The Egalet Corporation announced on 9th Jan 2017 that the FDA had approved Arymo™ ER (morphine sulphate extended-release tablets) [1] [2] for the treatment of severe pain requiring chronic round-the-clock treatment. The product is available in three strengths: 15 mg, 30 mg and 60 mg, the dose strength referring to the morphine content which is in the form of the pentahydrate sulphate salt. The dose for opioid-naïve or opioid non-tolerant patients is 15 mg every 8 or 12 hours. For patients on other oral morphine products, conversion to Arymo™ ER can be achieved by administering 50% of the patient's total daily dose as Arymo™ ER every 12 hours or 33% of the dose every 8 hours. For patients being switched to Arymo™ ER from other oral opioid products there are no standard conversion ratios and dosing must be initiated at 15 mg every 8 to 12 hours with inadequate pain relief being managed with rescue medication e.g. oral immediate release morphine, until the correct dose is established. The product can be administered with or without food.

The formulation exploits the company's Guardian™ technology which was originally developed in Denmark and Arymo™ ER is the first approved product based on this proprietary technology. The Guardian™ technology enables the development of an extended release formulation of morphine sulphate with abuse-deterrent properties. The formulation contains polyethylene oxide 400,000, butylated hydroxytoluene, polyvinyl alcohol, polyethylene glycol 3350, talc, and titanium dioxide plus different colouring agents for each dose strength. The capsule-shaped tablets are formed using a novel injection moulding technique. The tablets are very hard (>400N) and in vitro abuse deterrent studies showed that compared to morphine extended release tablets Arymo™ ER tablets are resistant to cutting, crushing, grinding or breaking using a variety of implements. In addition, the formulation hinders chemical extraction and forms a gelatinous mass in the presence of liquid that makes it difficult to syringe.

As the tablets become sticky and swell when exposed to fluid, patients are instructed to swallow one tablet at a time with sufficient water to ensure complete swallowing and not to pre-moisten the dosage form in any way prior to administration. Due to the propensity for the tablets to become sticky and swell once moist, they can predispose patients to intestinal obstruction and exacerbation of diverticulitis and should be used with caution in patients with swallowing difficulties and GI disorders, such as oesophageal cancer or colon cancer, which result in a smaller than normal GI lumen.
Approval was based on pharmacokinetic studies which showed that Arymo™ ER 15 mg, 30 mg and 60 mg are bioequivalent to the corresponding MS Contin® dose strengths and other studies that were carried out to assess the abuse deterrent properties of Arymo™ ER. These included a randomized cross-over study to determine the impact of tablet manipulation on morphine release and pharmacokinetics. This study involving 38 subjects compared the pharmacokinetics of orally administered manipulated Arymo™ ER to intact Arymo ER™ and crushed extended release morphine sulphate tablets (MS Contin®). It showed that the manipulated Arymo™ ER resulted in a higher mean Cmax (28.7 ng/ml) than non-manipulated tablets (17.8 ng/ml). The AUC obtained from both manipulated and non-manipulated Arymo™ ER were similar. However, compared with crushed morphine sulfate extended-release tablets, manipulated Arymo™ ER had a lower mean Cmax (28.7 ng/ml versus 42.3 ng/ml) and longer median Tmax (2.1 hours versus 0.9 hours).

An oral abuse potential study was also conducted in 39 non-dependent recreational opioid users comparing manipulated Arymo™ ER, intact Arymo™ ER, crushed extended release morphine sulphate and placebo for Drug Liking and Take Drug Again responses. However, although the results from the 38 subjects who completed the study, showed a difference in the extent of Drug Liking between the manipulated Arymo ER and the crushed extended release morphine tablets, there was no statistically significant reduction in the response to Take Drug Again.

