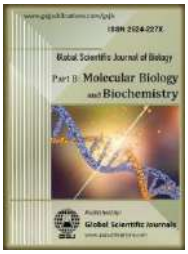
Global Scientific Journal of Biology 7 (2) 2022/ 82-92

Contents lists available at www.gsjpublications.com

Global Scientific Journal of Biology
Part B: Molecular Biology and Biochemistry
ISSN: 2524-227X

journal homepage: www.gsjpublications.com/gsjb



Review Article

Gene Therapy for the Treatment of Fanconi's Anemia

Rawaa Abdul-Ameer Abdul-jabbar, Ghanyia Jasim Shanyoor, Dalal A. Sattar

Biology Department, College of Science, Mustansiriyah University, Baghdad, Iraq.

ARTICLE INFO

Received: 28 Jun 2022,
Revised: 29 Jun 2022,
Accepted: 11 Jul 2022,
Online: 3 Aug 2022

Keywords:
FA, marrow, gene therapy, steam cells, blood.

ABSTRACT

Fanconi anemia (FA) is a disease that affects the bone, particularly the marrow causing decreasing in producing the blood cells (white cells, red cells and platelets). Previous studies mentioned that FA is passed from parents to children (inherited disease) and it may infect children and adults, low production of blood cells affect the immunity system and may end with cancer (different types of cancer). To minimize the consequences, scientists start since more than 20 years to find a treatment or a certain therapy to the bone marrow, among these procedures is steam cell therapy, hormone therapy, growth factor therapy, the therapy may involved with chemotherapy, radiotherapy, as well as surgery (transplant of bone marrow stem cells). Gene therapy is part of FA therapy, this type of therapy based on determining the damaged gene, corrects it and inserted in the patient using different ways.

Introduction

Gene therapy is a modern procedure that used to treat diseases by modifying the genes of the persons; it is a new and novel topic particularly in the current century because it was applied in curing diseases, the argument that surrounding this technique is changing the genes and patients are not sure about the consequences of modifying their genes [1, 2]. In general gene therapy is treatment that based on inactivating the gene that cause disease and/ or replacing this gene with a healthy reproduced (copy). The techniques that are applied in gene therapy can prevent and cure diseases, among these diseases are cancer and chronic diseases.

However, the idea of inserting genes to the vital tissues was under study and application since around 50 years, but the capability to recombinant the DNA and the development in this technology make the clinical trials of gene transfer possible especially to life threatening diseases such as cancers, inborn disorders [3, 4]. Nowadays, gene therapy is applied in many clinics and it is also considered for a numerous conditions that are not threatening life [5].

Mechanism and Types of Gene Therapy

The gene therapy has many mechanisms that describe it works, among them are [6, 7, 8]:

- Introducing a modified and / or new genes and insert it into the body in order to assist the body to treat the diseases.
- Inactivating the genes that cause diseases and is not work properly, and is considered as dysfunction gene.

Corresponding author:
E-mail address: rawaaattar@uomustansiriyah.edu.iq
doi: 10.5281/gsjb.2022.6963076

➢ Replacing the gene that causes diseases with other gene that considered as a healthy copy of it.

Recently, gene therapy is used to treat infectious diseases as well as genetic and cancer diseases. There are products to the types of gene therapy such as [9, 10]:

1. **Technology used to edit the human gene**: the purpose of this technology is to repair the genes that cause mutation and / or disrupt and disturb the dangerous the harmful and the risky genes.
2. **Bacterial vehicles**: In order to prevent bacteria from causing diseases, bacteria is modified and used as a vehicles *vectors) to carry and transfer the therapeutic genes and insert it into the tissues of the human beings.
3. **Modification of patient's genes**: In this type, the patient's cells are removed and their genes are modified (genetically modified), and after that the cells were injected in the patient.
4. **Viral vehicles**: As it is known, the viruses have the capability to deliver, carry and transport the materials of genes into the cells, thus, first, their genes are modify in order not to transfer infection, then it is used as a vector to carry the genes into the cells of the human as a therapeutic genes [11].
5. **Plasmid DNA**: currently, there is a wide application to this type, it is based on manufacturing genes via genetic engineering and insert it to the cells of the human as a gene therapy [12].

Plasmid is considered as the most recent gene therapy technique that can be applied in and extensive purposes i.e., PCR, cloning, restriction digestion, screening clones, sequencing, transfection and lot more, it is important to purified it from bacteria before using it via any above techniques. Figure 1 shows a diagram of manufacturing plasmid DNA.

