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JUSTIFY WHETHER CELL AND GENE THERAPY WAS HALAL

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Abstract

One of the responsibilities of Muslims is to eat halal food. Halal has become a universal signal for ensuring the quality of products and living standards due to obedience and commitment. For Muslims, the availability of halal items is a crucial necessity. As a result, the government is now required to provide halal goods, particularly in nations where the majority population is Muslim. Product awareness affects consumer behavior when selecting items in addition to halal certification. For Muslims, it is essential to have the necessary knowledge while purchasing and consuming halal items. It is crucial since a number of non-Muslim sources in addition to Muslims provide halal-certified goods. The use of pharmaceutical ingredients generated from animals is a significant source of concern for certain customers who have religious or cultural restraints. The use of gene therapy must be adjusted to the type of disease to be treated. Diseases and their genetic relationships must be known first before gene therapy is carried out. If a gene related to a particular disease can be identified, the potential for the disease to be treated will be even greater. Similar with above statement mention that when developing halal pharmaceuticals, it is necessary to investigate alternative materials that meet halal standards while reducing the usage of essential chemicals, as well as several key principles that must be obeyed. As a therapeutic ingredient, everything is regulated by the US Food and Drug Administration regulations. (FDA.gov) The FDA regulates everything regarding cell and gene therapy, starting from safety testing of human cells, the use of animal material for cell and gene therapy purposes, donor eligibility regulations to testing donors of human cells. Regarding whether cell and gene therapy can be categorized as halal or not, it can be seen from whether all the procedures and equipment used have met the requirements in the halal certification process or not.

Keywords: Halal, Muslim, Gene Therapy, Cell Therapy

Introduction

1. Basic Concept of Halal

One of the responsibilities of Muslims is to eat halal food, as Allah declares: O mankind! Eat food that is halal (lawful) or good for you on earth, and do not walk in the devil's (Satan's) footsteps (Quran chapter 2, verse 168). Halal has become a universal signal for ensuring the quality of products and living standards due to obedience and commitment (1). For Muslims, the availability of halal items is a crucial necessity. As a result, the government is now required to provide halal goods, particularly in nations where the majority population is Muslim (2).

The nation with the highest Muslim population is Indonesia. Based to BPS statistics from 2010, there were 207.17 million Muslims worldwide (87.18%). According to the Global Islamic State Report 2018/2019, Indonesia is the country with the highest overall expenditure of $170 billion on halal food

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and drinks (3). In 2017, the food and beverage industry saw a good trend in output growth, reaching 9.93% in both large and medium-sized micro-industries (4). For Indonesia's halal food and beverage business to have a sizable market potential, this industry is necessary.

For both Muslim and non-Muslim customers, the halal certification insignia often serves as a standard (5). This has to do with safety assurances and product hygiene (6). The sole recognized sign of halal food items in Indonesia are the halal certifications granted by LPPOM-MUI. LPPOM MUI has certified 58,959 halal items out of the total 655,725 that are on the market in the past five years (7).

Product awareness affects consumer behavior when selecting items in addition to halal certification. For Muslims, it is essential to have the necessary knowledge while purchasing and consuming halal items. It is crucial since a number of non-Muslim sources in addition to Muslims provide halal-certified goods (8).

The capacity to feel mindful of a situation or an item is known as awareness (9). A Muslim who is halal aware is one who emphasizes eating halal food and has sufficient understanding of what constitutes halal food, as defined by Islamic law (10). The better a person understands the concept of halal cuisine, the more cautious she becomes when purchasing and consuming any food or beverage items that are readily available in the community.

The question of halal has come to the attention of people all across the world, especially devout Muslims who are cautious about what they eat and drink and who buy leather goods, pharmaceuticals, cosmetics, and insurance. Halal items should be consumed, according to Islamic principles [11]. The genuine Hadiths of Islam clearly demonstrate the support of permitted and legal measures for healing ailments. "There is no disease that Allah has not created its treatment for," said the Prophet Muhammad (peace be upon him). This Hadith from Sahih Bukhari emphasizes the notion that there are cures for all diseases, highlighting the significance of getting medical attention.

As a result, Muslim communities are urged to investigate healthcare alternatives in accordance with halal principles, making sure that the medications utilized are devoid of any chemicals that are forbidden or dubious. The Hadiths included in the background section offer a formal and theological viewpoint on the importance of halal medications in Muslim societies. People can support halal ideals and improve the wellbeing of their communities by following medical procedures that align with Islamic teachings [12].

Animals, plants, and synthetic materials are among the many sources of pharmaceutical raw materials [13]. While some medications, such insulin and heparin, come from pig sources [14, 15], other pharmaceutical raw materials come from non-animal sources. The use of pharmaceutical ingredients generated from animals is a significant source of concern for certain customers who have religious or cultural restraints [16–19]. Therefore, it is imperative to find substitute materials in order to address the increasing demand for pharmaceutical products that are suitable for vegetarians and Muslims.

