

The Vehicle of Success – An Adaptive Approach to Genetic Medicines



Maintaining Quality in the Delivery of Genetic Medicines

Introduction

The ability to deliver genetic materials such as DNA and RNA into a cell for a therapeutic purpose has opened up new opportunities for treating numerous diseases. Coined as genetic medicines, these emerging technologies have shown great potential for treating various types of cancer, rare and infectious diseases, as well as enhancing the possibility of personalized medicine.

“The broadest application of genetic medicines is in gene therapy, where you introduce genetic material into a cell to either produce a protein or transform the cell at the genetic level,” explained Dr. Mansoor Amiji, University Distinguished Professor, Professor of Pharmaceutical Sciences and Professor of Chemical Engineering at Northeastern University, adding that this is an area that his lab is currently working in.



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There are various approaches to gene therapy, including inactivating a malfunctioning mutated gene, replacing a disease-causing mutated gene with a healthy copy, or introducing a new gene to help fight a disease. “There are numerous mechanisms of gene therapy, including gene silencing with RNA interference, mRNA-based therapies that lead to increased protein expression, and CRISPR-Cas9 gene editing tools which can correct for mutations that may be causing a disease,” said Dr. Amiji.

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Ensuring that the selected nucleic acid molecules are successfully delivered to cells requires a carrier vehicle known as a vector, which is engineered to deliver the genetic material of choice to the target cell either outside or inside the body. Currently, there are two main types of vectors used for gene therapy: viral and non-viral vectors. “Viral vectors use inactivated or transformed viruses as the delivery vehicle,” explained Dr. Amiji. “The viral genome is removed or changed and the specific genetic sequences that are going to provide the therapeutic effect are inserted.” There are several types of viral vector being used in gene therapy research, but the adeno-associated virus (AAV) is one of the most actively investigated gene therapy vehicles to date. In contrast, non-viral vectors use synthetic materials to develop the delivery system, such as lipid nanoparticles, polymers, or hybrid structures. The optimal vector or delivery system depends on the target cell and its characteristics, the duration of expression, safety especially if repeated administration are needed, and the size of the genetic material to be incorporated in the vector.

Satisfying Quality Standards

As the field of gene therapy continues to evolve, regulatory agencies across the globe have been working hard to keep pace with the research. “When it comes to regulation in the context of approval of any therapeutic product, the most important criteria for the regulators is the notion that these products are safe and effective,” noted Dr. Amiji. “With genetic medicines you are potentially transforming the cell in order to create a therapeutic benefit, so additional regulatory frameworks need to be established.”

The regulatory agencies are in frequent contact with manufactures of genetic medicines as there is no specific or prescribed guidance for these products. “There is constant evolution of the science in this area and so the agencies have to adapt in real time,” said Dr. Amiji. “This happened in the context of the mRNA COVID-19 vaccines developed by Moderna and Pfizer/BioNTech in the US, where the FDA was in constant dialogue with the companies to provide guidance on what types of studies had to be conducted, what quality requirements had to be in place, and how those quality and regulatory standards had to be satisfied.”

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Defining critical quality attributes (CQAs) for genetic medicines is key to developing a suitable manufacturing process, as well as establishing controls for assuring product quality and consistency. However, the complexity of these products means there is no one-size-fits-all approach – each product has a certain level of distinctive quality attributes that need to be considered. Quality by design (QbD) principles are also unique to each product; but some principles, especially those relating to manufacturing, can be translated from prior learnings. “Genetic medicines and complex pharmaceuticals are considered as biologicals and so there is a lot of common guidance in terms of QbD,” explained Dr. Amiji. “These principles can often be translated to help develop and implement quality processes. For example, in viral vector development, the process of culturing, harvesting, and purifying the viruses can all be optimized for quality.”

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Taking a Vigilant Approach

Due to the stringent regulatory oversight of genetic medicines, Dr. Amiji believes there are few concerns relating to the safety of these products. “Each has its own quality requirement and the regulatory agencies are careful to ensure that safety is paramount.” That said, he admits that for the lay audience, the prospect of changing the genetic makeup of the cell may be a bit frightening. This is particularly the case for CRISPR-based gene editing, where ethical concerns have been raised in the context of editing the embryo. “There was a case in China where a scientist tried to edit the embryo to remove potential receptors involved in HIV transmission to see if the children would be free of HIV infection,” said Dr. Amiji. “This is clearly unethical, and the regulators are trying to prevent these kinds of experiments. It is one of those interesting phenomena where sometimes the regulators are behind the scientists when it comes to advances, especially because these advances are happening at such a rapid pace. Genetic medicines raise some interesting questions and so the regulatory agencies must remain vigilant to ensure that companies are able to conduct studies to answer those questions.”

Reflecting on what we have learnt from the COVID-19 pandemic, it is evident that there will be exciting developments in the field of genetic medicines to come. “I think the next series of vaccines will have a very different regulatory framework than some of the

early trailblazers,” said Dr. Amiji. “The FDA scientists have now reviewed the data and as more products are developed, regulatory agencies will continue to adapt their requirements. Although it was almost a crash course for everyone involved, it has yielded some great lessons that we can carry forth.”

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Dr. Amiji’s lab has been working on genetic medicine delivery systems based on non-viral vectors for the past 18 years. “We think that non-viral vectors will provide a much safer alternative to some of the viral vectors, but in many instances non-viral vectors tend to be less efficient in transfection,” he concluded. “Non-viral vectors tend to have a much better safety profile and are more visible in terms of scale up and GMP manufacturing. We are very bullish about this and hope to see more of these products coming to the clinic in the future.”

About the Author

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Dr. Amiji received his undergraduate degree in pharmacy from Northeastern University in 1988 and his PhD in pharmaceuticals from Purdue University in 1992. Over the years, his research has received over \$40m in sustained extramural funding from the National Institutes of Health (NIH), National Science Foundation (NSF), foundations, and biotech/pharma industries.

Dr. Amiji has supervised research efforts of over 120 post-doctoral associates and graduate students. He has also edited 10 books, along with over 70 published book chapters and over 360 peer-reviewed articles.

Dr. Amiji has received several awards including the 2006 NSTI Award for Outstanding Contributions towards the Advancement of Nanotechnology, Microtechnology, and Biotechnology, and the 2007 American Association of Pharmaceutical Scientist’s (AAPS) Meritorious Manuscript Award. He is a Fellow of both AAPS and the Controlled Release Society. He has also received the Distinguished Alumni Awards from both Northeastern University School of Pharmacy and Purdue University College of Pharmacy.

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