Drug Delivery System

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DDS製品開発の最前線

特別寄稿

Nanotechnology in drug delivery

Sandra E Erb*

"Nanotechnology in drug delivery" によせて

DDS製品ホットニュースを提供する本誌"DDS製品開発の最前線"シリーズもスタートしてすでに2年が経過した．この欄では，最近国内で上市されたDDS製品について，製品の概要，用いられているdelivery技術の特徴と臨床上の効果，さらに開発の経緯なども含めて，わかりやすく解説していただいている．これらは有益な医薬品情報としてのみならず，DDS研究を実用化につなぐための貴重な現場情報として意義深いものがあり，執筆を担当していただいた諸先生方には感謝に堪えない．

さて，欧米にくらべやや遅くれるとはいえ，DDS製品はここしばらく年に10品目ほどのペースで上市されてきており，着実に医療の場に浸透してきている．また国内外の学会，シンポジウムでも明らかなように，DDS研究は依然活発であり，ここに登場するdelivery技術も多様で，まさに日進月歩で進化している感がある．なかでもナノテクノロジーは，最も技術革新が進んだ領域といえる．さまざまな機能を持つ微粒子キャリアの開発，あるいは原薬そのものに対するナノサイジングや表面修飾技術などにより，医薬品に従来とは異なる新たなdrug delivery機能を賦与できる可能性を秘めているが，これらの基盤技術がいまや応用の段階から実用の段階に移行しつつある．

このような現状を踏まえ，今回は特別企画として，最近のナノテクノロジーを活用した製品開発の状況についてアメリカTechnology Catalyst International社副社長のSandra E Erb氏より寄稿をいただいた．以下，ご一読いただければ，世界におけるナノテクノロジーを活用した製品開発の現状，最先端DDS技術の実用化へのチャレンジ，および今後の動向などをご理解いただけると思われる．

（学会誌DDS編集委員　吉野廣祐）

Summary

This article describes some of the technologies in development using nanotechnology and the areas of drug delivery challenges that they address. Areas of focus include processing technologies, delivery across the blood-brain barrier, targeted delivery and delivery of RNAi. The article is based on a large DDS database created in 1980, and maintained daily to date, involving DDS companies, DD technologies under development, and challenges facing the drug delivery industry.

key words : nanotechnology, RNAi delivery, targeted drug delivery, cancer targeting, blood-brain barrier

Nanotechnology, the science and engineering carried out on the nanoscale, has been under development for over two decades. During this time, researchers have discovered that the clusters of small numbers of atoms or molecules have properties that are significantly different than those found at the molecular or bulk scale. Initial applications have occurred in systems that use the nanoparticles in their free form. This has been the case in drug delivery where the initial application has been for the formation of small particles to improve the solubility and enhance the bioavailablity of poorly soluble drugs. Companies such as Elan have developed technologies that nano-size the therapeutic, increasing its surface area and thus increasing the solubility.

Indeed, four of the five launched drugs that use nanoparticle-based technology use the NanoCrystal® technology. These four are Emend, Megace ES, Rapamune, and Tricor. As shown in **Tab.1**, the total value of these five drugs has increased 22 percent in the period 2005-2007.

However, advancements in this field have continued. As a result, investigations into nanotechnologies have gone beyond just solubility improvement. **Fig.1** illustrates the various drug delivery applications for nanotechnology companies tracked by TCI. While solubility enhancement is still a major area of focus, process development and encapsulation technologies are also of great interest. Other areas

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Tab.1 Sales of launched drugs based on nanotechnologies

Brand name	2005 Sales ($MM)	2006 Sales ($MM)	2007 Sales ($MM)	AAGR (%)
Abraxane	$134	$175	$325	56%
Emend	$87	$131	$204	53%
Megace ES	$14	$43	$75	132%
Rapamune	$300	$337	$365	10%
Tricor	$927	$1,048	$1,218	15%
Total sales	$1,462	$1,734	$2,187	22%

