IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.301
Volume 3, Issue 3, December 2023

Review on Genetic Level Therapy for Neonatal Problem

Sahil V. Nandurkar[1], Farah Khan[2], Sushmita W. Gajbe[3], Sakshi P. Bawankule[4]
Students, B Pharmacy, New Montfort Institute of Pharmacy, Ashti, Wardha[1,3,4]
Asst. Prof. New Montfort Institute of Pharmacy, Ashti, Wardha[2]
sahilnandurkar184@gmail.com

Abstract: *This review paper explores novel techniques to treat genetic illnesses, congenital malformations, and other conditions affecting neonates, and it explores the potential field of genetic-level therapy for tackling neonatal difficulties. Gene therapy is a potent tool for addressing genetic disorders at their source since it makes use of cutting-edge methods like genome editing and CRISPR/Cas9. In addition, the use of RNA therapies, such as antisense oligonucleotides and mRNA, offers a flexible way to implement targeted interventions. One promising area for controlling gene expression and treating newborn illnesses is epigenetic alterations. This work highlights the results, difficulties faced, and lessons discovered from using genetic-level medicines in neonatal care through a review of successful case studies.*

Keywords: Newborn, Genetic Therapy, Neonatal, Treatment, gene.

I. INTRODUCTION

The fundamental structural and functional unit of heredity is a gene. DNA is what makes up genes. Certain genes function as instructions for the synthesis of proteins. Many genes, meanwhile, do not code for proteins. Genes in humans can range in size from a few hundred to over two million bases of DNA. Humans are thought to have between 20,000 and 25,000 genes, according to an international scientific project known as the Human Genome Project, which sought to discover the genes that make up the human genome and determine its sequence.

Each gene is inherited in two copies by each individual, one from each parent. The majority of genes are identical in all individuals, although a tiny percentage of genes—less than 1%—have minor variations.[1]

Gene therapy is a technique that uses a gene(s) to treat, prevent or cure a disease or medical disorder. Often, gene treatment works by adding new copies of a gene that is broken, or by replacing a defective or missing gene in a patient's cells with a healthy version of that gene. Both inherited genetic diseases (e.g., hemophilia and sickle cell disease) and acquired disorders (e.g., leukemia) have been treated with gene therapy.[2]

Treating genetic disorders and other illnesses directly is possible with gene therapy. Other comparable strategies exist as well, such as gene editing. Gene editing and gene therapy come in a wide variety of forms and methods. It all comes down to comprehending how genes

function and how variations in genes can impact our well-being. Many aspects of gene therapy and gene editing are being studied by researchers worldwide.[3]

Problems in infants might occur

- Before birth while the fetus is growing
- During labor and delivery
- After birth

9% of newborns require special care following delivery because of preterm, issues adjusting to life as a baby, low blood sugar, breathing difficulties, infections, or other anomalies. A neonatal intensive care unit (NICU) is frequently the setting for specialised care.[4]

Genetic-level therapy resolves congenital defects, genetic abnormalities, and other issues in neonates by using molecular and genetic therapies.[5] If gene therapy is applied to treat viral and hereditary illnesses in neonates, there may be a number of benefits. Gene therapy may be more effective in newborns than in older children or adults due to the

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.301
Volume 3, Issue 3, December 2023

limited negative impact of the underlying disease on the newborn's cells, the infants' small size, and the significant amount of future growth.[6]

Here are some key aspects of genetic-level therapy for neonatal issues:

Gene Therapy

Gene therapy is a technique that modifies a person's genes to treat or cure disease. Gene therapies can work by several mechanisms:

- Replacing a disease-causing gene with a healthy copy of the gene
- Inactivating a disease-causing gene that is not functioning properly
- Introducing a new or modified gene into the body to help treat a disease

Gene therapy products are being studied to treat diseases including cancer, genetic diseases, and infectious diseases.

