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Lipid-based Advances In Drug Delivery

Thought Leadership In Association With Exelead

by

Safe and efficient delivery is a fundamental challenge for personalized medicine, gene therapy and genetic medicine. Specialized and unique delivery systems are required, depending on the biology and the physiology of the target. Of the many and varied efforts to develop controlled-release, nano-compartmentalized therapeutic agents, Liposomes and Lipid-nanoparticle (LNP) systems are two of the most promising.

The decoding and study of the human genome have enabled incredible advances in understanding genetics and the development of gene-based medicines. Combined with the technological developments that have brought about artificial intelligence and machine learning, scientists have been able to create more targeted and personalized medicines. As a result, the pharmaceutical industry is moving away from the blockbuster model. But with these continuing advances toward more personalized medicine, which allow scientists to target rare diseases and small patient populations, the need for increasingly sophisticated diagnostics and specialized and precise drug delivery has grown.

Safe and efficient delivery is a fundamental challenge for personalized medicine, gene therapy and genetic medicine. Specialized and unique delivery systems are required, depending on the biology and the physiology of the target. Of the many and varied efforts to develop controlled-release, nano-compartmentalized therapeutic agents, Liposomes and Lipid-nanoparticle (LNP) systems are two of the most promising. They are being used within the pharmaceutical industry to deliver drugs including anticancer drugs, gene-based therapies, antibiotics, anesthetics and anti-inflammatories. In particular, LNPs have emerged in recent years as a successful delivery method for gene therapies, offering an alternative to traditional viral vectors. They also have as an advantage a biocompatible lipid matrix, which can encapsulate a variety of molecules. As a consequence, LNP systems are safer vehicles for gene delivery. They have lower rates of adverse immunogenic reactions, are relatively easy to scale up for manufacturing and can be

administered by different routes.

LNPs that are formulated to deliver genes are primarily synthesized using cationic, or positively charged, lipids that associate with anionic, or negatively charged, nucleic acids. Other lipid-based components can be added to modulate the delivery efficiency, pharmacokinetics and biodistribution of the genetic load.

Gene therapy is a rapidly advancing field for the pharmaceutical industry. Such therapies introduce genetic material into target cells with the aim of silencing, enhancing or correcting protein expression. The use of synthetic oligonucleotides in gene therapy is a means of modifying the gene or genes that play a part in a particular disease process. There are various ways of achieving this, some of which include the use of antisense nucleotide sequences specific to the target gene to disrupt gene transcription. Another way is through the use of short segments of RNA, (Small Interfering RNA or siRNA) to instruct the cell to disrupt translation of faulty mRNA and block protein expression. In contrast, mRNA-based therapeutics introduce synthetic mRNA strands that mimic natural mRNA, allowing the translation of therapeutic proteins. Importantly, all of these genetic strategies can be made feasible by formulation of an optimal, LNP-based delivery vehicle.

In their paper on LNP systems for siRNA-based therapeutics, published in 2014 in the journal Drug Delivery and Translational Research, C. Wan, T.M. Allen and P.R. Cullis explain that LNPs containing ionizable cationic lipids have features necessary for the systemic delivery of polynucleic acids, including small sizes, serum stability, low surface zeta potentials at physiological pH and cationic charge at acidic pH values (e.g., in endosomes). They add that “by taking advantage of ‘endogenous’ targeting processes due to association with ApoE following administration, highly efficient uptake into hepatocytes can be achieved following IV administration, leading to excellent gene-silencing capabilities.”

Nucleic acids are hydrophilic, negatively charged macromolecules, and they are easily broken down in biological fluids. This means that if they are administered systemically with no protection or carrier, they do not always facilitate effective results. LNPs can protect nucleic acids from digestion in biological fluids and have been shown to enter cells by endocytosis – a vesicular process by which a cell will engulf foreign matter. While researchers have made attempts to stabilize siRNA in serum by adding phosphonothioate linkages, high doses are required to effectively silence genes in humans. LNPs offer a protective, flexible and easy means of encapsulation. They can protect siRNA segments until they reach their intended location and facilitate their delivery into the target cells.

By their very nature, gene-based therapies are well suited to rare diseases, particularly in oncology. Cancer cells are different from other cells, and these differences are increasingly being understood, along with their relationship to genes, including abnormal or damaged genes. In

addition to successes in some cancer areas, there are now opportunities being investigated in central nervous system (CNS) diseases, in which traversing the blood–brain barrier has been a major challenge. The ability of gene therapies to inhibit disease-causing proteins or enable the expression of missing proteins makes them specifically useful in treating these types of CNS diseases.

Gene therapy success is expanding in rare diseases. The US FDA approved Biogen's Spinraza, an antisense oligonucleotide, in 2016. It is currently the only option of its kind available to spinal muscular atrophy (SMA) but Novartis and Avexis are developing a product with the potential to be a one-time gene replacement therapy in SMA. Moreover, ASOs have successfully reduced toxic protein levels in a Phase II/IIa clinical trial to treat Huntington's disease, according to a Frontiers in Molecular Neuroscience editorial. Finally, the FDA has approved Onpattro (patisiran) – the first ever, gene-silencing RNA interference-based therapeutic in a rare disease - hereditary transthyretin-mediated amyloidosis, mediated via an LNP platform.