Based on the entire package of abuse deterrent studies it was concluded that Arymo ER has the physical and chemical properties expected to make abuse by injection difficult. However, the FDA did not allow Egalet to make claims with respect to the product's deterrent properties to abuse via the nasal route, This was despite the results of simulated smoking studies which demonstrated that only a very small percentage of active was released and data from an intranasal human abuse liability study which showed that "snorting" of ground Arymo™ ER resulted in significantly lower scores for Drug Liking, Drug High, Take Drug Again, and Overall Drug Liking compared to that produced by the insufflation of ground MS Contin® in a Phase 3 Human Abuse Liability Study. The reason for this was the 3-year exclusivity that the product Morphabond™ (Daiichi Sankyo) has for this claim. This exclusivity expires on 2 Oct 2018 [3]. However, according to a press release on Egalet's website [4], the FDA has not objected to the company informing physicians of the data on nasal insufflation in their promotional material, provided the information is only circulated to healthcare professionals and appropriate disclosures are made.

Egalet received $40 million in senior secured debt financing based on the approval. This funding is associated with a right to receive an aggregate 1.5% royalty payment on net sales of Arymo™ ER. The product was launched on 30 Mar 2017 [5].

VANTRELA™ ER

Arymo™ ER was not the only oral controlled release opioid-containing product with abuse deterrent properties approved by the FDA in January 2017. Teva Pharma's Vantrela™ ER (hydrocodone bitartrate extended-release tablets) was also licensed by the agency [6] [7]. These tablets are available in five different strengths: 15 mg, 30 mg, 45 mg, 60 mg, and 90 mg and contain the following inactive ingredients: lactose monohydrate, ethyl cellulose, hypromellose, glyceryl behenate, and magnesium stearate. The tablet employs Teva's proprietary CIMA™ technology which is a multi-layer gel-forming polymer coating which results in both physical and chemical barriers (gelling, barrier and matrix) to hinder tampering with the tablet for the purpose of opioid abuse by crushing, extraction and dose dumping in alcohol. The starting dose for opioid-naïve and opioid non-tolerant patients is 15 mg tablets orally every 12 hours with the dose being increased every 3 to 7 days. The 90 mg dosage strength, a single dose greater than 60 mg, or a total daily dose greater than 120 mg, are only indicated for use in opioid-tolerant patients.

Again Vantrela™ ER is indicated for the management of severe chronic pain requiring constant treatment and for which the use of other pain relief options are inadequate. Its approval was based on its safety and efficacy in clinical studies plus the results of laboratory-based in vitro manipulation and extraction studies, pharmacokinetic studies, and clinical abuse potential (CAP) studies. In vitro testing demonstrated that the dosage form is resistant to crushing, breaking, and dissolution by various means and retains some extended-release properties even after manipulation. In addition, small volume extraction of Vantrela ER resulted in a viscous material that could not easily be injected.

The nasal pharmacokinetic study compared finely milled Vantrela™ ER delivered nasally with the intact dosage form taken orally and intra-nasal powdered hydrocodone powder. It demonstrated that the manipulated Vantrela™ ER tablet contents resulted in a higher Cmax and a shorter time to Tmax than taking intact Vantrela™ ER orally. However, the Cmax and Tmax were lower and longer respectively than after intra-nasal delivery of hydrocodone powder. Crushed Vantrela™ ER tablets were compared with the same comparators in an oral study. This demonstrated that although the Cmax was higher and Tmax shorter than with the intact tablets, the overall exposure in terms of AUC was the same and the crushed tablets maintained some of their extended release properties compared to the immediate release powder.

The clinical abuse potential of the manipulated tablets was evaluated in two randomized, double-blind active- and placebo-controlled studies in non-dependent opioid abusers, one to assess abuse potential via the oral route and one via nasal delivery. In both cases the administration of manipulated Vantrela™ ER was associated with statistically significantly lower mean and median scores for Drug Liking and Take Drug Again ($P<0.001$ for both), compared with powdered hydrocodone.

In addition to the abuse potential studies, the efficacy and safety of Vantrela™ ER was demonstrated in a randomized double-blind, placebo-controlled, multi-center clinical trial in opioid-naïve and opioid-experienced patients with moderate to severe chronic low back pain.

The commercialization of Arymo™ ER and Vantrela™ ER will widen the option for clinicians to treat severe chronic pain while reducing the likelihood of opioid abuse which is estimated to be the cause of 15,000 overdose deaths per year and 1 million visits to Accident and Emergency departments in the US alone in 2010 [quoted in [7].