2. Basic Concept of Cell and Gene Therapy

The development of science in the field of molecular biology and biotechnology has a major influence in solving problems faced by humans in various fields. The field of molecular biology began to develop after Watson and Crick in 1953 succeeded in finding the double-stranded structure (double helix) of DNA which became the basis for the development of the branch of biotechnology. Based on the double-stranded structure of DNA, scientists in the field of molecular biology can conduct a series of experiments related to this unique structure (Watson, 1968). The curiosity of scientists eventually led to the realization of a major project called the human genome project in 1990. Genetics Home Reference (2017), from the United States states that the genome is the complete set of DNA possessed by an organism including its original genes. Each genome has all the information an organism needs to grow, develop, and regulate its entire body activities. The human genome project has the main target to find out the complete sequence or sequence of human genes, the function of each gene, and the initiation

of the structural genome so that it can be applied in the world of health (Lin, et al., 2022). The project began publication in 2001, but scientists republished that the human genome project had succeeded in obtaining the entire sequence of human genes in 2003.

The completion of the human genome project opens up an opportunity to identify possible gene sequence abnormalities. The human genome has 23 pairs of chromosomes including 2 sex chromosomes (Figure 1) so that if there is an error in the genome sequence, it can result in disease or abnormalities in the body. With the knowledge of the genome sequence in humans, errors in the sequence will be easier to identify. One of the advantages of human genome sequences is that they can identify genetic abnormalities that cause genetic diseases. Diseases due to genetic disorders can be inherited if the abnormalities occur on the sex chromosomes. However, if abnormalities occur in the body's chromosomes, it will not be passed on to the next generation. The existence of these genetic disorders, the systems and functions of the human body will be disrupted and different from normal. In addition, the completion of the human genome project also allows researchers to identify the presence of genes related to certain functions so that when a function error occurs it can be easier to find a solution. Developments in the field of molecular biology also support developments in the field of biotechnology which can later be utilized by humans in various fields of life including health.

Biotechnology is a technology developed by utilizing organisms, both as a whole and parts only to produce products that are beneficial to humans. The development of modern biotechnology has come to the utilization of organisms at the molecular level and is related to genetic engineering. Genetic engineering involves the manipulation of genes in organisms so that they can be utilized both in agriculture, health, environment, industry, and others (Sharma, et al., 2022). The development of biotechnology in the health sector also supports the development of gene therapy as an alternative solution to health problems. Gene therapy can be used to treat diseases, both genetic and not. The existence of gene therapy provides another option for people with certain diseases to choose treatment methods.

The human genome project sparked advanced research in the fields of molecular biology and modern biotechnology. Human genome mapping and karyotyping allow the engineering of certain genes to produce the expected gene expression. Genetic engineering is a system of genetic modification of the genome of organisms using methods in biotechnology. Genetic engineering allows manipulation of genes so that gene expression can be controlled and the product can be utilized for specific purposes (Tsai, et al., 2022). This technique has been widely used to engineer functional genes and has also been widely used to produce transgenic organisms (Genetically Modified Organism).

The human karyotype (Figure 1) describes the entire human genome, visualizing cells, and individual chromosomes (Dutra, 2024). Genetic modification allows changes in base pairs, cutting of certain DNA fragments, or the addition or insertion of a gene. DNA from an organism is isolated and then combined with other target DNA. Genetic engineering is used by researchers to improve or even modify the characteristics of gene expression in an organism, including gene modifications that allow for the prevention and treatment of certain diseases. In the health sector, genetic engineering can also be used to treat diseases by means of gene therapy. Scientists in the field of biotechnology conduct a lot of research in the field of gene therapy, including replacement of mutated genes with healthy gene copies, inactivation (*knocking off)* of mutated genes, and the introduction of new genes to help overcome certain diseases (El-Kenawy A, et al., 2019). Lu X, et al., (2023) states that gene therapy is widely used for diseases caused by recessive single-gene disorders, such as cystic fibrosis, hemophilia, muscular disorders, and sickle cell anemia; as well as other diseases, such as cancer and AIDS (Acquired Immunodeficiency Syndrome).

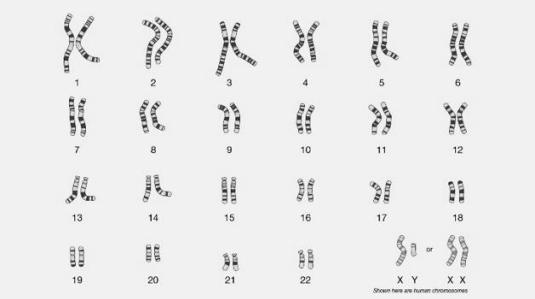


Figure 1. Karyotypes of the human genome (Dutra, 2024)

Gene Therapy

Gene therapy technology is inseparable from the principle of genetic engineering to produce GMOs (Genetically Modified Organisms) or commonly known as transgenic organisms. The idea for gene therapy is quite unique, namely by adding normal genes to parts of the genome that have mutations or damage so that the function of these genes can be improved (Herrick, 2024). The genetic engineering process in gene therapy technology includes the following stages: isolation of the target gene, insertion of the target gene into the transfer vector, transfer of the vector that has been inserted the target gene to the organism to be treated, transformation in the cells of the target organism. Target genes that have been inserted in the treated organism are expected to be able to replace the function of abnormal genes that cause disease in patients.