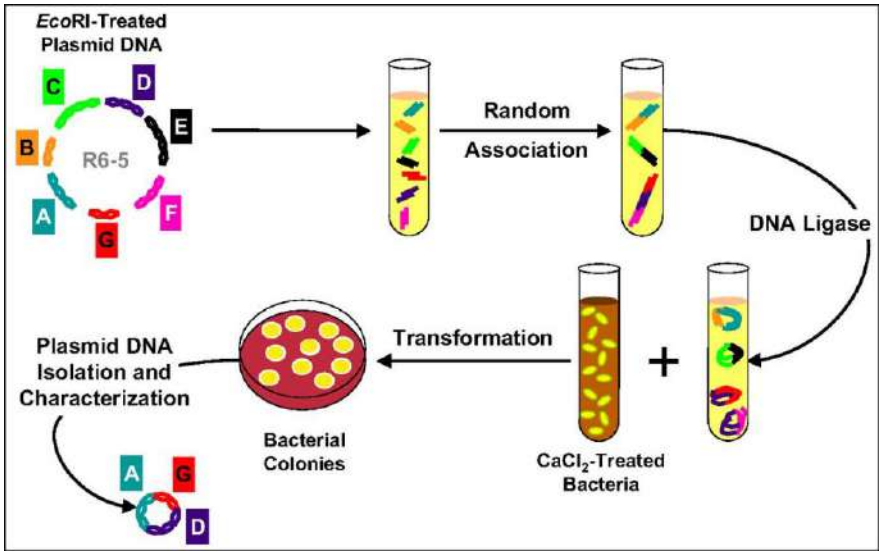


Figure 1: mechanism of the plasmid DNA synthesis [13]

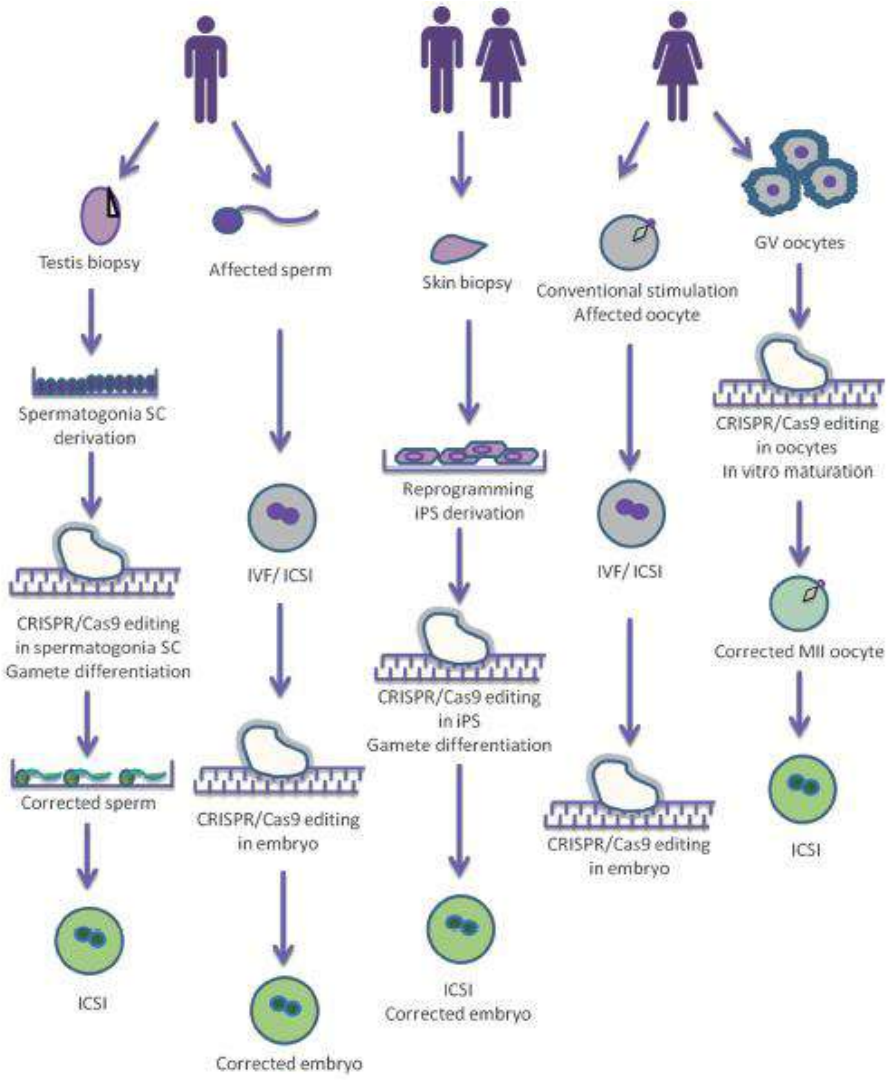
The most important step in gene therapy is transferring the gene inside the human body, once this succeed it will made a big development and revolution in treatment and medicine because this approach is able to treat the difficult diseases from its root [14].

Basically, gene therapy has two main types

➢ **Germline therapy: T**his type goal to produce and create reproductive cells in the body (sperm or ova) via transferring DNA. The aim of germline therapy to correct the gene variant that cause diseases (gamete cells) and can be passed down to the new generation, however and due to ethical consideration, and there are boundaries between enhancement, therapy and prevention

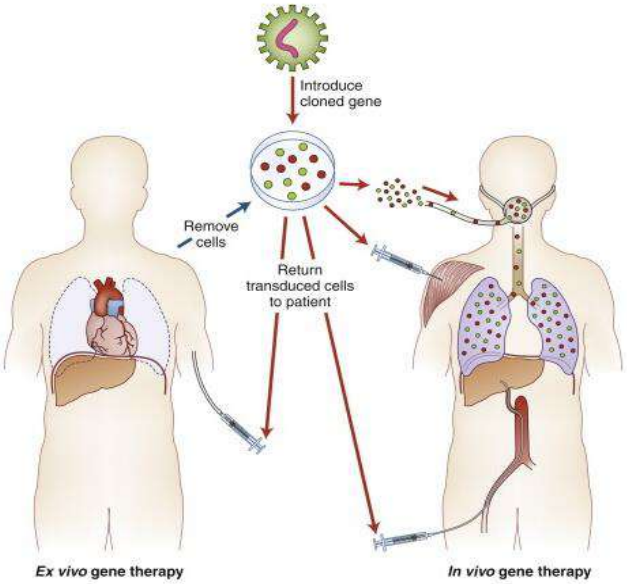
which are unclear in (HGL) human germline [15].