References and Further Information

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DRUG DELIVERY COMPANIES

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Provided by Dr. Kaspar van den Dries

CATALENT PHARMA SOLUTIONS (Somerset, NJ, USA)

Catalent Pharma Solutions is a leading global provider of advanced delivery technologies and development solutions for drugs, biologics and consumer health products. It employs roundabout 10,000 people, including over 1,400 scientists at more than 30 facilities across five continents. The company has more than 80 years' experience across prescription and consumer markets and has been involved in nearly 50% of all new molecular entities to have received FDA-approval in the past 10 years. The company offers expertise and services in both product development and manufacturing and packaging. With respect to the early phase development of prescription medicines, Catalent offers a broad tool-kit of development and bioavailability enhancing technologies. These include OptiMelt® hot-melt extrusion, Pharmatek™ Spray Drying, and extensive expertise in lipid-based drug delivery systems with RP Scherer softgel technologies.

The principle of softgel encapsulation has been developed to provide advanced delivery solutions including coated softgels to provide optimal drug release profiles through targeted delivery, modified release and fixed dose combination. Innovations including OptiGel™ Bio allow oral delivery of macromolecules, and OptiGel™ Micro technology uses cutting-edge manufacturing processes to produce smaller, spherical capsules. The OptiGel™ Lock abuse deterrence technology hinders abuse of narcotic or psychotropic drugs by inhalation, extraction or snorting.

Catalent's OptiForm® Solution Suite combines these technologies into a robust, data driven, parallel screening platform which assesses the optimal formulation pathway for small molecules with bioavailability challenges in just 12 weeks. Catalent recently expanded this offering to include OptiForm® Solution Suite Bio, which quickly screens small proteins and peptides for oral delivery potential. Catalent offers a range of innovative drug delivery technologies; including Zydis® fast dissolve orally dispersible tablets, OptiShell™ gelatin-free softgels, FlexDose™ stick-pack solutions, and extensive controlled and targeted release dose forms. Sterile technologies include ADVASEPT® glass-free injectables technology; as well as aseptic auto-injector and pre-filled syringe filling solutions. Catalent has also produced OTC, nutritional supplements and beauty care products since 1933, and today partners with 20 of the leading global consumer healthcare companies.

Catalent provides analytical services for large molecule products and has over 20 years of experience, and specific expertise in New Biological Entities, biosimilars, and antibody drug conjugates. From its sites in Kansas City, Missouri, and Madison, Wisconsin, Catalent offers both kinetic and quantitative binding assays for characterisation and GMP testing, and this forms part of the company's overall biologics development platform that includes GPEx® mammalian cell line engineering technology and SMARTag® antibody-drug conjugate technology.

Catalent operates 8 clinical supply facilities in the US, UK, Germany, Singapore, Japan and China, and maintains in addition an extended network of over 50 audited depots round the globe. Catalent's clinical supply teams can handle a broad range of international compliance and distribution requirements, which can help to expedite complex clinical trials and ensure reliable supply of clinical trial medication worldwide.

Fact sheet:

Founded:	2007 ("Spin-off" from Cardinal Health)
Location:	33+ Sites worldwide, Headquarter in Somerset, NJ, USA Sites in Germany are located in Eberbach and Schorndorf (Württ.)
Ownership:	NYSE Listed
Employees:	~10,000
Key technologies:	R.P.Scherer Softgel technology OptiShell™ Animal-derived gelatin free softgels ADVASEPT® Advanced aseptic blow-fill-seal technology Zydis® Orally dispersible tablets Bioavailability enhancement technologies
Products:	OptiForm® Solution Suite
Development status:	N/A
Partnerships:	N/A
Website:	http://www.catalent.com
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DRUG DELIVERY PEOPLE

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Provided by Dr. Lea Ann Dailey

DR CATHERINE TULEU is a Reader in Pharmaceutics at the University College London School of Pharmacy. In 1994, she became Docteur en Pharmacie from Université Paris V, France and thereafter, obtained an MSc (1995) and a PhD (1999) in the field of Pharmaceutical Technology from Université Paris XI. She relocated to UK then for a British Council postdoctoral fellowship at The School of Pharmacy, University of London.

