International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 1766-1773 www.ijprajournal.com ISSN: 2456-4494

Genetic Level disorders in Neonants

Ms. Tanvi U. Rathod and Ms. Ambika Nagarbhadiya
[1]B.Pharma student Ishwar Deshmukh Institute of Pharmacy, Digras,Maharashtra, India.
[2]Professor, Department of Pharmacology, IshwarDeshmukh Institute of Pharmacy, Digras, Maharashtra, India.

Submitted: 05-06-2022 Revised: 18-06-2022 Accepted: 20-06-2022

ABSTRACT: Neonatology is one of the areas of greatest development and evolution within paediatrics. The neonatal deaths are unequally distributed worldwide with 99% occurring in low and middle-income countries. The gene therapy is a promising alternate approach for treating a variety of genetic disorders. By the time patient reaches adulthood however, it is often too late for effective treatment. If both mother and father carry the trait for a genetically determined abnormality on disease, the baby has at least one in four chance of inheriting that condition.

Genetic tests can be done before and during pregnancy to determine if the mother and father carry traits for these diseases. At birth, newborn screening tests are important to the diagnosis of many of these disorders.

KEYWORDS: Neonate, congenital hypothyroidism and congenital hearing loss, blood disorders

I. INTRODUCTION

Neonate: A newborn child or an infant less than four weeks old. The newborn or neonate refers to an infant in the first 28 days after birth. After a month, a baby is no longer considered as neonate. The word neonate is derived from Latin word Neonatus..

Neonatology is a subspecialty of paediatrics that consists of the medical care of newborn infants, especially the ill or premature newborn. Though high infant mortality rates were recognized by the medical community at least as early as the 1865s advances in modern neonatal intensive care have lead to significant decline in infant mortality in the modern era.The vast majority of newborn deaths take place in developing countries where access to health care is low.

Genetic therapy: The introduction of normal genes into cells in place of missing or defective genes in order to correct genetic disorders. Gene therapy involves altering the genes inside your body's cells in an effort to treat or stop disease. The gene therapy replaces a faulty gene or adds a new gene in an attempt to cure disease or improve your body's ability to fight disease. Currently in the United States gene therapy is available only as a part of a clinical trial. Researchers are investigating several ways to do this, including:-

(1) Replacing mutated genes
(2) Fixing mutated genes
(3) Making diseased cells more evident to immune system.

Because of blood brain barrier is developmentally immature during the perinatal period. AAV-mediated neonatal gene therapy is a highly promising strategy for treating genetic neurological disease. Genetic therapy is a promising strategy for treating genetic neurological disease. Genetic therapy is a promising alternate approach for treating a variety of genetic disorders. By the time, the patient reaches adulthood, however it is often too late for effective treatment. But in several of these cases, neonatal gene therapy appears potentially useful against inherited disorders that are not obviously treatable through any other methods.

There are two different types of gene therapy depending on which type of cells are treated:-

A)Somatic gene therapy:-

-This is a transfer of a section of DNA to any cell of the body that doesn't produce sperm or eggs. Effects of gene therapy will not be passed on to the patient's children.

B)Germline gene therapy:-

-The transfer of a section of DNA to cells that produces eggs or sperm, effects of gene therapy will be passed onto the patient's children and subsequent generations.

Genetic disorders can range from a defect in a single base mutation in the DNA of one gene to chromosomal abnormalities that involves deletion or addition of entire chromosomes or set of chromosomes. Genetic disorder can be inherited, or passed from parent to offspring, or acquired due to changes in a individuals DNA that occurs during their lifetime. This short article is designed to give the reader a list of groups of diseases that shares

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 1766-1773 www.ijprajournal.com ISSN: 2456-4494

genetic problems that are similar in cause. The list have examples of genetic diseases types and are not all inclusive.