Scheme 2 [16].



Scheme 2: Outline of germline in women and men [16]

➢ **Somatic gene therapy (SGT)**: This type of technique aimed to introduce RNA into suitable tissue or cell in vivo to alter the pattern and the expression of the cell gene create curative effect and improve the ability of the body to fight diseases via somatic cells [17, 18], however there two types of SGT; in vivo and ex vivo as shown in scheme 3 [19].



Scheme 3: Types of somatic gene therapy

It is important to distinguish between the both types of gene therapy (SGT & GLT), among them are [20];

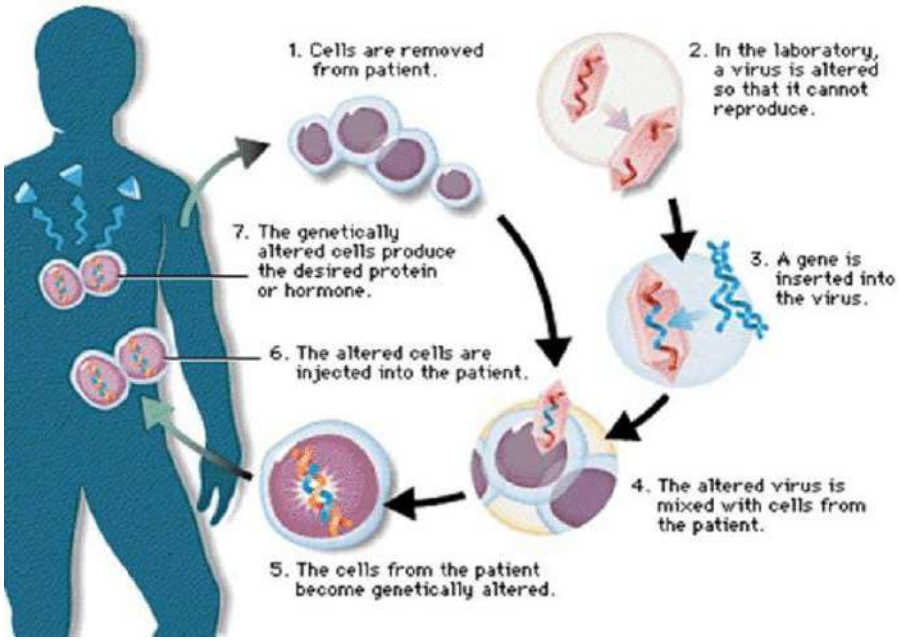
- SGT targeted blood cells, skin cells, and lung cells while GLT applied on eggs, sperm, and embryos.
- SGT cells are not inheritable, while GLT passed on upcoming generations.
- SGT was applied more than 25 years ago while GLT doesn't and applied recently.

There are also other significant differences between the two approaches of gene therapies as shown in table 1.

Table 1: some differences between somatic & germline therapies [21]

	Somatic therapy	Germline therapy
1	Healthy genes introduced into the somatic cells	Healthy genes introduced into the germ cells (sperm, egg, zygotes etc).
2	Changes are not heritable and is confined to the individual	Changes are heritable and will pass on to the future generations.
3	Techniques for somatic cell culture, introduction of healthy gene, and re implantation back to body. All these steps are successfully developed.	Many practical difficulties in introducing healthy genes to germ cells.
4	Not much ethical issues attached	Many ethical problems yet to be answered.
5	Most often it may not be possible to achieve normal level of expression similar to that of normal gene.	High frequency of insertional mutations are observed often lead to teratogenic consequences.

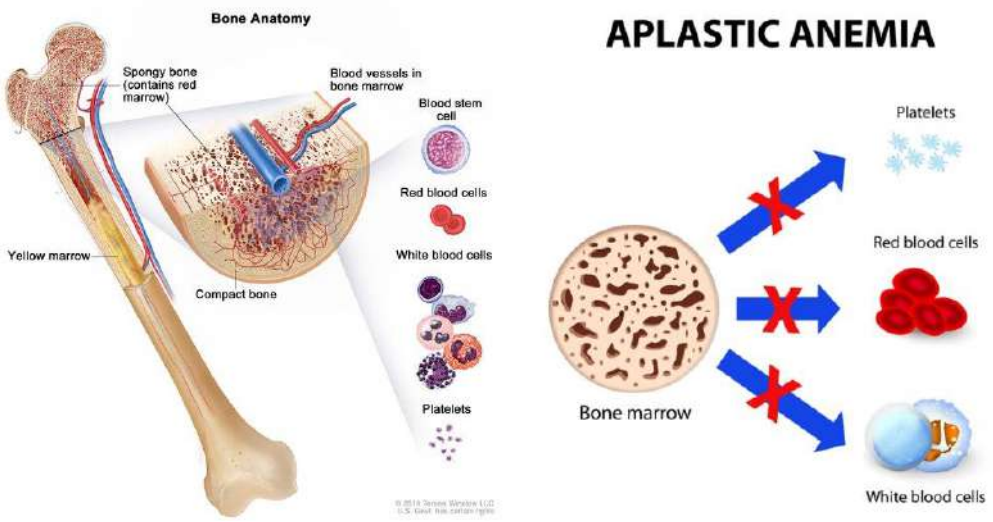
In general, the steps involving in gene therapy are summarized in scheme 4