During her career, Dr Tuleu has become one of the few leading experts in developing paediatric medicines. Her research inherently translational, ranges from formulation, process and methodology development to clinical implementation, integrating the following logically related topics:

- Safety and toxicity of excipients for paediatrics
- Formulating better medicines for children (reformulation, repurposing)
- Development of innovative age appropriate dosage forms especially for under 5s
- Administration issues (co-administration with food/beverages) and devices
- Taste assessment (in vitro, in vivo) and acceptability / likability of dosage forms

Her work involves industry, hospitals and other academic units as collaborators. It is supported by research grants from the EPSRC, MRC, Innovate UK, NIHR, the European Commission, Bill & Melinda Gates Foundation, and others. Among her scientific and academic roles, she also chairs the European Paediatric Formulation Initiative as well as acting as an expert advisor to the UK Medicines and Health Products Regulatory Agency and the EMA. In 2015 Dr Tuleu received the Academy of Pharmaceutical Science award and she was listed in the top 2 of The Medicine Maker magazine 2016 Power List of the 100 most influential people in drug development for her work in the field of paediatric drug formulations.

FEATURED ARTICLE

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CLINICAL RELEVANCE OF NUCLEIC ACID DELIVERY APPROACHES

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1. Gene delivery in the clinic

By 2012, over 1800 gene therapy clinical trials had been performed in 31 countries. Most of these trials (64.4%) focused on treatments of different cancers[1] since the five-year survival rates of certain cancers, such as liver (17.5%), lung (17.7%) and pancreatic cancer (7.7%), is still very low according to a report from the National Cancer Institute (2009-2013). Current pre-clinic research and clinical trials for gene therapies of cancer include several strategies. The first one is the replacement of mutated tumor suppressor genes such as p53. For example, Advexin® is a p53 encoding plasmid carried by an adenoviral vector. It showed antitumor activity and improved survival in clinical trials for treatment of head and neck cancer.[2] Another approach is the supplement of a 'suicide gene' encoding a viral/bacterial enzyme which can convert a pro-drug to an active drug in cancer cells.[3] Silencing of gene control tumorigenesis (e.g. proliferation and survival), metastasis and drug resistance is also a common approach.[4]

Gene therapy of inflammatory diseases only accounts for small portion of gene therapy clinical trials (0.7%).[1] However, a large global market for drugs for inflammatory diseases[5] has encouraged research groups and pharmaceutical companies to develop new therapies, consequently increasing the number of pre-clinical research approaches and clinical trials of gene therapy for inflammatory diseases. For example, gene therapy approaches to asthma include DNA vaccines to induce immune tolerance,[6] delivery of antisense oligonucleotides,[7] small interfering RNA (siRNA)[7-8] and deoxyribozymes (DNAzyme) for the selective silencing of asthma related genes. Currently, only one gene therapy approach for asthma has been evaluated in a clinical trial. This evaluated the use of SB010, a DNAzyme which can cleave GATA-3, a key factor in asthma pathogenesis. It achieved anti-inflammatory effects and improved lung function in asthma patients.[9]

2. Delivery challenges

Due to the immunologic limitations of viral vectors, the application and development of non-viral delivery has gained considerable interest in the past few years. Non-viral vectors have better and more easily tunable safety profiles than viral vectors. Biocompatible materials can be selected to achieve less immunogenicity and toxicity. Non-viral vectors can also be synthesized from biodegradable materials to reduce toxicity and accumulation in the body. Most importantly, because of the relatively simple chemical structure of non-viral vectors, such as polymer-based materials, various modifications have been exploited to achieve efficient and selective gene delivery, improved safety and optimal pharmacokinetic profiles[10]. However, despite the numerous studies which have been performed to develop and optimize non-viral vectors, their gene delivery efficiency is still relatively poor compared to their viral counterparts. Consequently, only a few non-viral vectors are mature enough to enter clinical trials [10].

Non-viral vectors encounter various challenges when they are used to deliver nucleic acids systemically. Nucleic acids are easily degraded by endogenous nucleases in the circulation. The half-life of nucleic acids in the bloodstream is short. For instance, the half-life of naked plasmid DNA injected intravenously (i.v.) has been reported to be 10 minutes in mice. Nucleic acids carried by non-viral vectors are not readily degraded by nucleases and have longer circulation half-lives. Chemical modification of the nucleic acid can also facilitate to protect them against cleavage by nucleases and increase their *in vivo* stability.