The use of gene therapy must be adjusted to the type of disease to be treated. Diseases and their genetic relationships must be known first before gene therapy is carried out. If a gene related to a particular disease can be identified, the potential for the disease to be treated will be even greater. Britanica (2024), states that genes are functional units related to heredity that have a specific sequence of bases. The sequence of these bases will later determine the type and function of the protein expressed. When a gene undergoes a mutation or change in its nitrogenous base sequence, the encoded protein will not be able to carry out its normal function and cause a genetic disorder. Gene therapy is here to be the latest therapeutic solution in diseases both inherited and not. Cornetta, et al., (2024), stated that as of December 2022 there have been as many as 592 clinical trials using gene therapy worldwide. Most clinical trials of gene therapy are conducted in patients with cancer and cardiovascular disease. The large amount of research in the field of gene therapy allows the development of this therapeutic method as an effective alternative treatment.

The gene therapy method began to be used in 1990 when the National Health Institute of the United States inserted the normal adenosine deaminase (ADA) gene into the leukocytes of acute combined immune deficiency patients aged 4 years. ADA gene therapy was approved by the Food and Drug Administration (FDA) in the United States in the same year (Aitui, et al., 2024). After initiation, research on gene therapy has grown. Gene therapy includes the use of nucleic acids both DNA and RNA in the treatment, treatment, and prevention of disease in humans. Based on the type of disease, gene therapy can be done by transferring functional genes that can replace missing or malfunctioning genes so as to reduce the negative effects of the condition (Freitas, et al., 2022).

Gene therapy in humans is defined as the transfer of nucleic acids in the form of DNA to the patient's somatic cells so that the gene has a medicinal effect on the patient's disease, both by correcting abnormalities in genes and over expression of proteins encoded by these genes. According to El-Kenawy A, et al., (2019), gene therapy has been widely used for the treatment of cancer, cardiovascular disease, infectious diseases, decreased body metabolic function, lymphatic disease, to radiation injuries and postoperative healing. However, it does not rule out the development of gene therapy to treat other types of diseases.

Rogers and his team were the first to demonstrate the concept of gene transfer using viruses as vectors. Rogers used the wild-type Shope papilloma virus to transfer arginase genes in two patients with urea cycle disorder, hyperargininemia (Carvalho, et al., 2017). SPV or Shope Papilloma Virus is also known as CRPV (Cottontail Rabbit Papilloma Virus) or Kappapapillomavirus 2. This virus results in keratinized carcinoma that metastasizes and interferes with the host's ability to eat. Papillomavirus belongs to the Papovaviridae Family which is a DNA virus that initiates the emergence of tumors. Rogers' research hypothesis states that the Shope papilloma virus can code for the gene responsible for arginase activity and this gene can be transferred to the body of hyperargininemia. However, the results of the study stated otherwise. There is no change in arginine levels or clinical condition of the patient (Asrani, et al., 2018).

Types of Gene Therapy

There are two main types of gene therapy, including embryonal cell gene therapy (germ line gene therapy) and body cell gene therapy (somatic gene therapy) (Chancellor, et al., 2023):

a. Embryonal cell gene therapy *(germ line gene therapy)*

In this sex cell gene therapy, male sex cells (sperm) and female sex cells (ova) are used which are modified by insertion of functional genes integrated with the genome.

b. Body cell gene therapy *(somatic gene therapy)*

In this body cell gene therapy, functional gene transfer is carried out into the patient's body cells so that malfunctions in the organs can be repaired. Kohn, et al., (2023) state that gene therapy of body cells is specific to each patient and is not passed on to the next generation.

In gene therapy using the germ line, genes will be transferred into the ovum or zygote so that when the ovum is fertilized with sperm to form a zygote, the zygote will develop by carrying the gene that has been inserted previously so that the new organism formed already has a gene that functions in the intended therapy. Embryonal cell gene therapy is usually performed on animals to form transgenic animals. This type of gene therapy allows genetic improvements that will begin to be seen when embryonal cells have developed into new individuals.