List of example of chromosome abnormalities genetic diseases:

Chromosome abnormalities usually result from a problem with cell division and arise because of duplication or absence of entire chromosome or pieces of chromosome.Examples of chromosome abnormalities disorders include:-

(1) Downs syndrome
(2) Cri-du-chat syndrome
(3) Patau syndrome (Trisomy 13)
(4) Edwards syndrome (Trisomy 18)

List of examples of Mitochondrial Genetic Inheritance Disorders:-

- Disorders are caused by the mutation in the DNA of mitochondria, small particle within cells. This DNA is unique in that it is not located on the chromosome in the cell nucleus. Mitochondrial DNA is always inherited from the female parent since egg cells (unlike sperm cells) keep their Mitochondrial DNA during the process of fertilization. Examples of Mitochondrial Genetic Inheritance disorder include:-

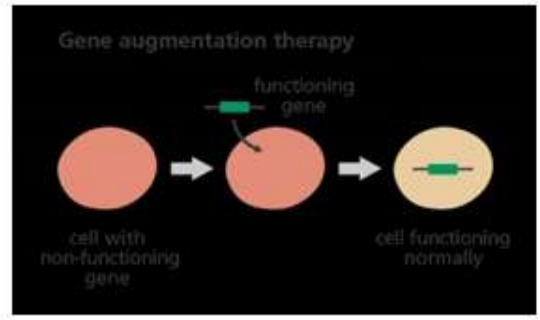
(1) Hereditary optic atrophy
(2) Birth syndrome
(3) Myoclonic epilepsy with ragged red fibres (MERRF)
(4) MELAS syndrome
(5) Neuropathy syndrome, ataxia retinitis pigmentose (NARP)
(6) Leigh's disease

-There are several techniques for carrying out gene therapy. This include:-

1] Gene Augmentation therapy
2] Gene Inhibition therapy
3] Killing of Special cells

1]Gene Augmentation therapy:

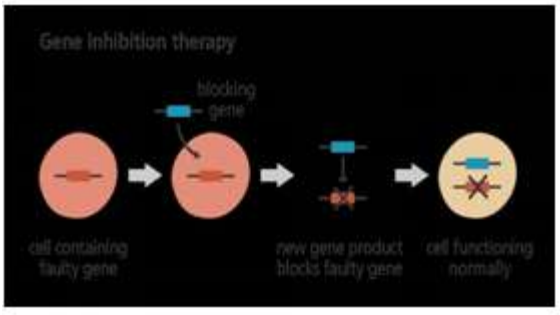
- This is used to treat diseases caused by mutation that stops a gene from producing a functional product, such as protein.
-This therapy adds DNA containing a functional version of the lost gene back into the cell.
-The new gene produces functioning product at sufficient levels to replace the protein that was originally missing.



-This is only successful if the effects of the disease are reversible or have not resulted in lasting damage to the body.
-For example, this can be used to treat loss of function disorders such as cystic fibrosis by introducing a functional copy of the gene to correct the disease.(See illustration in above image).

2]Gene Inhibition therapy:

-Suitable for the treatment of infectious diseases, cancer and inherited diseases cause by in appropriate gene activity.
-The aim is to introduce a gene whose product either
a) Inhibits the expression of another gene
b) Interferes with the activity of the product of another gene.
-The basis of this therapy is to eliminate the activity of a gene that encourages the growth of the disease-related cells.
-For example, cancer is sometimes the result of the over-activation of an oncogene(gene which stimulates cell growth). So, by eliminating the activity of that oncogene through gene inhibition therapy, it is possible to prevent further cell growth and stop the cancer in its tracts.



3] Killing of Specific cells:

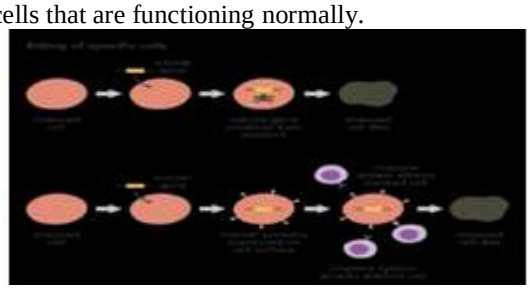
-Suitable for diseases such as cancer that can be treated by destroying certain groups of cells.
-The aim is to insert DNA into diseased cell that causes that cell to die:-

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 1766-1773 www.ijprajournal.com ISSN: 2456-4494

a) The inserted DNA contains a "suicide" gene that produces a highly toxic product which kills the diseased cell.

b) The inserted DNA causes expression of a protein that marks the cells so that the diseased cells are attacked by the body's nature immune system.