There are a variety of types of gene therapy products, including:

- Plasmid DNA
- Viral vectors Bacterial vectors
- Human gene editing technology
- Patient-derived cellular gene therapy products

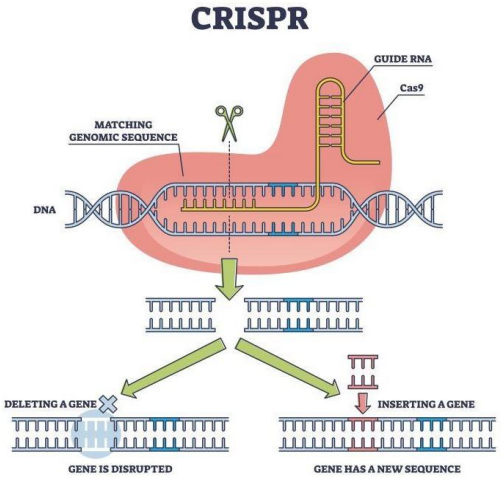
Gene therapy products are biological products regulated by the FDA's Centre for Biologics Evaluation and Research (CBER). Clinical studies in humans require the submission of an investigational new drug application (IND) prior to initiating clinical studies in the United States. Marketing a gene therapy product requires submission and approval of a biologics license application (BLA).[7]

In neonatal care, gene therapy aims to correct or mitigate genetic abnormalities responsible for various disorders.

CRISPR/Cas9 and Genome Editing

Genome editing (also called gene editing) is a group of technologies that give scientists the ability to change an organism's DNA. These technologies allow genetic material to be added, removed, or altered at particular locations in the genome. Several approaches to genome editing have been developed. A well-known one is called CRISPR-Cas9, which is short for clustered regularly interspaced short palindromic repeats and CRISPR-associated protein 9. The CRISPR-Cas9 system has generated a lot of excitement in the scientific community because it is faster, cheaper, more accurate, and more efficient than other genome editing methods.

CRISPR-Cas9 was adapted from a naturally occurring genome editing system that bacteria use as an immune defense. When infected with viruses, bacteria capture small pieces of the viruses' DNA and insert them into their own DNA in a particular pattern to create segments known as CRISPR arrays.



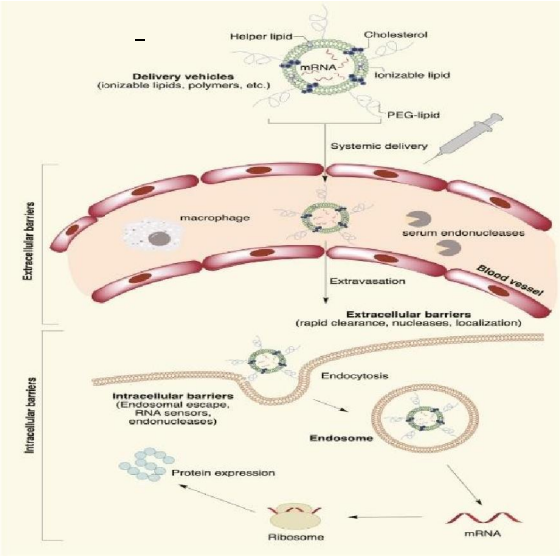
IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.301
Volume 3, Issue 3, December 2023

CRISPR -a gene editing tool

Researchers explore the use of CRISPR/Cas9 for correcting genetic mutations responsible for neonatal disorders, offering a potential cure at the genetic level.[8]

RNA Therapeutics

mRNA gene therapy has recently emerged as a candidate to enable multiple therapeutic applications including protein replacement therapy, vaccine immunology, and regenerative medicine. Messenger_RNA (mRNA) is a very promising gene therapy modality to enable several of these applications, especially in infectious disease, oncology, and protein replacement . This form of nucleic acid possesses some key advantages. Utilizing messenger RNA (mRNA) to deliver genetic instructions, mRNA therapies hold promise in correcting genetic defects.[9]