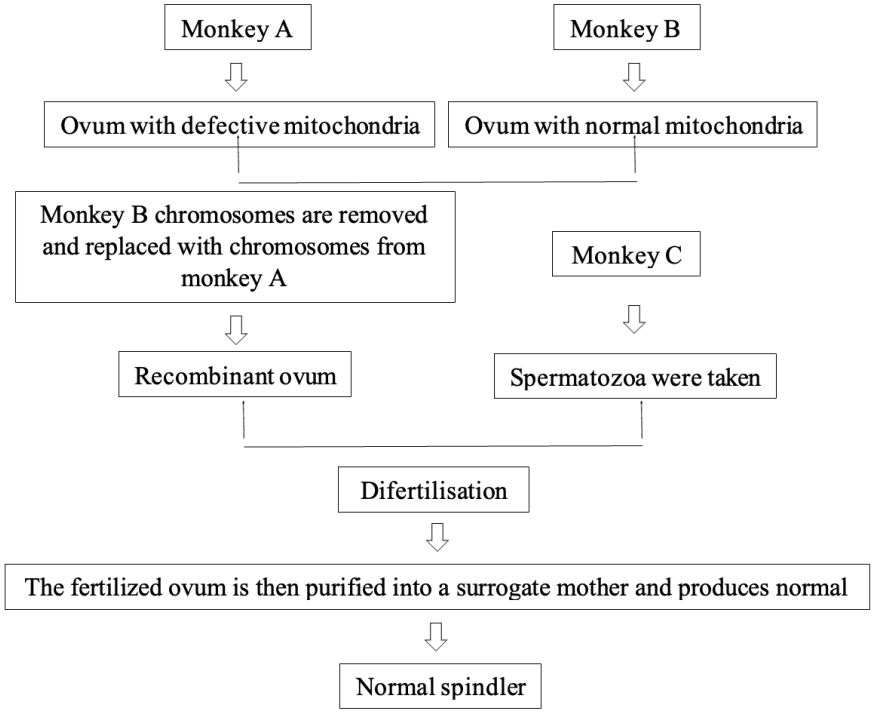


Figure 2. Embryonal cell gene therapy in Spindler (third monkey born from embryonal gene therapy (Oregon National Primate Research, 2015)

Figure 2 describes the stages in embryonal cell gene therapy in monkeys. There are two monkeys, namely monkey A which has abnormalities in its mitochondria and monkey B which is a normal monkey. To produce normal monkey A offspring without any abnormalities in mitochondria, gene therapy is carried out through embryonal cells. The chromosomes in monkey A's ovum are taken and then inserted into the ovum of monkey B which has normal mitochondria. The process of taking and inserting is carried out ex vivo. The ovum of monkey B that has been inserted in monkey A's genetic material is then fertilized by sperm from monkey C which is similar to monkey A. The ovum that has been fertilized by sperm is then inerted into the uterus of another monkey that acts as a host parent to then facilitate the embryo to grow and develop. The embryo will then be born with conditions without mitochondrial abnormalities.

In gene therapy with somatic cells, DNA containing genes for therapeutic function is transferred into somatic cells both in vivo and ex vivo. The gene transfer is usually aimed directly at a specific organ or tissue so that the gene can be expressed properly. In gene therapy with somatic cells will also not affect embryonal cells.

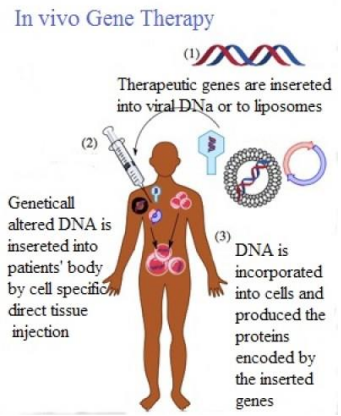


Figure 3. In vivo gene therapy (Samanthi, 2017)

In vivo gene therapy still uses vector assistance to transfer target genes into the tissues or organs of patients with certain diseases. Figure 3 shows the existence of a gene transfer vector in the form of a virus that is modified into a recombinant virus by inserting DNA with the target gene for therapy through the recombinant DNA technology method. The viral vector that already contains the target gene is then injected into the patient's body directly into the target tissue or organ where the gene for therapy is needed or expressed. In vivo gene therapy involves a transduction process directly in the body, is easier to implement and develop on a certain scale, and does not require special facilities because gene injection or transfer can be done by general methods or using a biolistic gene gun. However, Hosseinkhani, et al., (2023), stated that in vivo gene therapy has lower specificity and efficiency than ex vivo gene therapy.