-It is essential with this method that the inserted DNA is targeted appropriately to avoid the death of cells that are functioning normally.



-Current approaches of gene therapy of monogenetic diseases into mature organisms are confronted with several problems including the following:

1]The underlying genetic defect may have already caused irreversible genetic defect may have already caused irreversible pathological changes.

2] The level of sufficient protein expression to ameliorate or prevent the disease requires prohibitively large amounts of gene delivery vector.

3] Adult tissues may be poorly infected by conventional vector systems dependent upon cellular proliferation for optimal infection, for example, oncoretrovirus vectors.

4] Immune responses, either pre-existing or developing following vector delivery, may rapidly eliminate transgenic protein expression and prevent future effective intervention.

• Prevention is better than cure:

-Many genetic mutations probably result in such profoundly adverse consequences that a viable embryo or foetus never develops. However, a minority of mutations have sufficiently little impact during gestation, while the foetus remains on the maternal life support machine, such that only after birth do the devastating consequences arise.

-An example of this is with some inborn errors of metabolism. Infants with urea cycle enzyme defects, such as ornithine transcarbamoylase deficiency, may rapidly develop acute metabolic crisis characterised by hyperammonemia, coma, brain damage and death after birth and separation from placental circulation.

-Postnatal screening of phenylketonuria PKU can avoid severe brain damage due to metabolic intoxication but only at the price of, preferably lifelong, adherence to an unpalatable protein hydrolysate diet and foetal damage will occur if the diet is not strictly observed during pregnancy of PKU affected women (foetal PKU).

- Haemophilic neonates not infrequently suffer bleeding intracranial haemorrhage or bleeding beneath the scalp, at the site of venepuncture, at the umbelical stump or after circumcision. Although unchecked bleeding into the joints of neonates is uncommon, as the infant begins to crawl, unchecked haemarthrosis causes substantial and irreversible local damage.

- Therefore, a strong case for early prophylactic replacement of clotting factors, in the most severely affected, has been made. Even small increases in clotting factor concentrations lead to a profound amelioration in the bleeding tendency.

• Gene Therapy in Cystic Fibrosis:

-Theoretically, cystic fibrosis transmembrane conductance regulator (CFTR) gene replacement during the neonatal period can decrease morbidity and mortality from cystic fibrosis (CF). In vivo gene transfers have been accomplished in CF patients.

- Choice of vector, mode of delivery to airways, translocation of genetic information, and sufficient expression level of the normalised CFTR gene are issues that currently are being addressed in the field.

-The advantages and limitations of viral vector are a function of the parent virus. Viral vectors used in this setting include adeno virus (Ad) and adeno associated virus (AAV).

- Initial studies with Ad vectors resulted in a vector that was efficient for gene transfer with dose limiting inflammatory effects due to the large amount of viral protein delivered.

-The next generation of Ad vectors, with more viral coding sequence deletions , has a longer duration of

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 1766-1773 www.ijprajournal.com ISSN: 2456-4494

activity and elicits a lesser degree of cell-mediated immunity in mice.

- A more recent generation of Ad vectors has no viral genes remaining. Despite these changes, the problem of humoral immunity remains with Ad vectors.

-A variety of strategies such a vector systems requiring single, or widely spaced, administration's pharmacologic immunosuppression at administration, creation of stealth vector, modification of immunogenic epitopes, or tolerance induction are being considered to circumvent humoral immunity.

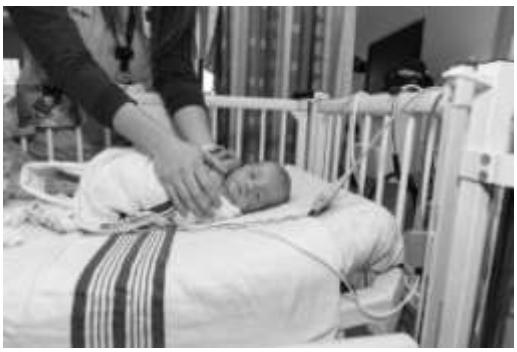
-AAV vectors have been studied in animal and human models. They do not appear to induce inflammatory changes over a wide range of doses. The level of (CFTR) messenger RNA expression is difficult to ascertain with AAV vectors since the small size of the vector relative to the CFTR gene levels no space for vector-specific sequences on which to base assays to distinguish endogenous from vector-expressed messenger RNA.