However, even non-viral vectors need to overcome several biological barriers to deliver nucleic acids to target cells/tissues. Most non-viral vectors contain polycations or cationic lipids to condense nucleic acids which have negatively charged backbones. Nucleic acids can electrostatically interact with non-viral vectors and form polyplexes or lipoplexes which commonly have a net positive surface charge. This positive charge can induce non-specific association with

non-target cells and interaction with serum proteins in the circulation. Vectors covered with a corona of serum proteins are easily recognized and trapped by the reticuloendothelial system (RES), such as the liver, spleen and bone marrow. Consequently, only a small dose of i.v. administrated cationic nanoparticles can be delivered and accumulate at the target site. One of the strategies to reduce the positive charge and non-specific delivery is to decorate the vectors with polyethylene glycol (PEG), a hydrophilic and charge-neutral polymer. PEG shields the polyplexes/lipoplexes in the blood stream and avoids non-specific delivery. Most importantly, it prevents interaction with serum proteins and reduces accumulation in the RES which significantly increases the circulation time of polyplexes/lipoplexes [11].

Another challenge is selective accumulation in the tissue of interest. The behavior of non-viral vectors of nucleic acids in the body is highly dependent on their size, shape and surface properties. Typical non-viral vectors carrying nucleic acids, such as lipoplexes and polyplexes, are of spherical shape and in the nanometer range. Large lipoplexes/polyplexes (> 200 nm) tend to accumulate in the liver and spleen and micrometer size particle (2-5 um) rapidly accumulate in the capillaries of the lung. Therefore, particle sizes around 100 nm are preferred [12]. Normal blood vessels have tight interendothelial junctions and prevent extravasation of lipoplexes/ polyplexes from the blood stream. In certain cases, such as inflammation and injury, leakage and dysfunction occur in the blood vessels and lead to accumulation of lipoplexes/polyplexes at these sites. This strategy is commonly utilized to target tumors. The blood vessels supporting tumor growth are fenestrated, and tumors often lack efficient lymphatic drainage. This phenomenon is termed the "enhanced permeability and retention (EPR) effect". Modifications in vectors to prolong circulation time, such as PEGylation, can increase the accumulation at the tumor site.

Once the lipoplexes/polyplexes reach their selective site, even if some hydrophobic vectors can diffuse directly through the cellular membrane, most vectors require active internalization. Vector modification with ligands can enhance cellular uptake via receptor mediated internalization. Therefore, escape from the endosome is required for vectors to avoid degradation and to release nucleic acids into cytoplasm. To facilitate endosomal escape, the vectors can be modified with endosomolytic peptides, such as melittin, to disrupt the endosomal membrane [13]. Cationic polymers which have a high buffer capacity, such as poly ethyleneimine (PEI), can absorb protons and lead to an increased influx of counter ions (chloride) and water. Eventually, the increased osmotic pressure leads to bursting of the endosome and the release of materials inside the vesicles. This theory is called "proton sponge effect". Another reason why cationic polymers and lipids can achieve efficient endosomal escape is called the "flip-flop" mechanism. The polymer/lipid with positive charge can electrostatically interact with vesicle membranes with negative charge and lead to membrane flipping and destabilization [11].

3. Local administration approaches for siRNA in the clinic

Due to the many barriers that need to be overcome by systemically administered nucleic acids, some local administration routes have been exploited that can circumvent the first-pass effect in the liver and lead to much higher siRNA concentrations in the target organ. In the late 2000s, when the first clinical trials of therapeutic siRNA were started, all of them exploited either intranasal, intraocular or intrathecal administration. The first clinical trial of siRNA therapy was initiated for the treatment of ocular disease by Opko Health Inc. In this trial, siRNA against vascular endothelial growth factor (VEGF), named Bevasiranib, was administrated intravitreally (IVT) to inhibit retinal neovascularization for the treatment of age-related macular degeneration (AMD), a leading cause of blindness among people aged 60 and older, and diabetic macular edema (DME). However, its Phase III results suggested that Bevasiranib cannot efficiently prevent vision loss in AMD. Afterwards, two other siRNA formulations, administrated IVT, for the therapy of AMD and DME which targeted the VEGF receptor-1 (VEGFR1) entered clinical trials. Unfortunately neither formulation could achieve sufficient therapeutic effects to prevent vision loss. However, when Macugen, a RNA aptamer against VEGF for AMD therapy, became the first RNA therapy approved by the US FDA, it encouraged pharmaceutical companies to keep exploiting this field. Since aptamers are generally very instable and easily degraded by nucleases, they are typically modified in their backbone or by introduction of unnatural nucleobases. In case of Macugen (pegatinib sodium), the riboses are either 2'-fluorinated or 2'-O-methylated. Additionally, the aptamer is stabilized by two polyethylene glycol (PEG) chains at its 5' prime end.

