East African Scholars Journal of Biotechnology and Genetics
Abbreviated Key Title: East African Scholars J Biotechnol Genet
ISSN: 2663-189X (Print) & ISSN: 2663-7286 (Online)
Published By East African Scholars Publisher, Kenya

OPEN ACCESS

Volume-1 | Issue-1 | Jan-Feb -2019 |

Review Article

Gene Therapy for Hemophilia & Sickle Cell Disease, what's new?

Wala M Elfatih Mahgoub[1], Ibrahim A Ali[2]

[1]Department of Anatomy, Faculty of Medicine, The National Ribat University, Sudan. Email: walla_9@live.com
[2]Department of Physiology, Faculty of Medicine, The National Ribat University, Sudan. Email:hemamedicine@gmail.com

*Corresponding Author
Dr. Wala Mohamed Elfatih Mahgoub AbdAlla

Abstract: Gene therapy holds a great deal of promise for the future of medical treatment. It involves the introduction of genetic material into a cell DNA to treat a disease. The ambitious objective of gene therapy is to edit a defective gene sequence in situ to achieve complete reversion of a disease phenotype for the lifetime of the patient. In spite of recent successes in site-specific correction of defective gene sequences, the focus of most gene therapy strategies to date is on gene addition rather than gene replacement. Adenovirus vectors are still being pursued as a means of obtaining long-term expression of both Factor VIII and Factor IX in hemophilic patients. Improved liver-specific promoters and further redesign of production methods resulted in long-term expression of Factor VIII in canine models of hemophilia A. Good candidates for gene therapy include autosomal recessive disorders (such as Sickle cell disease SCD) because a normal phenotype can be restored in diseased cells with only a single normal copy of the mutant gene (Goncz 2002). Gene therapy, provides a viable alternative for permanent correction of the abnormal gene in SCD.

Keywords: Hemophilia, Sickle cell disease, SCD, Gene therapy.

Gene Therapy for Hemophilia:

INTRODUCTION

The ambitious objective of gene therapy is to edit a defective gene sequence in situ to achieve complete reversion of a disease phenotype for the lifetime of the patient. In spite of recent successes in site-specific correction of defective gene sequences, the focus of most gene therapy strategies to date is on gene addition rather than gene replacement (Urnov *et al.*, 2005). This simplified approach relies on a delivery mechanism to provide a corrected copy of the defective gene without removal of the error-containing genomic sequence. While literally hundreds of animal models of disease can now be effectively treated by gene transfer, a select few diseases remain the primary focus of much gene therapy research.

Aspects influencing gene treatment for hemophilia:

A combination of factors including prevalence of disease, width of therapeutic window, ability to accommodate the corrected gene sequence in a gene transfer vector, reliability and availability of animal models of the disease, and funding and support from disease-specific foundations, all contribute to the over representation of these few diseases. Hemophilia A and B are among the most extensively researched diseases in the field of gene therapy. Small and large animal models of both diseases are available for preclinical testing. Importantly, treatment of the disease can be quantitatively measured through well-defined coagulation assays, eliminating a problem that plagues gene therapy efforts for many other disease entities. Another important aspect of the treatment of hemophilia by gene transfer is that there is a relatively low threshold for success. If long-term expression of the defective coagulation factor at 2–3% of wild-type levels could be achieved, then a substantial reduction in the clinical manifestations of the disease would be expected (Herzog *et al.*, 1999; Sarkar *et al.*, 2000). Expression of greater than 30% of the wild-type level of the defective coagulation factor would result in a phenotypically normal patient under most circumstances (Pollak and High, 2001), although higher levels may be required in the face of haemostatic challenge (Plug *et al.*, 2006).

Another advantage of haemophilia B in the development of gene therapy strategies is the relatively small size of F9 cDNA (approximately 1.4 kB of coding sequence). This is amenable to insertion into many different gene transfer vectors and allows the addition of numerous transcriptional regulatory elements to both

Quick Response Code

Journal homepage:
http://www.easpublisher.com/easjbg/

Article History
Received: 15.01.2019
Accepted: 12.02.2019
Published: 28.02.2019

DOI: 10.36349/easjbg.2019.v01i01.004

improve and restrict transgene expression in select cell types. F8 cDNA is much larger than that of F9 (>8 kB), and is not as readily accommodated in gene transfer vectors. Several strategies have been employed to overcome this difficulty.