-In general, AAV vectors appear to be safe and havesuperior duration profiles. Cationic liposomes are lipid-DNA complexes. This vectors generally have been less efficient than viral vectors but do not stimulate inflammatory and immunologic responses. Mi

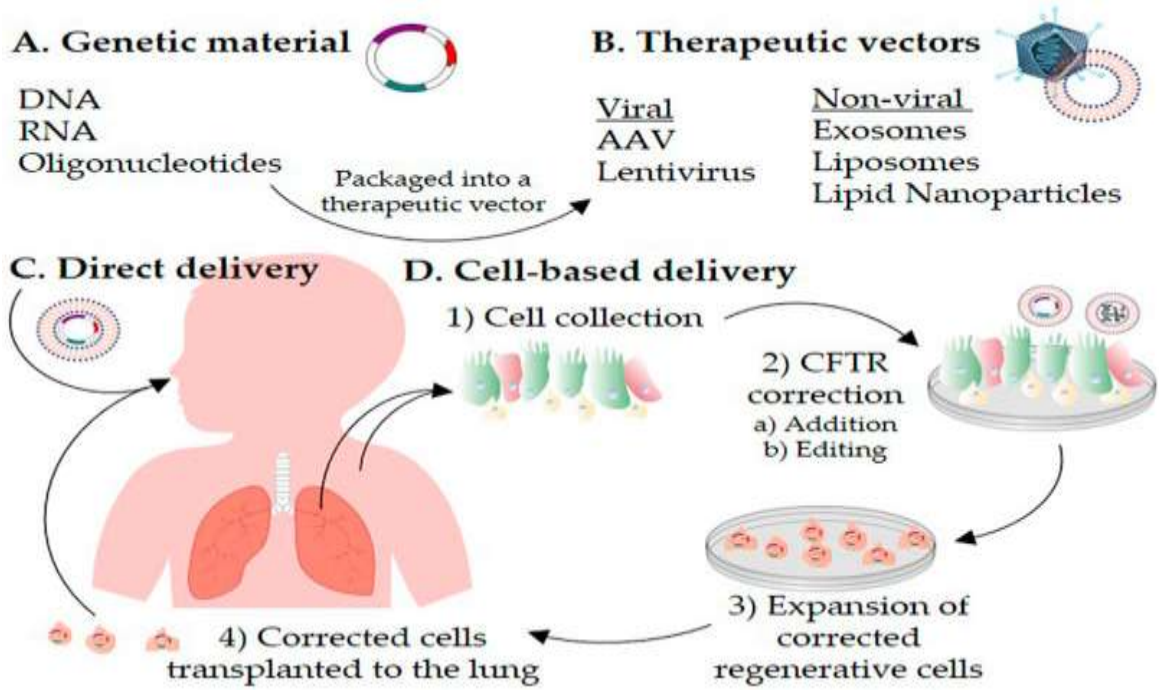
-Another challenge to the development of clinically feasible gene therapy is delivery mode. Early pulmonary delivery systems relied on the direct instillation of aerosolized vectors, which can result in the induction of adverse reactions because vector is delivered into the lung parenchyma.

-More recent studies has examined the potential for using spray technologies to target aerosolised AAV vectors to the larger central airways, thereby avoiding alveolar exposure and adverse effects. Comparisons of long deposition with nebulized delivery of aerosol and spray delivery indicate that spraying result in a more localised deposition pattern (predominantly in proximal airways) and significantly higher deposition fractions that nebulization.

- These findings could lead to more efficient and targeted lung delivery of aerosolized gene vectors in the future.