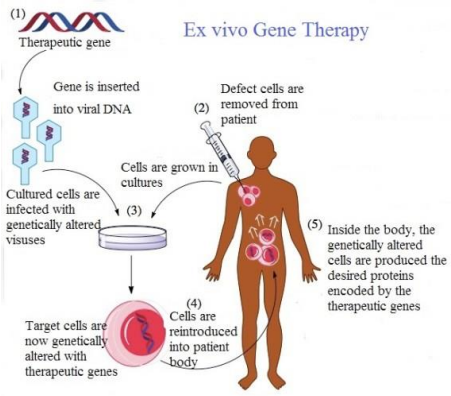
Gene therapy ex vivo has more complex stages than in vivo. This therapy involves transduction in the laboratory with certain specific conditions so that it requires more complete laboratory facilities. This ex vivo method also results in a lack of a population of proliferated cells. Figure 4 shows the stages in the ex vivo gene therapy method consisting of several steps, namely:

a. Isolation of cells that have abnormal genes from patients with certain diseases.
b. Isolated cells are grown on certain culture media that are in accordance with cell characteristics.
c. Target cells that have been cultured are then infected with retroviruses that contain recombinant genes in the form of normal genes to replace abnormal genes in the cells.
d. Production of rDNA from recombinant RNA (if the viral vector is a virus with genetic material in the form of RNA) by reverse transcription.

e. Normal gene translation in the cytoplasm of cells produces proteins responsible for damaged genes (integration occurs between target genes for therapy with genes in cultured cells.

f. Selection, multiplication, and testing of cells that have been transfected to obtain normal cells whose abnormal genes have been successfully replaced by new genes.

g. Reinjection of cells that have been successfully engineered with gene therapy into the patient's tissues or organs.



Gambar 4. Terapi gen secara ex vivo (Samanthi, 2017)

Gene Transfer

The success of gene therapy is strongly influenced by several factors, especially the efficiency of gene transfer and expression in target cells. Transfer of functional genes into target cells in gene therapy requires competent vectors and can carry target genes well. Normal genes are inserted into the organism's genome to replace the abnormal genes that cause disease. According to Papapetrou, et al., (2016), the gene insertion stage is the most difficult in all stages of gene therapy because at this stage determines the success of gene therapy itself. The vector to be used for gene insertion in gene therapy must meet several characteristics, namely having high specificity, being able to efficiently insert one or more genes of a certain size, not recognized by the patient's immune system, and can be purified in large quantities. The target gene carrier vector must not be recognized by the patient's body system so that it will not cause allergic or inflammatory reactions. The insertion of the target gene via the vector must be safe for the patient and the environment. Gene insertion vectors must also be able to facilitate target gene expression as long as therapy is needed, even throughout the patient's lifespan.

Gene insertion in gene therapy generally uses vectors in the form of viruses (viral vectors) or compounds or molecules other than viruses (non-viral vectors). Gene transfer in gene therapy using vectors in the form of viruses is referred to as transduction while transfer with vectors other than viruses is referred to as transfection. The ideal vector should be able to deliver genes to specific cell types, accommodate foreign genes to adjust their size, achieve the level and duration of transgenic expression that is able to repair gene damage or abnormalities, and be safe and nonimmunogenic (Quintana-Bustamante, et al., 2022).

The ideal characteristics that must be possessed by the type of virus that will be used as a vector in gene therapy must have the ability to be produced in high titers easily and efficiently, have no toxicity to target cells or other effects that can negate their ability to transduct genes into target cells, can integrate with specific sides of the target cell that allows expression for gene therapy, have good transduction capacity in specific cells, and must have the ability to infect cells that can still proliferate. Viruses used as gene-carrying vectors must also have the ability to evade the immunity of target cells (Shirley, et al., 2020).

If a virus has been developed and has ideal characteristics as mentioned, it is possible to use it as a gene-carrying vector in gene therapy.

According to Wang & Shao (2023), viruses that are used as target gene carrier vectors in gene therapy must be harmless viruses even though the virus itself can evolve and deliver genes to human cells through pathogenic pathways. However, the pathogenicity of the vector virus must be ensured that it will not have side effects on patients treated with the gene. Lundstrom (2023), stated that some viruses used as vectors in gene therapy include retroviruses, adenoviruses (types 2 and 5), adeno-associated virus (AAV), herpes virus, smallpox virus, human foamy virus (HFV), lentivirus, and several other types. Vectors in the form of viruses must be modified genomes by cutting certain sequences so that their pathogenicity can be reduced or eliminated. Vectors in the form of viruses must be safe when used in the gene therapy process so that the target gene to be used as a substitute for the abnormal gene can be expressed properly without causing side effects for patients treated. Gene therapy is often unsuccessful due to errors in the preparation of vectors to be used for gene transfer. The viral vector used for gene transfer must be adapted to the genome of the target cell, for example Retroviruses have a good capacity to integrate with the genome of mammalian cells both in vivo and in vitro (Poletti & Mavilio, et al., 2017). The process of gene recombination must also be considered so that normal gene insertion can be successful and can be used as a substitute for abnormal gene function.