Scheme 4: Summery of steps involving gene therapy [22]

Fanconi anemia (FA)

It is a situation that has an effect on numerous parts of the body; particularly it is a failure in bone narrow (BNF) (failure in producing blood cells), organ defect and physical abnormality that increase the cancer risk. It is an inherited disease from a plastic anemia [23, 24]. FA is a disorder in genes that can be distinguished via BMF which can leads to cancer, the homeostasis in gene and FA proteins can be maintained via processes that repairs DNA and mutation in germline genes that causes FA [25]. Scheme 5 shows a plastic anemia (FA) and the anatomy of bone.

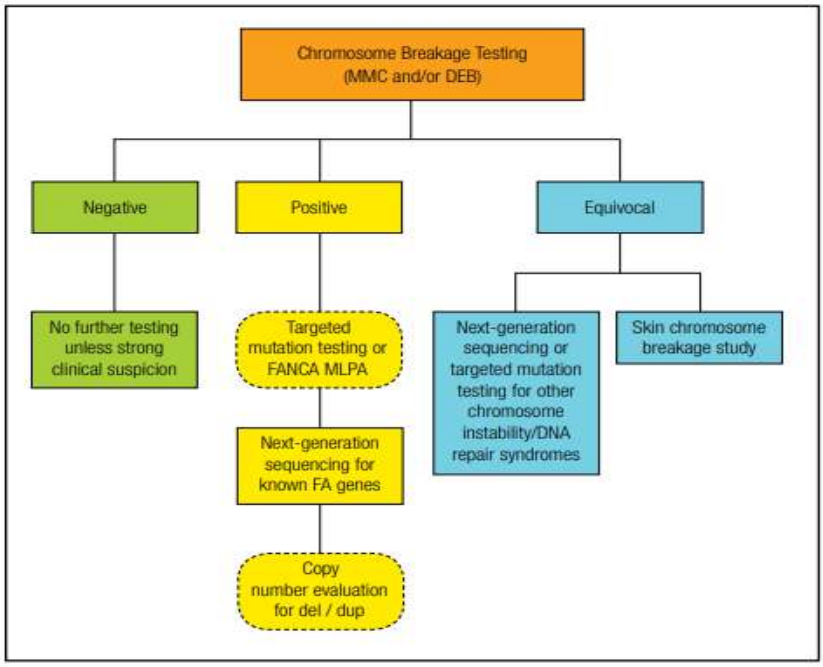


(A) **(B)**

Scheme 5: A: Bone anatomy; B: Fanconi anemia [26]

In 1927 Guido Fanconi (1892-1979) is the first Swiss scientist who discovered and characterized this disease, he described it in 3 brothers and he described an inheriting disease that related to the bone narrow failure (BNF) which leads to a consequences such as hyperpigmentation, hypogonadism, short stature, and many physical abnormalities [27, 28].

The main test that should be carried out to diagnose the FA, is a test that discover chromosome breakage that can be noticed from sample of patient's blood and achieved in cytogenetic clinical lab [28]. This test involved with T-Cell Mitogen to encourage and initiate the division of lymphocytes and then treated with MMC (Mitomycin) as a DNA cross-linking agent, DEB (Diepoxybutane) can also be used, then, the rates and the types of rearrangements and breakages were measured and evaluated [29, 30]. Scheme 5 shows the flowchart of the lab test steps [31].



Scheme 5: Lab test flowchart [31]

Statistically, FA usually affect from 1 to 5 per million [32], it is considered as a very rare, there are a number of genes that are involved in FA and thus it is a multigenic disorder and it may threaten children as well as adults and may end with certain epithelial malignancies, acute nonlymphocytic leukemia (AML), and myelodysplasia [33, 34, 35 and 36].

Up to now, the main thing of FA disease is instability in genes (cytogenic disorder) and can be identified through alkylating agents that can response to the breakage in chromosomes [37, 38]. However there are many classical clues that accompanied with FA among them are; radial ray defects, *café-au-lait* spots, small head size and growth retardation [39], however in adults, FA may come with no congenital defects, and environment interaction may paly a certain role in infection with FA disease [40].

Levitus et al., 2004 [41] carried out a somatic cell fusion research, and the study determined eleven groups that are complemented with FA, these are; J, I, L, G, F, E, D2, D1, C, B, and FA-A [41]. Table 2 shows the most important genes that involved with FA disease.