Data from Company Annual Reports and Filings

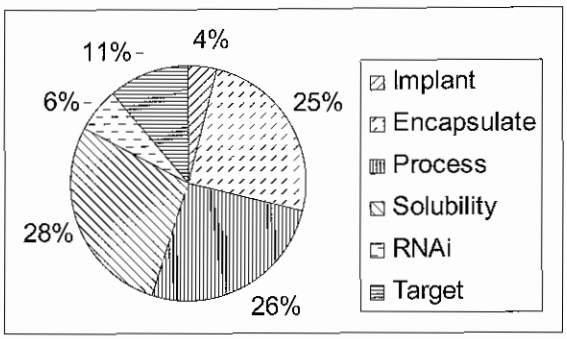

Fig.1 Nanotechnologies in development for drug delivery
Data based on TCI's proprietary database(*NDDS OnLine*)

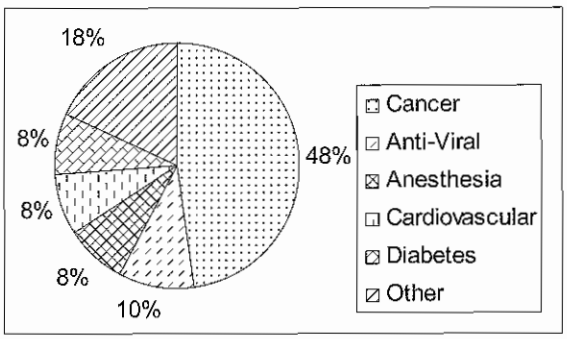

Fig.2 Pipelines in nanotechnologies
Data based on TCI's proprietary database(*Unlaunched Drugs*)

of interest for nanotechnology include improved coatings for implants, targeting areas such as the blood-brain barrier (BBB), and the delivery of RNAi and antisense therapeutics into the cell. As for the pipeline, nanotechnologies are concentrating on cancer, anti-viral, anesthesia, cardiovascular, and diabetes. The distribution of compounds in the pipeline in nanotechnology formulations is shown in **Fig.2**.

This article will briefly highlight some of the nanotechnologies under development for solubility improvement, as well the progress being made in the newer areas of drug delivery.

Solubility improvement

The initial drug delivery applications for nanotechnology have been in the creation of nanocrystals with reduced particle size. This results in the more efficient delivery of poorly soluble drugs into the body. The process of producing ever finer drug particles (nano-ization) further increases the drug's surface area and may improve dissolution velocities. Benefits of using nanosuspensions include smaller dosages (due to higher drug absorption), potentially increased formulation stability, and simpler formulation development. As a result, Nanotechnologies can be used to formulate parenteral dosage forms, as well as oral capsules, tablets, and suspensions.

The formation of nanoparticles with high solubilizing rates also eliminates the need for toxic solvents in parenteral formulations. If the nanosuspension is to be successfully administered intravenously, the maximum particle size should be less than 200 nm. The goal is to prepare relatively homogeneous nanoparticles with a mean diameter of 100 nm or less. When delivering an intravenous nanosuspension containing particles less than 50nm, the drug suspension avoids the reticuloendothelial system filtration mechanisms and circulates for several hours.

One challenge with nanoparticle technology has been consistently controlling the particle size while creating a system that will maintain its integrity through the sterilization process and provide an acceptable shelf life. Therefore, the main strategies employed to reduce particle size have been milling, homogenization, supercritical fluid techniques, and solvent-precipitation reactions. The processing of pharmaceutical materials with supercritical fluids to produce drug substances in a particulate form with specific physicochemical and size properties has received increasing interest in recent years. A wide

variety of supercritical fluid-based processes have been reported in the literature for the design and engineering of particles of poorly soluble drugs. This can increase their dissolution rate by controlling size and crystalline structure wherein the surface area and surface dissolution are enhanced.