The percentage of frequently used viral vectors according to Wiley and Sons, (2017) is shown in Figure 5. Adenovirus is the main vector that is widely used as a vector for gene transduction to replace abnormal genes in a disease. In addition, retroviruses are also widely used as vectors in gene therapy in accordance with their ability to transduce target genes that can be used to substitute abnormal genes that cause certain diseases. Both types of viruses are considered the best vectors and are easily applied in gene therapy. Papapetrou & Schambach, (2016) stated that adenovirus is a virus with nucleic acid in the form of DNA while retroviruses are viruses that have nucleic acids in the form of RNA so that it takes longer for gene expression.

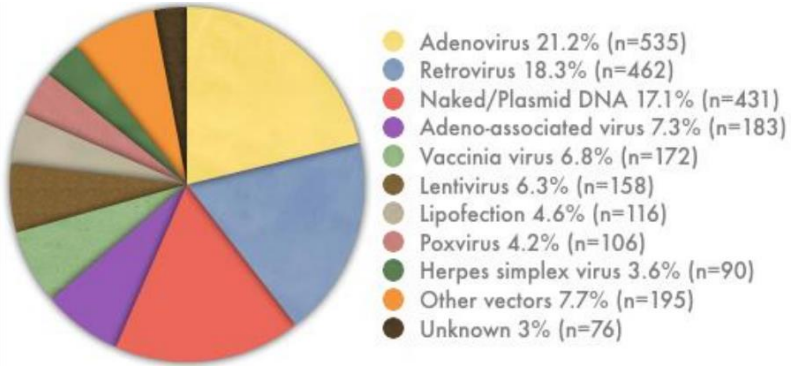


Figure 5. Percentage of vector types used in gene therapy (Wiley and Sons, 2017)

Zittersteijn, et al., (2021) states that RNA in retroviruses can be transcribed back into complementary DNA (cDNA) so that target genes can be inserted for gene therapy. The three viral vectors widely used in gene therapy are:

a. Adenovirus

Adenovirus belongs to icosahedral viruses measuring between 90–100 nm, has 252 capsomeers with 240 hexons and 12 pentons. Adenoviruses have fibrous proteins extending out of the penton and these structures are known to support adenoviruses' ability to recognize and bind to target cell receptors (Figure 6) The adenovirus genome consists of linear, double-stranded, and unsegmented DNA between 26–45 Kbp. The adenovirus genome has at least 22–40 different genes (Mat Isa, et al., 2019). Adenovirus has the ability to infect human cells and allow the emergence of diseases in the respiratory, digestive, and sensory systems (Ricobaraza, et al., 2020).

Adenovirus infection is initiated by the high binding affinity between fibrous proteins on pentons with target cell surface receptors, such as CAR (coxsac-kievirus and adenovirus receptor) and MHC-I

α2 domain followed by interaction between pentons with αvβ3 and αvβ5 integrin proteins (Elina, et al., 2022).

Bulcha, et al., (2021) stated that adenovirus is a DNA virus that has a good ability to transfer target genes to cells, high transduction efficiency for different cell types and has a fast gene expression time to support the effect of gene substitution in therapy, can facilitate gene expression effectively in both proliferating and non-proliferating cells, and has a high enough efficiency to infect tar-get cells. However, adenoviruses have high specificity against the type of target tissue or organ that can be infected so that it cannot infect tissues or organs other than the target. Adenovirus also has immunogenicity that is high enough so that it tends to be easily recognized by the patient's immune system and results in a reduced ability to insert genes into the patient's body.

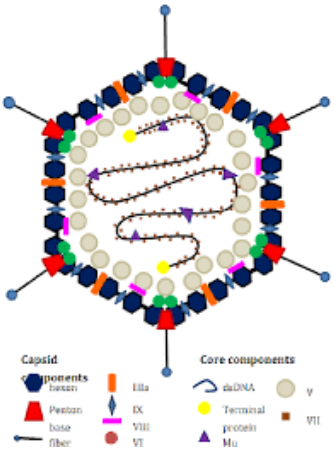


Figure 6. The structure of adenoviruses consists of two main proteins, namely the core protein and the capsid protein (Waye & Sing, 2010)

b. Retrovirus

Retroviruses are one of the viruses that infect animal cells, including humans. The first time the identification of retroviruses was successfully carried out in infection of chickens as one of the oncogenic factors. Retroviruses have spherical structures between 80–100 nm in diameter (Figure 7). Retrovirus virions have reverse transcriptase enzymes, integrases, and also have two identical RNA subunits that bind to form dimer bonds to their capsids. Retroviral RNA will be re-transcribed when this virus infects the host cell (Köppke, et al., 2024).