Table 2: FA genes [40]

Gene	Prevalence of Mutations in Patients with FA (%)	Chromosomal Location	Exon Number	Amino Acid Residues (kDa)
FANCA	70	16q24.3	43	1455 (163)
FANCB	1	Xp22.31	10	859(95)
FANCC	10	9q22.3	14	558 (63)
FANCD1 (BRCA2*)	1	13q12.3	27	3418 (384)
FANCD2	1	3p25.3	44	1451 (155,162)
FANCE	5	6p21.3	10	536 (60)
FANCF	2	11p15	1	374 (40)
FANCG	10	9p13	14	622 (48)
FANCL (PHF9)	1	2p16.1	11	373 (43)
FANCI	Not known	Not known	Not known	Not known
FANCJ	Not known	Not known	Not known	Not known

* Although a BRCA2 null genotype is an embryonic lethal phenotype, certain homozygous BRCA2 mutations that lead to C-terminal truncations, lead to FA of the D1 complementation group.

In 2020, Toksoy and the coworkers [42] explained FA as a hetrogenous syndrome in genes that includes findings related to hematology due to BMF with defect in skeletal system and other symptoms, such as; pigment changes of the skin, kidney malformations, congenital heart defects, deafness, microcephaly, low birth weight, small stature, hands with thumb deformities, however Wu 2013 [43], described that FA could be more repeatedly in marriages between relatives (consanguineous marriages).

Wegman-Ostrosky and Savage 2017 [44], mentioned that the patients who affected with FA diseases have a risk to leukemia-myelodysplastic syndrome further than myeloid leukemia by which the cancer cells rapidly reproduce in different areas such as anogenital regions, neck and head [44].

FA Treatment

A team of specialists must supervised the therapy among them are; kidney specialists, urologists, oncologists, cardiologists, surgeons, and others. The specialists, and before starting treatment, must study the followings factors [45]:

- Overall health.
- Age.
- Medical history.
- Severity of other disease.

Transplant of bone Marrow Stem Cells

In this type of therapy, the procedure focused on the diseased or damaged marrow that may destroyed by chemotherapy or radiation and after that they were replaced with healthy one (from healthy donors), and this process named as transplantation of the stem cell because the diseased marrow cannot produce enough blood cells which are below the needs of the immune system [46, 47]. The transplant may cure cancer and considered as long term recovery, however the steam cell therapy (STC) doesn't considered as an effective treatment and solution [48].

Androgen Therapy

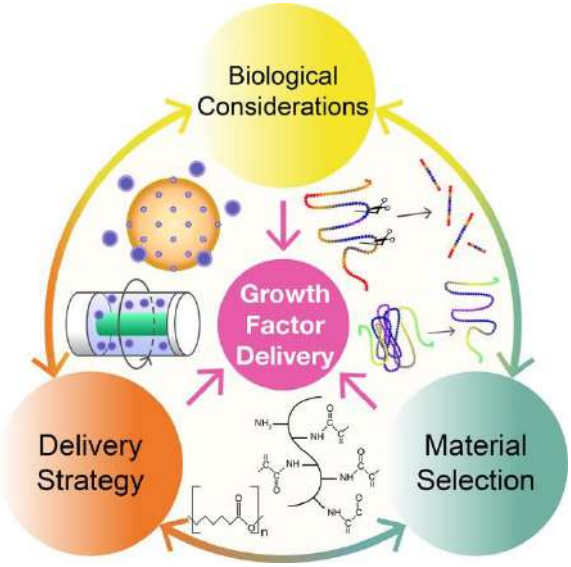
It is also named as hormone therapy; it is usually used to cure prostate cancer, the therapy based on reducing testosterone male hormone [49], the therapy usually based on the following steps:

- Block the synthesis and the production of androgen.
- Blocking the androgen action.
- Minimizing the production of androgen in testicles [50].

The above three steps can be achieved by medication, radiation and /or chemotherapy, hormone therapy also can be participate in increasing the production of the blood cells, however, it is not recommended by the specialists because it may cause liver diseases.