Manufacture

Personalized medicines need to be manufactured in small batch sizes for single patients or small populations and the result frequently is less than one liter of product. In contrast, traditional drug manufacturing results in much larger batches, often resulting in the production of thousands of liters of the drug at scale. Personalized medicine requires a unique approach, and each batch must be manufactured under stringent current good manufacturing practice (cGMP) conditions.

The manufacture of such small-batch therapeutics can require expensive active pharmaceutical ingredients (APIs) and a quick turnaround time. Having a single manufacturer to support a product from development to market can be advantageous and more efficient than switching manufacturers based on the expertise required at different stages of the development journey. Working with a single manufacturer can help drug development organizations avoid potential hurdles that can arise in technology transfer and minimize contamination risks to patients due to a lack of sterility from multiple-team involvement at different stages. It can also result in cost savings.

Exelead provides a single manufacturing solution from pre-commercial to commercial manufacturing. As a contract development and manufacturing organization (CDMO), Exelead has the experience and expertise to support Phase I and earlier development through commercial material and can offer services to reduce clinical development time. Importantly, when it comes to liposomal or LNP formulations, the company has been manufacturing lipid-based medicines since the 1990s. Exelead has wide experience and understands the importance of establishing a clear and detailed development program to make a product ready for GMP manufacturing, along with ensuring safety and sterility and managing endotoxin testing. Additionally, the Exelead

team manages the scalability of processes – the end goal being to rapidly and efficiently manufacture a commercial product while still meeting stringent quality control standards throughout the process.

Exelead works with partners on drug products that are being used in clinical trials, as well as commercial products. For some products and projects, Exelead guides the manufacturing process all the way through from discovery to commercialization.

Abelcet

One of Exelead's earliest commercial products was Leadiant's Abelcet, an amphotericin B lipid complex injection that is used primarily in a hospital setting to treat a range of serious fungal infections, particularly in patients who cannot tolerate or respond to regular amphotericin treatment or other medication. The product is often the last resort and a life-saving drug for a small patient population. Exelead has been manufacturing this drug product for nearly 20 years at their Indianapolis location.

Abelcet is formulated as a large microparticle with the critical API – Amphotericin-B – held within a multicomponent lipid complex. This formulation allows for selective interaction with fungal sterols, eventually lysing the disease microorganisms.

Years of experience in manufacturing this product have built understanding and expertise, particularly in terms of meeting and comprehending susceptibility test interpretive criteria, associated test methods and quality control standards laid down by the FDA. Exelead produces Abelcet as a sterile, opaque suspension in 20-mL glass, single-use vials, each of which contains 100 mg of amphotericin B in a 20-mL suspension.

The product requires an *eight-day* formulation process, which brings challenges in terms of maintaining sterility and consistency in every batch. Many pharmaceutical drug products can be formulated in as few as 12 hours, meaning they are at much lower risk for contamination. Processing Abelcet through its complex, sterile bulk formulation, and then delivering it into vials is the kind of exacting task that Exelead works to tackle.

Gianfranco Fornasini, senior vice president of scientific affairs at Leadiant, confirmed this, explaining: "The complexity of the molecules they handle is very high. The way they handle this liposomal formulation is with additional care. To avoid contamination, they must be experts in sterile processes, monitoring and controlling for undesirable variables."

LNPs An Indispensable Asset

It is now recognized that R&D surrounding the use of liposomes as therapeutic carriers has

advanced considerably. Liposomes protect therapeutics from external degradation, “and their similarity to biological membranes provides unique opportunities to deliver drug molecules into cells or subcellular compartments … In addition, various physicochemical properties of liposomes – including their size, charge, and surface functional ligands – can be altered, resulting in functionalities favoring specific drug delivery tasks,” note researchers W. Gao, C.-M.J. Hu, R.H. Fang and L. Zhang in their paper on Liposome-like nanostructures for drug delivery published in 2013 in the Journal of Materials Chemistry B, Materials for Biology and Medicine. These findings have resulted in liposomes and LNPs becoming a leading drug delivery platform that offers a variety of clinical applications.

Although personalized medicine has the potential to treat almost any disease, current R&D is focused mainly on immunotherapies, conventional therapies that are enhanced through the application of pharmacogenomics and biomarker-related cancer treatments. Liposomes and LNPs have application as delivery vehicles for each of these categories of drug products, making them an indispensable asset in this new field of pharmaceutical development. Furthermore, they have the potential to move into additional fields as the scientific understanding of rare diseases and application of personalized medicine grows.

Exelead is the kind of contract manufacturing partner that can rise to meet these challenges with considerable experience in this increasingly complex drug delivery environment. For more information go to www.exeleadbiopharma.com.