Some of the processing technologies tracked by TCI include[*1)] :

- Supercritical fluid technologies from companies such as CrititechEiffel, Ferro, FeyeCon, Lavipharm, Pierre Fabre, and Thar Technologies
- Mechanochemical Processing™(MCP)Technology under development by Advanced Nanotechnology
- Precipitation technologies from companies such as CeraMem, NanoMaterials, and SOLIQS
- Sol-Gel technologies from companies such as CeramiSphere and Sol-Gel Technologies
- Biodegradable polymers by ElizaNor
- Controlled Flow Cavitation™ by Five Star Technologies
- PRINT™(Particle Replication In Non-wetting Templates) technology by Liquidia Technologies
- Carbon nanotubes by Nanocyl
- Nanotemplate Engineering™ by NanoMed Pharmaceuticals

These technologies are designed to produce uniform reproducible nanoparticles for use in the production of therapeutic dosage formulations. For example, the Five Star's Particle Management Technology™ (PMT) is based on Controlled Flow Cavitation™ (CFC). Hydrodynamic cavitation has been recognized for more than 100 years as a powerful, naturally occurring physical phenomenon. Uncontrolled, cavitation releases energy that can pit and erode even hardened metal surfaces. Five Star's patented CFC technology controls the location, size, density, and implosion intensity of bubbles in the cavitation zone to create optimum process conditions. PMT is then used to create nano- and micro-structured materials and formulations. One of the Five Star platforms is PMT-Crystallization. The platform is a robust and flexible proprietary platform for solvent and anti-solvent precipitation of nano- and micro-scale active ingredients.

[*1)] Strategies for Bioavailability Enhancement of Poorly Soluble or Poorly Permeable Drugs-6th Edition (published January 2007)

Targeted delivery

Targeted delivery of therapeutics to specific organs or tissues is another area being investigated by various companies in the nanotechnology drug delivery space. Two areas of focus are crossing the blood-brain barrier and targeting cancer cells.

1. Blood-brain barrier

Despite the thorough infiltration of brain tissue with blood capillaries, most therapeutic molecules are not able to freely pass from the blood into the brain due to its protective barrier, commonly referred to as the blood-brain barrier (BBB). The BBB exists because the endothelial cells lining brain capillaries are sealed tightly together, forming continuous tubes that do not leak. This barrier is critical to the health of the brain as it excludes potentially harmful molecules circulating in the blood. Fortunately, the concept of blood being completely sealed off from brain tissue is misleading, as a large number of molecules do move across the capillary endothelial cells. It is more useful to consider the brain vasculature as a type of molecular sieve allowing certain molecules to enter the brain, while excluding others.

The BBB is a critical yet underdeveloped part of neurotherapeutics. Unfortunately, large pharmaceutical companies only develop certain classes of drug molecules and lack effective technologies for solving the BBB delivery problem. Since large molecule drugs do not cross the BBB without facilitation, many protein-based therapeutics or gene medicines are not being developed for the brain, even though they may have the potential to yield more favorable therapeutic results.

New drug delivery advances and techniques, such as the use of nanoparticles, are also being developed for targeting the blood-brain barrier. However, these technologies have limitations and very few have been able to advance through the clinic.

One company that has invested time and resources into the delivery of nanoparticles to the brain is NanoDel Technologies. The use of the NanoDel's nanoparticle-doxorubicin formulation for the treatment of brain tumors has led to a significant reduction of the serious side-effects (reduced cardiotoxicity, reduced testicular toxicity) of doxorubicin, as well as to a sufficient bioavailability of the cancer drug. To test efficacy, rats with intracranially transplanted

glioblastomas cells were treated with doxorubicin-loaded nanoparticles. These animals were sacrificed and a beneficial effect was documented by histological examination of the brain. The animals treated intravenously with doxorubicin-loaded nanoparticles and coated with polysorbate 80 showed a significant extension of survival time compared to the untreated control. Conversely, histological examination of the tumors of treated animals showed a strong reduction of tumor growth, central necrosis, and locations of apoptosis. Histological examination of other organs showed no pathological changes. As a result, doxorubicin-nanoparticles currently remain in preclinical development at NanoDel.