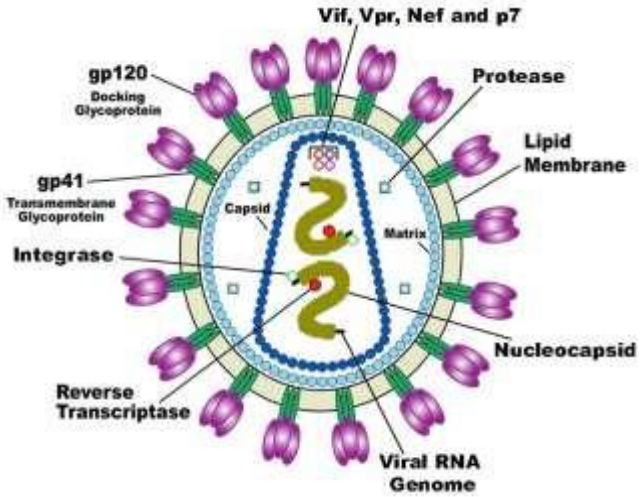


Figure 7. Structure of retroviruses (US National Institute of Health, 2016)

Retroviral vectors are one type of viral vector that is widely used in embryonal and somatic cell gene therapy. Retroviruses can infect dividing cells because they have the ability to penetrate nuclear pores during the mitotic cycle (Figure 8). Based on this ability, retroviruses are widely used for in situ gene therapy (Vagas, et al., 2016). The genetic material of retroviruses tends to be less stable because it is RNA. To be able to insert the target gene to be transferred to the target cell, retrovirus RNA must be re-transcribed first to form cDNA (complementary DNA) before inserting the target gene. Retrovirus cDNA can be integrated with host or patient DNA efficiently to then be referred to as a provirus. Proviruses have the ability to be transcribed and translated like any other gene. The results of provirus expression already contain target genes to be used for therapy as well as genes from the retrovirus itself.

Chancellor, et al., (2023), stated that there are weaknesses in the use of retroviruses as transfer vectors in gene therapy. This weakness is the possibility of insertion of viral genes in any genome fragment on the host cell where it can cause mutations if the insertion of viral genes occurs in the middle part of the host cell genome. In addition, uncontrolled insertion can result in uncontrolled cell division that occurs so that it can lead to cancer. However, several solutions have been studied to minimize the weakness of the retrovirus vector.

The addition of zinc finger nuclease or the inclusion of beta globin sequences as a locus of control can ensure the insertion and integration of genetic material in the appropriate sequence.

c. Adeno-associated virus (AAV)

Adeno-associated virus (AAV is an envelop virus (Figure 9). This virus is quite small (25 nm) and has a genome in the form of linear single-stranded DNA. AAV infection will only be effective if there are helper viruses, both adenovirus and herpesvirus (Weitzman & Linden, R.M., 2011). AAV has a genome size of 4.7 Kbp and has rep and cap genes. The rep gene encodes non-structural proteins that will play a role in genome replication, packaging, and integration, while the cap gene encodes structural proteins such as VP1, VP2, and VP3 that will combine to form a viral capsid that plays a role in gene transfer (Drouin & Agbandje-McKenna, (2013).

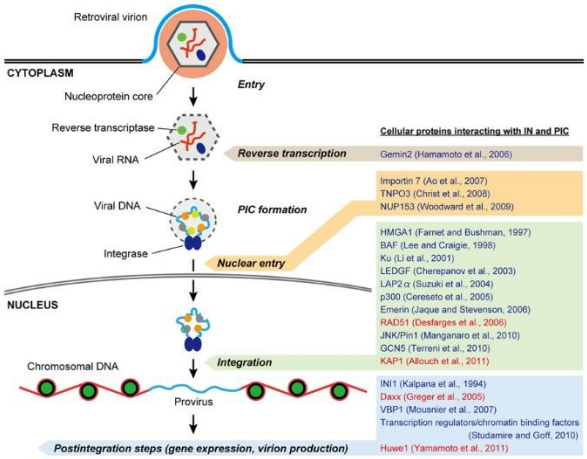


Figure 8. The process of integration of retrovirus genetic material with the host (Suzuki, at al, 2012)

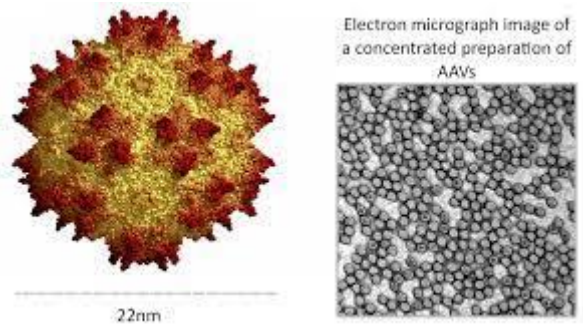


Figure 9. Adeno-associated virus structure (Weitzman & Linden, R.M., 2011)

Gene therapy with AAV vectors is commonly used in in situ therapy because the integrated genes present in recombinant AAV can be directly infected in host cells. In the target host cell, recombinant genes from the vector are released to be expressed into specific functional proteins that can substitute abnormal genes in the cell. In the presence of functional gene expression that has been inserted with the AAV vector (Figure 10), diseases due to gene abnormalities can be treated.