Schematic Representation of Extra- and Intracellular Barriers for mRNA Delivery

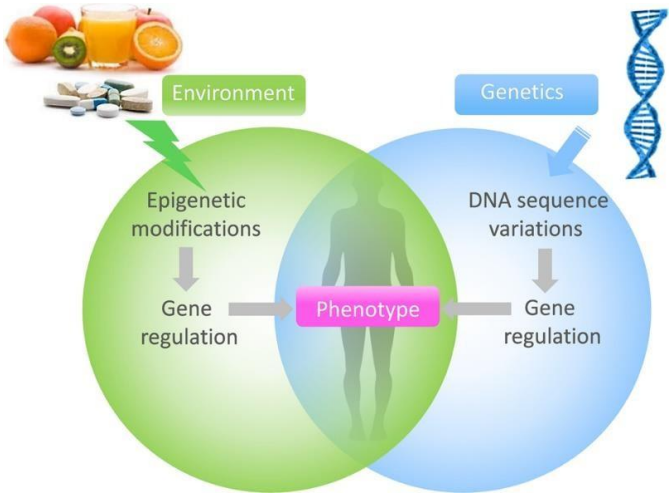
Among the many barriers to function, mRNA must cross the cell membrane in order to reach the cytoplasm . The cell membrane is a dynamic and formidable barrier to intracellular delivery. It is made up primarily of a lipid bilayer of zwitterionic and negatively charged phospholipids, where the polar heads of the phospholipids point toward the aqueous environment and the hydrophobic tails form a hydrophobic core.[10] Various ion pumps and ion channels help maintain a negative potential (–40 to –80 mV) across the cell membrane, and they keep the cytoplasmic space negatively charged by controlling the balance of most of the essential metal ions (e.g., K^+, Na^+, Ca^{2+}, and Mg^{2+}).[11] The negative potential across the cell membrane creates a formidable barrier for highly negatively charged mRNA molecules. Unsaturated lipids, especially the *cis*-double-bonded ones, increase cell membrane fluidity by introducing defects in the membrane structure.

Epigenetic Modifications

The term, “epigenetics,” was first used to refer to the complex interactions between the genome and the environment that are involved in development and differentiation in higher organisms. Today, this term is used to refer to heritable alterations that are not due to changes in DNA sequence. Rather, epigenetic modifications, or “tags,” such as DNA methylation and histone modification, alter DNA accessibility and chromatin structure, thereby regulating patterns of gene expression. These processes are crucial to normal development and differentiation of distinct cell lineages in the adult organism. They can be modified by exogenous influences, and, as such, can contribute to or be the result of environmental alterations of phenotype or pathophenotype. Importantly, epigenetic programming has a crucial role in the regulation of pluripotency genes, which become inactivated during differentiation. [12]

Researchers explore the modulation of epigenetic factors to regulate gene expression and potentially correct or manage neonatal disorders

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.301
Volume 3, Issue 3, December 2023



Epigenetic Modification

Current Challenges and Future Directions:

In recent years, gene therapy has been raising hopes toward viable treatment strategies for rare genetic diseases for which there has been almost exclusively supportive treatment.[13]

Gene therapy for neonatal applications faced several challenges, and researchers were actively working on addressing these obstacles. It's important to note that developments in the field may have occurred since then. Here are some common challenges and potential future directions in gene therapy for neonates:

Current Challenges[14]:

Delivery Challenges:

- *Neonatal Tissues:* Ensuring efficient and targeted delivery of therapeutic genes to specific neonatal tissues poses a challenge due to the unique physiological characteristics of newborns.

Safety Concerns:

- *Off-Target Effects:* Minimizing off-target effects and unintended genetic modifications is crucial to ensure the safety of gene therapy interventions in neonates.
- *Immune Responses:* Addressing immune responses to viral vectors or gene- editing tools used in gene therapy, especially in the developing neonatal immune system.

Ethical Considerations:

- *Informed Consent:* Developing appropriate protocols for obtaining informed consent from parents or guardians for genetic interventions in newborns.
- *Long-Term Implications:* Anticipating and addressing potential long-term ethical implications associated with altering a neonate's genetic makeup.