Growth factor

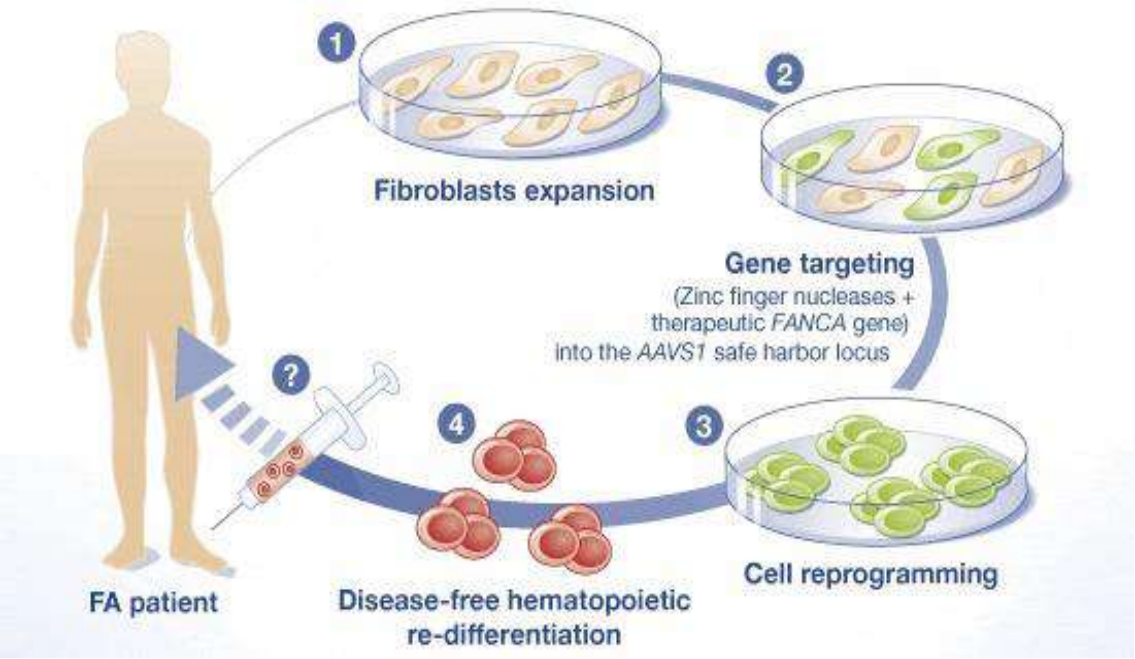
This type of therapy is based on secreting active molecules that has an effect on growing of the cells particularly inhibit the unusual mitosis of cancer cells which eventually change the expression of the gene, the molecules may have different activity precisely on initiating the synthesis of blood cells and increase it in the body via a process named as single transduction [51, 52, 53]. Scheme 6 shows a diagram represent the process of growth factor [54].



Scheme 6: Delivery of growth factor [54]

FA Gene Therapy

Verhoeyen et al., 2017 characterized FA as a genetic disease (syndrome) that progressed and developed to failure in bone marrow (the part of the body that is in charge in the production of the blood cells) [55]. Scheme 7 summarized the gene therapy steps.



Scheme 7: FA gene therapy [56]

Conclusions

1. Fanconi anemia FA is a disease that passes from parents to children.
2. There are changes that occur (mutation) in a certain genes responsible for FA.
3. FA is a disease that affects the bone marrow (the sponge center of the bone) that is in charge of producing and synthesis of blood cells.
4. FA may affect both children and adults as well.
5. FA therapy may involved with medications, radiation, chemotherapy and Transplant of bone Marrow stem cells
6. FA gene therapy concerned with repairing the genes from there damages.

References

[1]. Cotrim AP,Baum BJ. Gene Therapy: Some History, Applications, Problems, and Prospects. Toxicologic Pathology. 2008; 36: 97-103.

[2]. Patil SR, Al-Zoubi IA, Raghuram PH, Misra N, et al. Gene Therapy: A Comprehensive Review. International Medical Journal. 2018; 25(6): 361-364.

[3]. Sitaraman R. Prokaryotic horizontal gene transfer within the human holobiont: ecological-evolutionary inferences, implications and possibilities. Microbiome. 2018; 6(1): 163. doi: 10.1186/s40168-018-0551-z.

[4]. Bello-López JM, Cabrero-Martínez OA, Ibáñez-Cervantes G, Hernández-Cortez C, et al. Horizontal Gene Transfer and Its Association with Antibiotic Resistance in the Genus Aeromonas spp. Microorganisms. 2019; 7: 363. doi:10.3390/microorganisms7090363

[5]. Brito IL. Examining horizontal gene transfer in microbial communities. Nat Rev Microbiol. 2021; 19(7): 442-453. doi: 10.1038/s41579-021-00534-7.

[6]. Aiuti A, Cattaneo F, Galimberti S, Benninghoff U, et al. Gene therapy for immunodeficiency due to adenosine deaminase deficiency. N. Engl. J. Med. 2009; 360: 447–458. doi: 10.1056/NEJMoa0805817

[7]. Ahmed SS, Gao G. Gene therapy for Canavan's disease takes a step forward. Mol. Ther. 2013; 21: 505–506. doi: 10.1038/mt.2013.25

[8]. Aimiuwu OV, Fowler AM, Sah M, Teoh JJ, et al. RNAi-based gene therapy rescues developmental and epileptic encephalopathy in a genetic mouse model. Mol. Ther. 2020; 28: 1706–1716. doi: 10.1016/j.ymthe.2020.04.007

[9]. Crystal RG. Adenovirus: the first effective in vivo gene delivery vector. Hum Gene Ther. 2014 Jan; 25(1): 3-11. doi: 10.1089/hum.2013.2527.