International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 1766-1773 www.ijprajournal.com ISSN: 2456-4494

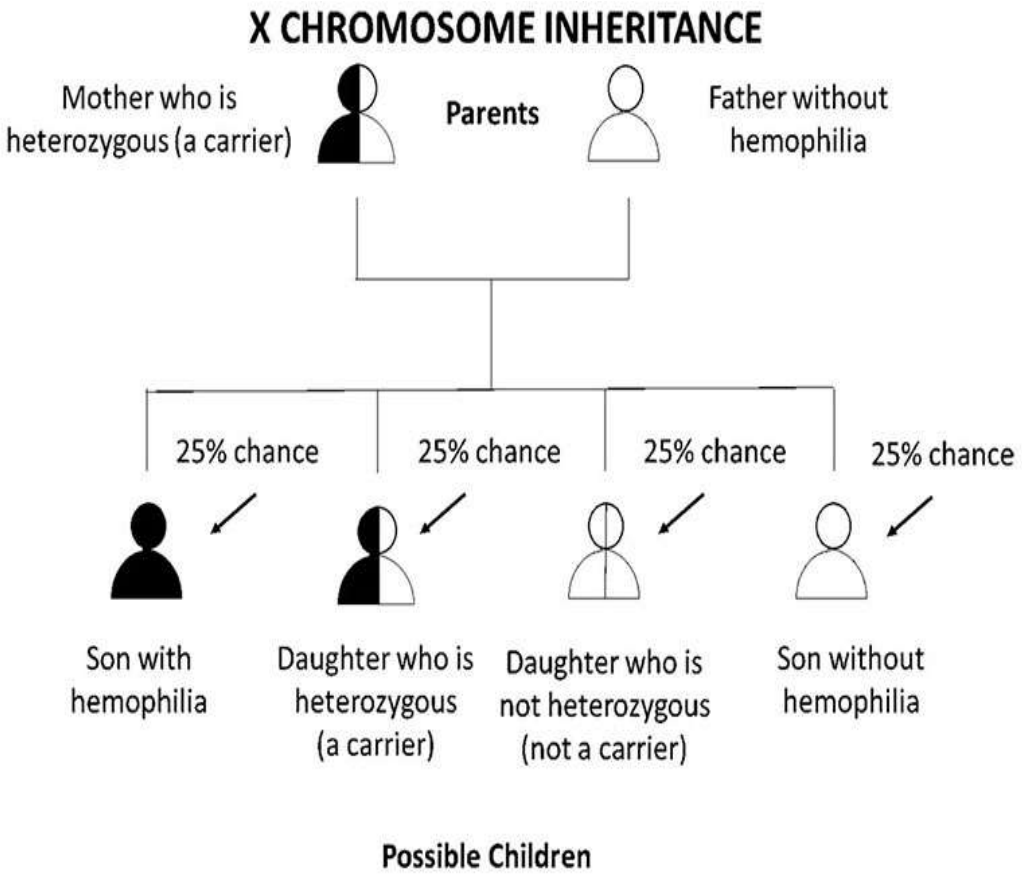


•Haemophilia A:-

Haemophilia A gene therapy has been hampered by immune responses to vector associated antigens and by neutralizing antibodies or inhibitors against the factor VIII (FVIII) protein; these 'inhibitors' more commonly affect haemophilia A patient's than those with haemophilia B.

-A gene replacement strategy beginning in the neonatal period may avoid the development of these immune responses and lead prolonged expression with correction of phenotype of phenotype, thereby avoiding long-term consequences. Or serotype rh10 adenoassociated virus (AAV) was developed splitting the FVIII coding sequence into heavy and light chains with the chicken beta-actin promoter or CMV enhancer for dual recombinant adeno associated viral vector delivery.

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 1766-1773 www.ijprajournal.com ISSN: 2456-4494



-Virions of each FVIII chain where co-injected intravenously into mice on the second day of life. Mice express sustained level of FVIII antigen greater than or equal to 5% upto 22 months of life without development of antibodies against FVIII.
-Phenotypic correction was manifest in all AAV-FVIII-treated mice as demonstrated by functional assay and reduction in bleeding time. This study demonstrated the use of AAV in a gene replacement strategy in a neonatal mice that establishes both long term phenotypic correction of haemophilia A and lack of antibody development against FVIII in these disease model where AAV is administered shortly after birth. This study support the consideration if a gene replacement therapy for disease that are diagnosed in utero or in the early neonatal period.