Another company developing technology that has the potential to cross the BBB is Midatech. The nanoparticles produced by Midatech have the smallest diameter made-to-date (~800 picometers). They are water soluble and can be derivatized at the self-assembly stage to contain up to 90 different ligands including lipids, carbohydrates, peptides, DNA, RNA, or almost any chemical entity. The nanocells can present multiple ligands which allows for multivalent drug or multi-drug delivery on a single particle. The nanoparticles are made in a single step and are self-associating.

Because of their size, the nanoparticles can be used for drug delivery via different routes of administration, such as parental or intranasal. The nanoparticles possess unique characteristics that make them ideally suited for use in numerous medical and diagnostic applications for :

- Drug delivery across the blood-brain barrier for the treatment of Parkinson's, Alzheimer's, and other CNS diseases
- Magnetic imaging : a gold nanocell core can be supplemented with iron atoms to enhance contrast
- Synthetic vaccines
- Delivery of siRNA and DNA-based therapeutics
- Carriers of antibiotics
- Targeted delivery vehicles for small molecule drugs

2. Cancer cell targeting

Current cancer therapies inadvertently result in the non-specific killing of healthy cells ; thus the therapeutic efficiency is extremely low. Development of a nanoparticle system that can specifically target, detect, and kill cancer cells remains a great challenge. Tumor targeting results in increased drug levels in the tumor and reduced drug uptake by healthy organs, thereby improving efficacy and reducing toxicity.

CytImmune's approach to tumor-targeting simultaneously binds polyethylene glycol (PEG) -Thiol and tumor necrosis factor (TNF) to the surface of colloidal gold nanoparticles. The use of PEG masks the particles from immune recognition, thus preventing uptake via the liver and spleen and allowing TNF-targeting molecules to bind selectively to receptors. As a result, the reaction elicits rapid absorption rates of the drug at the tumor site. Coating nanometer-sized colloidal gold particles with CytImmune's patented technology completely alters the biodistribution of these particles, allowing them to find solid tumors and deliver therapeutic payloads while bypassing normal cells. Essentially, CytImmune's platform specifically attacks tumors by targeting the blood supply to the desired site, and/or specifically interacting with or stimulating the immune system ; targeted biodistribution of cancer therapeutics will enable such drugs to have the maximum efficacy while minimizing adverse side effects.

In addition to delivering protein biologics to tumors, CytImmune plans to use this technology to deliver small molecules, such as derivatives of taxol and/or other chemotherapeutics as a targeted drug therapy. Aside from tumor-targeting agents, the self-assembling colloidal gold nanoparticles also can be used to formulate wholly human monoclonal antibody therapeutics.

Tab.2 shows the CytImmune pipeline.

Another novel technolgy that enables the delivery of macromolecules to targeted tissues and cells is NanoCR™, under development by GeneSeques. NanoCR technology condenses and encapsulates drugs into 50 nm targeting protein carrier constructs that are covered with a novel, 100 percent ligand-crystallized shell. The technology entails nano-sizing for optimal cellular uptake, full encapsulation of the drug to prevent enroute degradation, and capsule-coating formulations that can incorporate a wide range of proteins and/or peptides for targeted, cell-specific delivery. The nanocapsules are designed to use a flexible formulation process and can carry large or small molecules, 'custom target' delivery to different organs, tissues and cells, and be applied several ways including topically, intravenously, or via devices or

Tab.2 CytImmune pipeline

Compound	Partners	Targets	Stage of development	Formulation
Doxorubicin		Solid tumors	Formulation stage	IV-targeted
Interleukin-12		Solid tumors	Formulation stage	IV-targeted
Interleukin-2		Solid tumors	Formulation stage	IV-targeted
Paclitaxel		Solid tumors	Preclinical	Nanoparticle
Tumor necrosis factor	Undisclosed	Solid tumors - veterinary	Phase I	IV-targeted
Tumor necrosis factor	National Cancer Institute, Ben Venue Labs	Solid tumors - human	Phase I complete	IV-targeted
Tumor necrosis factor + Paclitaxel		Cancer	Preclinical	IV-targeted

Data based on TCI's proprietary database(*Unlaunched Drugs*)

tablets.