[10]. Coutant F, Sanchez David RY, Félix T, Boulay A, et al. A nonintegrative lentiviral vector-based vaccine provides long-term sterile protection against malaria. PLoS One. 2012;7(11):e48644. doi: 10.1371/journal.pone.0048644. Lee CS, Bishop ES, Zhang R, Yu X, et al. Adenovirus-mediated gene delivery: Potential applications for gene and cell-based therapies in the new era of personalized medicine. Genes and Diseases. 2017; 4(2): 43-63. doi:10.1016/j.gendis.2017.04.001

[11]. Bulcha JT, Wang Y, Ma H. Viral vector platforms within the gene therapy landscape. Sig Transduct Target Ther. 2021; 6: 53. https://doi.org/10.1038/s41392-021-00487-6

[12]. Schmeer M, Buchholz T, Schleef M. Plasmid DNA Manufacturing for Indirect and Direct Clinical Applications. Hum Gene Ther. 2017 Oct;28(10):856-861. doi: 10.1089/hum.2017.159.

[13]. Cohen SN. DNA cloning: A personal view after 40 years. Proceedings of the National Academy of Sciences PNAS September 24 2013; 110(39): 15521-15529; https://doi.org/10.1073/pnas.1313397110

[14]. Kay MA, Glorioso JC, Naldini L. Viral vectors for gene therapy: the art of turning infectious agents into vehicles of therapeutics. Nat Med. 2001;7(1):33e40.

[15]. David R, Pamela L. Human Germline Gene Therapy Reconsidered. Human gene therapy. 2001; 12: 1449-1458. 10.1089/104303401750298607.

[16]. De Wert G, Heindryckx B, Pennings G, et al. Responsible innovation in human germline gene editing: Background document to the recommendations of ESHG and ESHRE. European Journal of Human Genetics. 2018; 26: 450–470. https://doi.org/10.1038/s41431-017-0077-z

[17]. Goswami R, Subramanian G, Silayeva L, Newkirk I, et al. Gene Therapy Leaves a Vicious Cycle. Frontiers in Oncology. 2019; 9: 297. DOI=10.3389/fonc.2019.00297

[18]. Mavilio F, Ferrari G. Genetic modification of somatic stem cells. The progress, problems and prospects of a new therapeutic technology. *EMBO Rep*. 2008;9 Suppl 1(Suppl 1):S64-S69. doi:10.1038/embor.2008.81

[19]. Rosenberg LE, Rosenberg DD. Chapter 17 - Detection and Treatment of Genetic Disorders. Human Genes and Genomes, Academic Press, 2012, Pages 289-314, https://doi.org/10.1016/B978-0-12-385212-0.00017-2.

[20]. Evans JH. Setting ethical limits on human gene editing after the fall of the somatic/germline barrier. The National Academy of Sciences. 2021; 188(22): e2004837117. 10.1073/pnas.2004837117

[21]. https://www.biologyexams4u.com/2013/02/difference-between-somatic-and-germline.html

[22]. Adamu SM, Koki AY, Adamu S, Musa AM, Abdullahi AS. Biotechnology as a Cradle of Scientific Development: A Review on Historical Perspective. Journal of Advances in Biology & Biotechnology. 2016; 10(4): 1-12.

[23]. Alter BP. Fanconi's anemia and malignancies. Am J Hematol. 1996 Oct; 53(2): 99-110. doi: 10.1002/(SICI)1096-8652(199610)53:2<99::AID-AJH7>3.0.CO;2-Z.

[24]. Tischkowitz MD, Hodgson SV. Fanconi anaemia. Journal of Medical Genetics. 2003; 40(1): 1-10. 10.1136/jmg.40.1.1

[25]. Nalepa, G., Clapp, D. Fanconi anaemia and cancer: an intricate relationship. Nat Rev Cancer, 2018; 18: 168–185. https://doi.org/10.1038/nrc.2017.116

[26]. https://medlineplus.gov/genetics/condition/fanconi-anemia/#causes

[27]. Fanconi G. Familiare infantile perniziosaartigc Andmie (pernizioses Bluthild und Konstitution). Jahrb Kinderh, 1927; 117: 257-80.

[28]. Auerbach AD (2009) Fanconi anemia and its diagnosis. Mutat Res 668(1-2):4-10.

[29]. Castella M, et al. (2011) Chromosome fragility in patients with Fanconi anaemia: diagnostic implications and clinical impact. J Med Genet 48(4):242-250.

[30]. Ahammad F, Rupa HS, Rashid AKMM, Rasul CH. Fanconi anemia. Bang Med J Khulna 2017; 50: 46-48.

[31]. https://www.fanconi.org/images/uploads/other/Chapter_2_Guidelines_4th_Edition.pdf

[32]. Joenje H, Patel KJ. The emerging genetic and molecular basis of Fanconi anaemia. Nat Rev Genet. 2001; 2(6): 446–459.

[33]. Auerbach AD, Allen RG. Leukemia and preleukemia in Fanconi anemia patients. A review of the literature and report of the International Fanconi Anemia Registry. Cancer Genet Cytogenet. 1991 Jan;51(1):1-12. doi: 10.1016/0165-4608(91)90002-c.

[34]. Alter BP. Fanconi's anemia and malignancies. Am J Hematol. 1996 Oct;53(2):99-110. doi: 10.1002/(SICI)1096-8652(199610)53:2<99::AID-AJH7>3.0.CO;2-Z.

[35]. Alter BP. Cancer in Fanconi anemia, 1927-2001. Cancer. 2003 Jan 15;97(2):425-40. doi: 10.1002/cncr.11046.