PF-655 is a siRNA formulation targeting an upstream regulator, apoptosis stress-response gene RTP801/REDD1, controlling VEGF production. Phase II results suggested that IVT administration of PF-655 can improve mean visual acuity. Another formulation of siRNA for ocular disease is based on eye drops. SYL040012, a siRNA formulation against β2-adrenergic-receptor (ADRB2), was developed by Sylentis, S.A. for treatment of open angle glaucoma. It was well-tolerated in patients with ocular hypertension or glaucoma in a Phase I study. A completed Phase II study suggested that SYL040012 (300 µg/ eye/ day) can significantly reduce intraocular pressure compared to placebo. The same company initiated another clinical trial of a siRNA eye drop formulation, SYL1001, targeting transient receptor potential cation channel subfamily V member 1 (TRPV1) for alleviation of ocular pain related to dry eye syndrome. Its recent Phase II results reported that one dose (1.125 %) among four different doses (0.375%, 0.75%, 1.125% and 2.25%) can alleviate ocular pain and hyperaemia compared to placebo.[14-15]

An intranasal delivery formulation of siRNA against nucleocapsid protein of respiratory syncytial virus (RSV), ALN-RSV01, was developed by Alnylam Pharmaceuticals. ALN-RSV01 was proposed for use in lung transplant patients with RSV infection. Phase II results indicated that ALN-RSV01 treatment achieves a promising clinical outcome including a reduced incidence of new/progressive bronchiolitis obliterans syndrome on day 90 and day 180 post-treatment. However, no Phase III trial has been initiated since 2012.[15] While Alnylam has switched its approach to modified siRNA-conjugates made with cholesterol or N-acetylgalactosamine (GalNAc) in the meantime, ALN-RSV01 was a non-modified

siRNA double strand of 19 paired nucleotides with an overhang of 2 unpaired thymidine nucleotides at the 3' end. Another approach to locally deliver siRNA to the lung is inhalation. Excellair™ is an inhaled siRNA formulation targeting spleen tyrosine kinase (Syk), an important factor involved in the inflammation process, for treatment of asthma. As reported by ZaBeCor Pharmaceuticals, the Phase I study suggested that Excellair™ was well tolerated and safe. Furthermore, Excellair™ treatment can improve the lung function of patients with asthma and reduced frequency of using immediate relief medication. The Phase II trial of Excellair™ was announced in 2009, however, no results have been reported yet.[15]

Systemic administration approaches for siRNA in the clinic

Currently, systemic siRNA therapies in clinical trials are mostly formulated as lipid nanoparticles (LNP). Since LNP preferentially accumulate in the liver and kidneys, the goal of many systemically administered siRNA therapies in development aim to target hepatic genes. TKM-ApoB is a siRNA therapy targeting apolipoprotein B (ApoB), the major apolipoprotein in low-density lipoprotein particles (LDL) which are generated primarily in the liver, for the treatment of hypercholesterolemia. This formulation is administrated i.v. and the therapeutic siRNA is formulated in the first generation of stable nucleic acid lipid particles (SNALP). Reduced ApoB/LDL was observed after TKM-ApoB treatment; however, some patients experienced flu-like symptom indicating potential immunostimulation by TKM-ApoB. Later, Alnylam Pharmaceuticals initiated a clinical trial using the same carrier SNALP to pack two sequences of siRNA against VEGF and kinesin spindle protein (KSP), important factors involved in cell survival and proliferation, for the therapy of primary and secondary liver cancer. Successful suppression of VEGF was achieved in some patients who received siRNA treatment. A liver targeted strategy has been developed to more selectively deliver siRNA to the liver with lower doses and reduced toxicity. siRNA conjugated with triantennary N-acetylgalactosamine (GalNAc) can trigger internalization of hepatocyte-restricted asialoglycoprotein receptor (ASGPR). A GalNAc conjugated siRNA (ALN–PCS02) targeting proprotein convertase subtilisin/kexin type 9 (PCSK9), an enzyme specifically degrading LDL receptor, was developed by Alnylam Pharmaceuticals for treatment of hypercholesterolemia. In a Phase I trial, a single dose of i.v. administration of ALN–PCS02 can reduce PCSK9 by 70% and LDL in circulation by 40%. A subcutaneous administrated formulation of the drug, ALN–PCS sc, entered a Phase I study to evaluate its efficacy in terms of reducing blood LDL. According to a 2015 press release, treatment of ALN–PCSsc was well tolerated and can achieve up to 83% reduction of LDL. More importantly, Phase I results suggested a potential for a bi-annual dosing.[15]