II. CONCLUSION:-

-The Conclusion of the present article explains that after the reviewing of numerous literature the scenario shown with some examples of frequent problems and interventions involved in neonatal care highlights the need for a complex and comprehensive therapeutic approach. In gene therapy for neonatal is more than 90% of those neonata have been cured of their disorder. To date, the FDA has approved four gene therapy products which insert new genetic material into a patient's cell.

Gene therapy has the potential to cure numerous genetic diseases and that the procedures appear to have minimal risks to the patient, but the efficiency of gene transfer and the gene expression of the corrective genes in the human patients is still very low. In 1990, 4-year-old Ashanthi de Silva became the first gene therapy success story.

REFERENCES:

[1]. Waddington, S Kennea, N, Buckley, S. et al. Fetal and neonatal gene therapy: benefits and pitfalls. Gene Ther 11, S92-S97 (2004). https://doi.org/10.1038/sj.gt.3302375
[2]. Ponder, Katherine P. Current Gene Therapy, volume 7, Number 5, 2017, pp. 403-410(8), Immunology of Neonatal Gene Transfer,

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 1766-1773 www.ijprajournal.com ISSN: 2456-4494

Bentham Science Publishers, https://doi.org/10.2174/15665230778215

[3]. Tomatsu, S., Azario, I., Sawamoto, K. et al. Neonatal cellular and gene therapies for ucopolysaccharidoses: the earlier the better?. J Inherit MetabDis **39,** 189-202 (2016). https://doi.org/10.1007/s10545-015-9900-2

[4]. J. E. Mikulska, L. Pablo, J. Canel, N.ESimister, Immunogenetics, European Journal of Immunogenetics, (2008), Volume 27, pp. 231-240, Clonning and analysis of gene encoding the human neonatal FC receptor, https://doi.org/10.1046/j.1365-2370.2000.00225.X

[5]. G. S. Lipshutz, Volume 19, pp.1166-1176, (2012), AAV-based Neonatal gene therapy for haemophilia A : long-term correction and avoid once of immune responses in mice.

[6]. Sun MS et al. Sustained hepatic and renal glucose-6-phosphatase expression corrects glycogen storage disease type la inmice. Hum Mol Genet 2002; **11**: 2155-2164.

[7]. Xu L et al. Transduction of hepatocytes after neonatal delivery of a Moloneymurine leukemia virus retroviral vector results in long term expression of beta-glucuronidasein mucopolysaccharidosis VIII dogs. MolTher2002; 5: 141-153.

[8]. Ponder KP et al. Therapeutic neonatal hepatic gene therapy in mucopolysaccharidosisVII dogs ProcNatl Acad Sci USA 2002; **99**: 13102-13107.

[9]. Xu L et al.Evaluation of pathological manifestations of disease in mucopolysaccharidosis VII mice after neonatal hepatic gene therapy MolTher 2002;**6**: 745-758.

[10]. Waddington SN et al. Permanent phenotypic correction of Haemophilia B in immunocompetent mice by prenatal gene therapy. Blood 2004(In Press).

[11]. DE Sabatino,et al.,Persistent expression of hF.IX after tolerance induction by in utero or neonatal administration of AAV-1-F.IX in hemophiliaB mice.MolTher**15**, 1677-1685 (2007).

[12]. S. Kersten, Physiological regulation of lipoprotein lipase, Biochim. Biophys.Acta, 1841 (2014), pp.919-933.

[13]. A. Chait, S. Subranian, Hypertrigltceridemia: pathophysiology, role of genetics, consequences, and treatment. In Endotext, MDText.com (2000), https://www.ncbi.nlm.nih.gov/books/NBK326743/GoogleScholar

[14]. J Wight, S Paisley, The epidemiology of inhibitors in haemophilia A: A systematic review. Haemophilia **9**, 418-435 (2003).

[15]. P Lollar, Pathogenic antibodies to coagulation factors. Part one: Factor VIII and factor IX. J ThrombHaemost**2**, 1082-1095 (2004).

[16]. SC Cunningham, AP Dane, A Spinoulas, GJ Logan, IE Alexander, Gene delivery to the juvenile mouse liver using AAV2/8 vectors. MolTher**16**, 1081-1088 (2008).