Recent development in gene transfer for hemophilia:

Adenovirus vectors are still being pursued as a means of obtaining long-term expression of both Factor VIII and Factor IX. Improved liver-specific promoters and further redesign of production methods resulted in long-term expression of Factor VIII in canine models of hemophilia A, although some hepatotoxicity remains evident and could complicate translation into clinical trials (Andrews *et al.,* 2002; Chuah *et al.,* 2003; Brown *et al.,* 2004). Specifically, inter-subject variation and a small therapeutic index make the safe use of adenoviral vectors difficult for stable gene transfer in humans. As a result of their inherent immunogenicity, adenoviral vectors are now more frequently used as vaccine delivery vehicles (Tatsis & Ertl, 2004). New developments in the field of retroviral vectors are more promising for application in the treatment of hematological disorders. One of the most important innovations has been the development of lentiviral vectors, which have several advantages over the first-generation retroviral vectors. First, they are capable of transducing non-dividing cells, making them more suitable for transduction of, for example, hepatocytes and haematopoietic stem cells. Second, while retroviral vectors preferentially integrate their genomes near transcriptional start sites, lentiviral vectors show a random integration pattern into the open reading frames of genes (Mitchell *et al.,* 2004). While this difference does not eliminate the risk of insertional mutagenesis, it seems likely to mitigate the risk by reducing the number of full length gene transcripts that might be activated through vector genome insertion. Improvements in insulator elements flanking coding sequences within the vector genome itself further reduced the potential for undesirable insertional activation events (Chung *et al.,* 1997). Naldini et al showed that the use of a liver-specific promoter in place of a CMV promoter could alone be a determinant of stable lentiviral transduction of hepatocytes (Follenzi *et al.,* 2004). With a ubiquitous CMV promoter driving expression of either green fluorescent protein (GFP) or human Factor IX, expression was short-lived and the loss of expression was accompanied by both antibody formation against the transgene and T cell infiltrates in the liver. In contrast, use of a liver-specific promoter resulted in long-term, stable expression of GFP or human Factor IX in wild-type mice with expression levels of the latter reaching 200 ng/ml. In a subsequent study, Naldini et al also showed that the incorporation of four copies of a micro RNA target sequence in the vector genome could selectively mark vector transcripts for destruction in cells expressing the corresponding micro RNA (Brown *et al.,* 2006). Using this lineage-specific suppression strategy, selective down regulation of transgene expression in hematopoietic cells was achieved.

Gene Therapy for Sickle Cell Disease:

Sickle cell disease (SCD) is a group of genetic conditions that result from the inheritance of abnormal hemoglobin genes; thereby resulting in the production of abnormal hemoglobin in red blood cells (Akinyanju, 1989).Hemoglobin is responsible for transporting oxygen around the body packaged in red blood cells. In people with SCD, the red blood cells contain abnormal haemoglobin and change from their normal round disk shape to narrow sickle forms. The sickle shape is the end result of a series of complex biochemical and biophysical events within the red cell after deoxygenation of Hb S. The sickle-shaped cells do not flow smoothly through small blood vessels the way disk-shaped red blood cells do; they block the vessels, causing pain and organ damage. About 5% of the world's population carries genes responsible for haemoglobinopathies with most of the people living in, or originating from sub-Saharan Africa (WHO 2006). Each year about 300,000 infants are born with major haemoglobin disorders, including more than 200,000 cases of sickle cell anaemia in Africa (WHO 2006). Some parts of Africa have up to 10% to 30% of people of African descent carry one sickle gene in the United States of America (USA) and the Caribbean (Ohene-Frempong 1994; Serjeant 1992).

Recent Development in Gene Therapy of SCD:

Good candidates for gene therapy include autosomal recessive disorders (such as SCD) because a normal phenotype can be restored in diseased cells with only a single normal copy of the mutant gene (Goncz 2002). Gene therapy provides a viable alternative for permanent correction of the abnormal gene in SCD. It circumvents the problem of donor shortage and avoids complications related to graft versus host rejection that are involved with bone marrow or other forms of stem cell transplant. Gene therapy has been used to correct SCD in mice (Nathan 2001). Despite the technical problems faced, to apply gene therapy in human trails, major progress in the globin gene therapy field has been achieved. This progress has advanced the possibility of gene therapy for hemoglobin disorders such as SCD in near future (Persons 2003; Chang 2006).