Specificity and Precision:

- *Precision Targeting:* Achieving greater specificity and precision in targeting the causative genetic mutations while minimizing impact on non-diseased genes.

Genetic Heterogeneity:

- *Genetic Variability:* Accounting for the genetic heterogeneity in neonatal populations, as different genetic mutations may lead to similar clinical conditions.

Regulatory Pathways:

- *Regulatory Approval:* Navigating regulatory pathways for the approval of gene therapies in neonates, which may involve unique considerations compared to therapies for adults.

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.301
Volume 3, Issue 3, December 2023

Future Directions:

Advancements in Delivery Systems:

- Developing innovative delivery systems, such as nanoparticles or non-viral vectors, to improve the efficiency and specificity of gene delivery to neonatal tissues.

Technological Innovations:

- Harnessing advancements in gene-editing technologies beyond CRISPR/Cas9, exploring newer tools with enhanced precision and reduced off-target effects.

Integration of Omics Technologies:

- Utilizing omics technologies, such as genomics, transcriptomics, and proteomics, to better understand individual genetic profiles and optimize personalized gene therapy approaches.

Early Diagnosis and Intervention:

- Emphasizing the importance of early diagnosis through advanced genetic screening methods, enabling timely and targeted interventions in neonates.

Collaborative Research Efforts:

- Encouraging collaboration among researchers, clinicians, and regulatory bodies to facilitate the translation of promising gene therapy strategies from the lab to clinical applications.

Patient and Public Engagement:

- Promoting awareness and engagement of parents, families, and the public in discussions about the ethical and social aspects of gene therapy for neonates.

II. CONCLUSION

In conclusion, gene therapy for neonatal applications holds significant promise in addressing a spectrum of genetic disorders and congenital anomalies at their root causes. While advancements in this field have been remarkable, several challenges persist, necessitating ongoing research and innovation. Delivery hurdles, safety concerns, and ethical considerations underscore the need for careful consideration and refinement of gene therapy approaches tailored to the unique characteristics of neonates.

REFERENCES

[1]. https://medlineplus.gov/genetics/understanding/basics/gene/
[2]. https://www.genome.gov/genetics-glossary/GeneTherapy#:~:text=Gene%20therapy%20is%20a%20technique,healthy%20version%20of
[3]. %20that%20g ene
[4]. https://en.wikipedia.org/wiki/Gene_therapy#:~:text=Gene%20therapy%20may%20be%20classified,gametocyte %2 C%20or%20undifferentiated%20stem%20cell.
[5]. https://www.msdmanuals.com/en-in/home/children-s-health-issues/general-problems-in- newborns/overview-of-general-problems-in-newborns
[6]. https://chat.openai.com/c/89110ec0-3c45-4b14-beb7-484b4aaecd1a
[7]. https://pubmed.ncbi.nlm.nih.gov/9240965/#:~:text=Because%20of%20the%20minimal%2 0adverse,in%20older%20children%20or%20adults.
[8]. https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/what-gene- therapy
[9]. https://medlineplus.gov/genetics/understanding/genomicresearch/genomeediting/
[10]. Randall A. Meyer a , Sarah Y. Neshat ''Materials Today Advances''R.A. Meyer, S.Y. Neshat, J.J. Green et al. 29 March 2022
[11]. Harayama T., Riezman H. Understanding the diversity of membrane lipid composition. *Nat. Rev. Mol. Cell Biol.* 2018;**19**:281–296.
[12]. Honig B.H., Hubbell W.L., Flewelling R.F. Electrostatic interactions in membranes and proteins. *Annu. Rev. Biophys. Biophys. Chem.* 1986;**15**:163–193.

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.301
Volume 3, Issue 3, December 2023

[13]. Handy DE, Castro R, Loscalzo J. Epigenetic modifications: basic mechanisms and role in cardiovascular disease. Circulation. 2011 May 17;123(19):2145-56.
[14]. https://www.frontiersin.org/articles/10.3389/fnmol.2021.695937/full
[15]. https://chat.openai.com/c/89110ec0-3c45-4b14-beb7-484b4aaecd1a