[36]. Rosenberg PS, Socié G, Alter BP, Gluckman E. Risk of head and neck squamous cell cancer and death in patients with Fanconi anemia who did and did not receive transplants. Blood. 2005 Jan 1;105(1): 67-73. doi: 10.1182/blood-2004-04-1652.

[37]. Sasaki MS, Tonomura A. A high susceptibility of Fanconi's anemia to chromosome breakage by DNA cross-linking agents. Cancer Res. 1973; 33(8): 1829–1836

[38]. Fagerlie S, Lensch MW, Pang Q. et al. The Fanconi anemia group C gene product. Signaling functions in hematopoietic cells. Exp Hematol. 2001; 29(12):1371–1381.

[39]. Bagby GC, Lipton JM, Sloand EM. et al. Marrow failure. Hematology Am Soc Hematol Educ Program. 2004:318–336.

[40]. Bagby, GC. The Genetic Basis of Fanconi Anemia. In: Madame Curie Bioscience Database [Internet]. Austin (TX): Landes Bioscience; 2000-2013. Available from: https://www.ncbi.nlm.nih.gov/books/NBK6302/

[41]. Levitus M, Rooimans MA, Steltenpool J, Cool NF, Oostra AB, Mathew CG, Hoatlin ME, Waisfisz Q, Arwert F, de Winter JP, Joenje H. Heterogeneity in Fanconi anemia: evidence for 2 new genetic subtypes. Blood. 2004 Apr 1;103(7):2498-503. doi: 10.1182/blood-2003-08-2915.

[42]. Toksoy G, Uludağ Alkaya D, Bagirova G, Avcı Ş, Aghayev A, Günes N, Altunoğlu U, Alanay Y, Başaran S, Berkay EG, Karaman B, Celkan TT, Apak H, Kayserili H, Tüysüz B, Uyguner ZO. Clinical and Molecular Characterization of Fanconi Anemia Patients in Turkey. Mol Syndromol. 2020 Nov;11(4):183-196. doi: 10.1159/000509838.

[43]. Wu Z-H. The concept and practice of Fanconi Anemia: from the clinical bedside to the laboratory bench. Transl Pediatr. 2013;2(3):112–9.

[44]. Wegman-Ostrosky T, Savage SA. The genomics of inherited bone marrow failure: from mechanism to the clinic. Br J Haematol. 2017; 177(4): 526–542.

[45]. Shafqat S, Tariq E, Parnes AD, Dasouki MJ, Ahmed SO, Hashmi AK. Role of gene therapy in Fanconi anemia: A systematic and literature review with future directions. Hematology/Oncology and Stem Cell Therapy. 2021; 14(4): 290-301.

[46]. De Rocco D, Bottega R, Cappelli E, Cavani S, Criscuolo M, Nicchia E, et al. Molecular analysis of Fanconi anemia: the experience of the bone marrow failure study group of the Italian association of pediatric onco-hematology. Haematologica .2014; 99(6): 1022–1031. doi.org/10.3324/haematol.2014.104224

[47]. Henig I, Zuckerman T. Hematopoietic stem cell transplantation—50 years of evolution and future perspectives. Rambam Maimonides Med J. 2014; 5(4): e0028.

[48]. Balistreri, C.R., De Falco, E., Bordin, A. *et al.* Stem cell therapy: old challenges and new solutions. Mol Biol Rep. 2020; 47: 3117–3131. https://doi.org/10.1007/s11033-020-05353-2

[49]. Myers JB, Meacham RB. Androgen replacement therapy in the aging male. Rev Urol. 2003; 5(4): 216-226.

[50]. Lee RJ, Smith MR. Hormone Therapy for Prostate Cancer. In: Chabner BA, Longo DL, eds. *Cancer Chemotherapy and Biotherapy: Principles and Practice*. 5th ed: Wolters Kluwer: Lippincott Williams & Wilkins; 2011.

[51]. Stone WL, Leavitt L, Varacallo M. Physiology, Growth Factor. [Updated 2021 May 7]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK442024/

[52]. Naderali E, Khaki AA, Rad JS, Ali-Hemmati A, et al. Regulation and modulation of PTEN activity. Mol Biol Rep. 2018; 45(6): 2869-2881.

[53]. Sharma D, Jaggi AS, Bali A. Clinical evidence and mechanisms of growth factors in idiopathic and diabetes-induced carpal tunnel syndrome. Eur J Pharmacol. 2018 Oct 15; 837: 156-163.

[54]. Caballero Aguilar LM, Silva SM, Moulton SE. Growth factor delivery: Defining the next generation platforms for tissue engineering. Journal of Controlled Release. 2019; 306: 40-58.

[55]. Verhoeyen E, Roman-Rodriguez FJ, Cosset FL, Levy C, Rio P. Gene Therapy in Fanconi Anemia: A Matter of Time, Safety and Gene Transfer Tool Efficiency. Curr Gene Ther. 2017; 16(5): 297-308.

[56]. Paula R, Rocio B, Angelo L, Oscar Q-B, et al. Targeted gene therapy and cell reprogramming in Fanconi anemia. EMBO Molecular Medicine. 2014; 6(6): 835-848.