GeneSegues' NanoCR is the industry's first and only encapsulated, sub-50 nanometer biologic drug carrier with site-selective function. Fifty nanometers is an important threshold for drug delivery, particularly for effective cellular uptake. The size and structure of the s50 capsules allows for efficient distribution to primary and distant disease cells. It has the ability to deliver its nucleic acid cargo intact to the nucleus of the targeted cell. Preliminary data shows high precise delivery that uniquely enables GeneSegues to down-regulate a key protein found in all known cancer cell pathways.

A third company, Nanobiotix is developing nanoXray™, a technology platform that is expected to be turned "on" and "off" outside the body to selectively treat a variety of cancers safely and noninvasively. Use of NanoXray is intended to resolve radiation therapy's biggest drawback : destruction of healthy tissue and its subsequent deleterious side effects when a high Xray dose is necessary.

The nanoXray platform is being developed by Nanobiotix for use with NanoBiodrugs™, nanoparticles with a controlled diameter smaller than 100 nanometers. The core of the nanoparticle is a nanoprodrug in an inactive form that can subsequently be activated to generate the therapeutic effect. The surface of the NanoBiodrug contains a specific recognition bioagent enabling molecular targeting. This targeting directs the nanoprodrug towards the pathological cells or tissues. After the NanoBiodrug accumulates in the target tissues, an external physical activation is applied that generates a local and physical therapeutic effect destroying the pathological cells. Activation is achieved by a magnetic field similar to that of an MRI machine, or by a laser (or other energy field such as X-Ray or ultrasound). This mechanism offers the major advantage of total control of the therapeutic effect.

3. Other targets

NanoViricides, Inc. is developing NanoViricide™, a non-particulate nanomaterial that may contain an encapsulated active pharmaceutical ingredient to target a specific type of virus. A NanoViricide drug micelle injected in the patient's bloodstream specifically seeks, attaches to, engulfs, and thereby neutralizes circulating virus particles. Many viruses are expected to be dismantled by the NanoViricide attack. In addition, any encapsulated active pharmaceutical ingredient is also injected into the virus by the NanoViricide micelle, thus completely destroying the virus. The second generation NanoViricides will be designed to go one step further and destroy the viral genome.

The anti-viral spectrum of the NanoViricide drug is completely tunable. The company can design drugs that are specific to a virus type such as their FluCide™-I product that targets all influenza types and strains. Other examples include broad spectrum FluCide-HP™ that protects against the highly pathogenic subgroup of influenza A viruses, where most pandemic threats emerge from, and AviFluCide™-I, which is active against H5N1 or avian flu, the current pandemic threat. The company can also make a single NanoViricide drug to specifically treat a large number of viral diseases by mixing and matching the set of ligands that specify the locations

Tab.3 Nano viricide pipeline

Compound	Partner	Indication	Stage of development	Formulation
Anti-avian influenza drug		Avian influenza	Preclinical	Nanoparticle
Undisclosed anti-hepatitis C drug		Hepatitis C	Preclinical	Nanoparticle
Undisclosed HIV drug	TheraCour	HIV	Development	Nanoparticle
Undisclosed HIV drug	TheraCour	HIV	Preclinical	Nanoparticle
Undisclosed anti-influenza drug	TheraCour	Influenza	Preclinical	Nanoparticle
Undisclosed anti-influenza drug		Influenza	Preclinical	Parenteral
Undisclosed anti-rabies drug		Rabies infection	Preclinical	Nanoparticle

Data based on TCI's proprietary database (*Unlaunched Drugs*)

of the viruses.

NanoViricide has recently announced that its anti-HIV drug candidates demonstrated significant therapeutic efficacy in recently completed preliminary animal studies. Additional biological tests and data analysis also showed that animals treated with the anti-HIV drug candidate, HIVCide™-I, demonstrated a substantially greater reduction in viral load when compared to the animals given an anti-HIV "cocktail" in a preliminary animal study.

The NanoViricide pipeline is shown in **Tab.3**.