Applications of siRNA therapies in cancers attract large attention since there is no effective treatment for some cancers which lead to high mortality rates. A siRNA carried by anionic liposomes and targeting breakpoint cluster region–Abelson murine leukemia oncogene (bcr-abl) tyrosine kinase was proposed as a therapy for Chronic Myeloid Leukemia (CML). A patient with imatinib-resistant CML received siRNA formulation i.v. (10 µg/kg body weight) on day 426 post-transplantation of blood stem cells. Additionally, 300 µg siRNA was injected into one subcutaneous CML node. Later, 2 additional doses were given to the patient within 32 days of the first dose. The siRNA treatment transiently reduced the bcr-abl mRNA in CML cells slightly and *ex vivo* results suggested that the treatment can inhibit proliferation and induce apoptosis in CML cells. However, *ex vivo* transfection results also suggested that CML cells may develop resistance to siRNA application.[16] Ligand coated nanoparticles have been applied to increase the delivery efficiency of siRNA targeting tumors in the clinic. Calando Pharmaceuticals developed a delivery system containing three components in the carrier including 1) a cationic cyclodextrin based polymer to carry siRNA, 2) an adamantane polyethylene glycol which could enhance the stability in the bloodstream and 3) a human transferrin to target the tumor. This formulation CALAA-01 targeting the M2 subunit of ribonucleotide reductase, an important factor involved in cancer cells proliferation, was evaluated in the clinic for treatment of relapsed or refractory cancers/solid tumors. The siRNA induced mRNA cleavage was confirmed by a rapid amplification of complementary DNA ends (RACE) PCR. However, two patients experienced dose-limiting toxic events. Moreover, no objective anti-tumor effect was observed, and 29% patients showed increased tumor sizes which lead to termination of this trial. Despite more optimization still being required to achieve efficient *in vivo* gene knockdown using nanoparticles, this trial demonstrated the feasibility of systemically administrating ligand guided polymeric nanoparticles.[17]

4. Summary and outlook

In summary, nucleic acid therapeutics still face a serious delivery challenge. Many disease areas that currently lack efficient treatments are also still the holy grail of gene therapy. While delivery systems for nucleic acids have been developed for a multitude of administration routes, it appears that nanoparticle based delivery can only be successfully exploited for targets in the liver or after local administration. However, most tumors and metastases cannot be treated with locally applied therapeutics. And thus, tumor targeting with nanoparticles still seems to be out of reach. While ocular, nasal, mucosal, and pulmonary administration routes gain interest for nucleic acid therapeutics, the disease areas that can be treated via these routes appear to have less therapeutic impact. It remains to be seen in which direction the gene therapy field is moving with the latest discoveries in genome editing, such as CRISPR-Cas9 technology. CRISPR (Clustered regularly interspaced short palindromic repeats) are prokaryotic DNA repeats that are a part of the bacterial host defense system. In combination with the endonuclease Cas9 (CRISPR associated protein 9), CRISPR-Cas9 is currently used on lab scale but also in therapeutic preclinical approaches to edit genome mutations. However, CRISPR-plasmids currently face exactly the same nucleic acid delivery problems that we have not been able to solve efficiently in the previous decades.

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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:

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