REFERENCES

1. Akinyanju, Olufemi O. "A profile of sickle cell disease in Nigeria." *Annals of the New York Academy of Sciences* 565.1 (1989): 126-136.
2. Andrews, J. L., Shirley, P. S., Iverson, W. O., Sherer, A. D., Markovits, J. E., King, L., ... & Connelly, S. (2002). Evaluation of the duration of human factor VIII expression in nonhuman primates after systemic delivery of an adenoviral vector. *Human gene therapy*, *13*(11), 1331-1336.
3. Bodine, D. M. (2003). Gene therapy for sickle cell disease marches on. *Blood*, *102*(13), 4247-4247.

4. Brown, B. D., Shi, C. X., Powell, S., Hurlbut, D., Graham, F. L., & Lillicrap, D. (2004). Helper-dependent adenoviral vectors mediate therapeutic factor VIII expression for several months with minimal accompanying toxicity in a canine model of severe hemophilia A. *Blood*, *103*(3), 804-810.
5. Chung, J. H., Bell, A. C., & Felsenfeld, G. (1997). Characterization of the chicken β-globin insulator. *Proceedings of the National Academy of Sciences*, *94*(2), 575-580.
6. Follenzi, A., Battaglia, M., Lombardo, A., Annoni, A., Roncarolo, M. G., & Naldini, L. (2004). Targeting lentiviral vector expression to hepatocytes limits transgene-specific immune response and establishes long-term expression of human antihemophilic factor IX in mice. *Blood*, *103*(10), 3700-3709.
7. Wiely. (2016, june). Gene Therapy Clinical Trials Worldwide Database. *The Journal of Gene Medicine.*
8. Goncz, K. K., Prokopishyn, N. L., Chow, B. L., Davis, B. R., & Gruenert, D. C. (2002). Application of SFHR to gene therapy of monogenic disorders. *Gene therapy*, *9*(11), 691.
9. Herzog, R. W., Hagstrom, J. N., Kung, S. H., Tai, S. J., Wilson, J. M., Fisher, K. J., & High, K. A. (1997). Stable gene transfer and expression of human blood coagulation factor IX after intramuscular injection of recombinant adeno-associated virus. *Proceedings of the National Academy of Sciences*, *94*(11), 5804-5809.
10. Mitchell, R. S., Beitzel, B. F., Schroder, A. R., Shinn, P., Chen, H., Berry, C. C., ... & Bushman, F. D. (2004). Retroviral DNA integration: ASLV, HIV, and MLV show distinct target site preferences. *PLoS biology*, *2*(8), e234.
11. Nathan, S. (2001). Gene Therapy for Sickle-Cell Disease? Science News, 160, (24)-372.
12. Ohene-Frempong, K., & Nkrumah, F.K. (1994). Sickle cell disease in Africa. Sickle cell disease: basic principles and clinical practice. *New York: Raven Press Ltd*.
13. Persons, D. A., and A. W. Nienhuis. "Gene therapy for the hemoglobin disorders." *Current hematology reports* 2, no. 4 (2003): 348-355.
14. Plug, I., Mauser-Bunschoten, E.P., Brocker-Vriends, A.H., van Amstel, H.K., van der Bom, J.G., van Diemen-Homan, J.E., Willemse, J. & Rosendaal, F.R. (2006) Bleeding in carriers of hemophilia. Blood, 108, 52–56.
15. Pollak, E.S. & High, K.A. (2001) Hemophilia B: factor IX deficiency. In: The Metabolic & Molecular Bases of Inherited Disease (eds by C.R. Scriver, A.L. Beaudet, W.S. Sly & D. Valle), *McGraw-Hill Medical Publishing Division, New York, (3), 4393–4413.*
16. Tatsis, N., & Ertl, H.C. (2004). Adenoviruses as vaccine vectors. *Molecular Therapy, (10), 616–629.*
17. Urnov, F. D., Miller, J. C., Lee, Y. L., Beausejour, C. M., Rock, J. M., Augustus, S., ... & Holmes, M. C. (2005). Highly efficient endogenous human gene correction using designed zinc-finger nucleases. *Nature*, *435*(7042), 646.
18. World Health Organization.(2008, 06 June). Sickle-cell anaemia. Report A59/9. Provisional agenda item 11.4. 59th World Health Assembly. www.who.int/gb/ebwha/pdf_files/WHA59/ A59_9-en.pdf 2006.