[17]. DE Sabatino, et al., Persistent expression of hF.IX after tolerance induction by in utero or neonatal administration of AAV-1-F.IX in haemophilia B mice. MolTher**15**, 1677-1685 (2007).

[18]. SO Kyosen, et al. Neonatal gene transfer using lentiviral vector for murine Pompe disease: Long-term expression and glycogen reduction. Gene Ther**17**, 521-530 (2010).

[19]. CA Pacak, et al., Recombinant adeno-associated virus serotype 9 leads to preferential cardiac transduction in vivo. Circ Res **99**, e3-e9 (2006).

[20]. SN Waddington, et al., Fetaland neonatal gene therapy:Benefits and pitfalls. Gene Ther**11**, S92-S97 (2004).

[21]. Ding Z, Hardling CO Thony B. State-of-the-art 2003 on PKU gene therapy. Mol Genet Metab2004; **81**: 3-8.

[22]. Kulkarni R, LusharJ. Perinatal management of newborns with haemophilia. Br J Haematol 2001; **112**: 264-274.

[23]. Park F et al. Efficient lentiviral transduction of liver requires cell cycling in vivo. Nat Genet 2000; **24**: 49-52.

[24]. Wu X, Li Y, Crise B, Burgess SM. Transcription start regions in the human genome are favoured targets for MLV integration. Science 2003; **300**: 1749-1751.

[25]. Cantero G. et al., Rescue of the functional alterations of motor cortical circuits in arginase deficiency by neonatal gene therapy. The Journal of Neuroscience. 2016;**36**(25):6680-6690.

[26]. Heldermon CD et al., Disease correction by combined neonatal intracranial AAV and systemic lentiviral gene therapy in Sanfilippo syndrome type B mice. Gene therapy. 2013;**20**(9):913-921.

[27]. Srivastava A. Et al., Guidelines for the management of Haemophilia, 2013;e1-e47.

[28]. Yang Y. et al., Cellular immunity to viral antigen limits E1-deleted adenoviruses for

gene therapy, Proc. Natl. Acad. Sci. USA. 1994; **91**: 4407-4411.
[29]. Kay M. A., High K., gene therapy for the haemophilia. Proc. Natl. Acad. Sci. USA. 1999; **96**: 9973-9975.
[30]. Shi Y. et al., Role of antigen-specific regulatory CD4+CD25+T cells in tolerance induction after neonatal IP administration of AAV- hF.IX. Gene Ther. 2013; **20**: 987-996.
[31]. Waddington S. N. et al., Permanent phenotypic correction of haemophilia B in immunocompetent mice by prenatal gene therapy. Blood. 2004; **104**: 2714-2721.
[32]. J Wight,SPaisley,Theepidemiology of inhibitors in haemophiliaA:A systemic review.haemophilia**9,**418-435(2003).
[33]. Brownstein Z et al., (2020) Spectrum of genes for inherited hearing loss in the Israeli Jewish population, including the novel human deafness gene ATOH1. **Clin Genet 98**: 353-364.
[34]. Cartwright S, Karakesisoglou (2014) Nesprins in health and disease. **SeminCell Dev Biol 29**: 169-179.
[35]. Tolar J, Teitelbaum SL, Orchard PJ. Osteopetrosis., N Engl J, Med, 2004, vol.351(pg.2839-2849).
[36]. Schambach A, et al., Dependence of different modules for posttransctiptional enhancement of gene expression from retroviral vectors, MolTher, 2000, vol.2 (pg. 435-445).
[37]. Johansson M, et al. Neonatal haematopoietic stem cell transplantation cures oc/oc mice from osteopetrosis , Exp Hematol, 2006, vol.34 (pg. 242-249).
[38]. de Vries TJ, et al., Effects of CD44 deficiency on in vitro and in vivo osteoclast formation., J Cell Biochem, 2005, vol. 94 (pg. 954-966).
[39]. Miyake N, et al., Long term correction of biochemical and neurological abnormalities in MLD mice model by neonatal systemic injection of an AAV serotype 9 vector. Gene therapy. 2014; **21**(4): 427-433.