A different approach to pathogen targeting involves NanoBio's NanoStat™ technology. This drug delivery platform employs high-energy, oil-in-water emulsions that are manufactured at a size of 150-400 nanometers and are stabilized by surfactants. NanoStat employs a physical process to disrupt the outer membrane of pathogens by fusing with and killing lipid-containing organisms (including viruses, bacteria, fungi, spores, and protozoa). The technology-derived products are selectively toxic to microbes while non-irritating to skin and mucous membranes. When applied to the skin, the nanoemulsion particles rapidly penetrate through pores and hair shafts to the site of an infection.

The NanoStat technology also enables a platform of nanoemulsion-based mucosal vaccines. When either whole virus or a recombinant protein antigen is mixed with the nanoemulsion and placed on the naso-pharynx, the nanoemulsion serves as a potent adjuvant. This results in the production of both mucosal immunity and systemic immune response. Virtually any bacterial or viral disease that results in a human immune response is a potential candidate for the development of a NanoStat mucosal vaccine. For example, NanoBio has shown that a NanoStat-based nasal hepatitis B vaccine elicits a dramatic immune response in animals without requiring three vaccinations, sterile syringes, or refrigeration-three factors that impede the delivery of current hepatitis B vaccines.

Lastly, NanoBioMagnetics (NBMI) is pioneering an emerging area of nanomedicine referred to as Organ Assisting Device (OAD) technologies. The company is developing a process by which magnetically-responsive nanoparticles (MNP) drive a desired physiological event. NBMI's OAD technologies have significant potential for treatment of a range of human health diseases functioning as either vehicles for site-specific drug delivery or as biostable implants for organ movement. NBMI's MNP, superparamagnetic nanoparticles, respond to an applied external magnetic field and return to their normal state when the field is removed. This in effect creates a biomagnetic switch.

The company has also designed magnetic vectoring (EVU) technology for site-specific delivery of drugs based on three-dimensional manipulation of an external magnetic field to drive MNP movement and concentration. When MNP-drug constructs are injected into the gradient of this localized magnetic field that is shaped to focus on the target site, the particles are magnetically drawn to that site. This is followed by cellular internalization of the construct and results in the internal release of the therapeutic agent.

NBMI believes that OAD technologies will lead

to a new class of site-specific delivery vehicles for the treatment of a range of human health disorders, specifically in the delivery of cancer therapeutics. The company is developing two application platforms based on its proprietary nanofabrication technology. The first platform, Biostable Implants™, uses implanted MNP to drive tissue movement or vibration in an oscillating magnetic field. The second platform, Vectored Drug Delivery™, uses an external magnetic field to specifically drive and position MNP-Therapeutic constructs.

Delivery of RNAi and oligonucleotide drugs[*2)]

Delivery of RNAi and oligonucleotide therapeutics to achieve sufficient gene suppression at therapeutic levels is the single most challenging aspect of this new and upcoming area of pharmaceutical technology. The success of RNAi and antisense drugs hinges on successful delivery of the gene silencing molecules. Historically, "drug delivery" has come to mean the route of administration of the drugs into the body, i.e. oral, transdermal, or inhalation. In the case of gene silencing drugs, delivery usually refers to the delivery of the drug into the cell. Except for a few RNAi drugs that are being developed for delivery via inhalation (Alnylam) and oral (Cequent), almost all of the therapies, at least initially, will be delivered *in vivo* parenterally, either as injections or intravenous infusions.

There are many delivery strategies that companies employ to improve the efficiency of transporting siRNA and oligonucleotide therapeutics through the circulation and across the cell membrane. Among these, liposomal encapsulation systems and nanoparticle delivery are two common methods for *in vivo* delivery of RNAi and antisense molecules. In fact, some of the first nanoparticle products used liposomes and their phospholipid bilayer as the delivery mechanism. Although liposomal delivery is technically "nanoparticle delivery", current usage differentiates between the two because liposomes are used for encapsulation of the drug while with other types of nanoparticles ; the drug is adsorbed on the surface. A brief description of some nanoparticle technologies used by companies for *in vivo* delivery RNAi are given below.

Calando's cyclodextrin-containing polymers form the foundation for its three-part RNAi/Oligonucleotide Nanoparticle Delivery (RONDEL™) technology. It has a linear, cyclodextrin-containing polymer that binds to the anionic siRNA backbone. The polymer and siRNA self-assemble into nanoparticles that protect the siRNA from nuclease degradation in the serum. The cyclodextrin in the polymer enables the surface of the particles to be decorated by stabilizing agents and targeting ligands. The siRNA delivery system has been designed for intravenous injection. Upon delivery to the target cell, the targeting ligand binds to membrane receptors on the cell surface and the aiRNA-containing nanoparticle is takenup via endocytosis and the siRNA is released from the delivery vehicle.

MirusBio (now part of Roche) developed the Dynamic PolyConjugates™ (DPC) technology. This proprietary polymer-based formulation chemistry mimics the natural viral targeting and disassembly process and efficiently targets gene silencing complexes to specific cells. Fully assembled DPCs form nanoscale structures of an optimal size for facilitating bioavailability. When injected into the bloodstream, DPCs circulate as a protected complex until they attach to a target cell where they are internalized via receptor-mediated endocytosis. The complex dissociates in the endosome due to the acidity within this compartment and releases the siRNA molecule into the cytoplasm, whereupon it can silence gene activity via the RNAi mechanism. Keys to the success of this formulation are (1) the endosomolytic potency of the polymer, (2) the unique ability of the complex to respond to location-specific environmental cues, and (3) efficient cellular targeting.

RXi Pharmaceuticals has developed novel and proprietary nanotransporters to deliver RNAi compounds to target tissues. A nanotransporter is a chemical that is mixed with an RNAi compound to form minute particles which transport the RNAi compounds to tissues. The nanotransporters are of a defined size (<80 nm complex), are readily formulated and have a core to which layers are added by chemical synthesis. The final layer has positive charges that attract and bind to negatively charged RNAi compounds. The design and effective delivery of synthetic RNAi compounds are important factors for therapeutic applications.

[*2)] Technical Business Review on Gene Silencing Therapeutics (in press)

Intradigm's RNAi Nanoplex™ (NPX) delivery technology is a modular, multi-component delivery vector that carries active siRNA molecules in its core with the flexibility to attach a PEG layer and/or a targeting ligand to a cationic polymer-siRNA core to improve its pharmacological properties. The flexibility allows the company to build a broad range of proprietary RNAi therapeutic candidates, known as RNAi NPXs.

A proprietary RNAi NPX consists of a core component of siRNA sequences that are designed to silence a gene product. These siRNA sequences are complexed through electrostatic bonds with a cationic polymer to form a proprietary RNAi NPX. Intradigm has identified multiple polycationic polymers that are peptide-based, chemically homogeneous, and biodegradable. This proprietary class of polypeptides is called PolyTran™. PolyTran is designed to facilitate cell internalization and endosomal release of its siRNA payload in the cytoplasm. A hydrophilic steric polymer can be added to the RNAi NPX usually in the form of a PEG layer. In addition, a binding ligand can be attached to guide the RNAi NPX to receptors expressed in the specifically targeted disease tissue which enables receptor-mediated uptake by the cells of interest. Targeting ligands are readily interchangeable depending on the disease and siRNA payload.

Conclusions

Though initially commercialized for use in improving solubility by increasing a drug's surface area, nanotechnologies have evolved to tackle a wide variety of drug delivery challenges. We have highlighted a few of the companies and technologies that are showing promise in addressing the problems faced by the pharmaceutical industry. From improving the solubility and bioavailability of drugs to crossing the blood-brain barrier to targeting specific tissues or delivering therapeutics to a cell, nanotechnology is answering challenges that the pharmaceutical industry is facing. Still to come are the combination of nano-devices and therapeutics that will allow for programmed delivery of drugs. The future of nanotechnology in drug delivery is in the ability to manipulate molecules and supramolecular structures to produce devices with programmed functions.