The method of gene transfer through viral vectors has indeed been widely done, but in gene therapy, this method still has some weaknesses. Vectors in the form of viruses are feared to be virulent again when in the patient's body so that they can actually endanger the patient's health. On June 24, 2010, Eureka Network conducted a project called EUREKA project E! 3371 Gene Transfer Agents that examine compounds derived from the amphiphilic cation 1,4-dihydropyridine/ 1,4-DHP (cationic amphiphilic 1,4 dihydropyridin) that can be used as a normal gene introduction into the cell nucleus and replace previously damaged genes. The project allows the development of nonviral vectors to insert genes in gene therapy in certain diseases. This vector product has advantages that are considered potential to be developed, namely that it is ready to be produced on a large scale, more effective than other organic compounds, and because its characteristics are different from viral vectors, the recipient's immune resistance can be avoided. The existence of this project provides another alternative in gene therapy, namely by using vectors other than viruses.

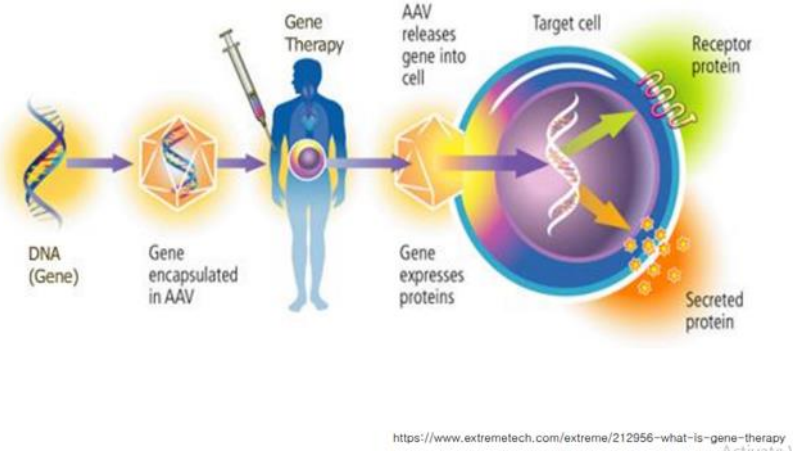


Figure 10. Gene therapy with AAV vectors (Wiley and Sons, 2017)

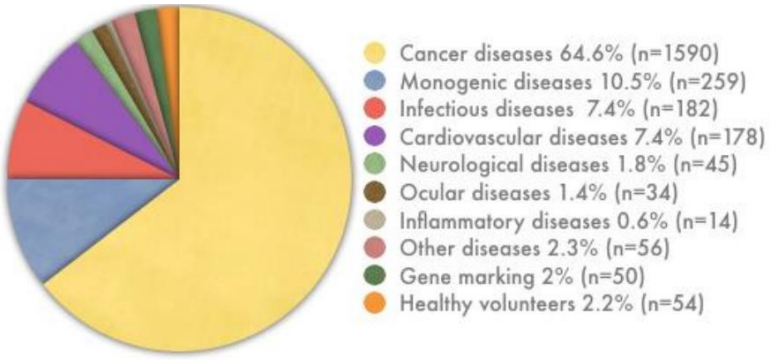


Figure 11. Some diseases that can be treated with gene therapy (Wiley and Sons, 2017)

Applications of Gene Therapy

Gene therapy can be used as an alternative treatment for diseases that have not been found a cure or vaccine. Figure 11 shows several types of diseases that are assumed to be curable with gene therapy. These diseases can be treated if the genes associated with the emergence of the disease have been successfully identified and functional genes can be found that can substitute the abnormal gene. The first order of disease that genes are treated with is cancer. Some types of cancer, especially those associated with abnormalities in a gene, have been successfully treated by inserting certain functional genes.

3. Cell and Gene Therapy in Indonesia

For almost ten years, stem cell research has gained popularity in Indonesia. The range of study includes both human and animal trials in addition to in vitro investigations. But there was no proof of its trend. The current state of cell and gene therapy research is summed up by Imam Rosadi et al. After being obtained from Scopus, the data for the paper were subjected to bibliometric analysis. Data analysis using statistics was done. The findings demonstrated that stem cell research has been steadily growing in Indonesia throughout time, with the bulk of publications concentrating on the fields of medicine, pharmacology, toxicology, and pharmaceutics, as well as biochemistry, genetics, and molecular biology. A total of 260 relevant articles had been published, it was discovered.

The authorship network analysis revealed nine author groups, with Rantam being the most productive writer. In the papers that were examined, the terms "stem cells," "culture," "proliferation," "differentiation," and "tissue engineering" were most frequently utilized. All things considered, this study offers insightful information on how stem cell research has evolved in Indonesia and could influence future funding and research choices in this area.

HALAL CERTIFICATION

According to Muslim teachings, halal certification provides a security guarantee that food products are fit for consumption by Muslims (9). Halal certification is the equivalent of the halal certificate that MUI issues following a rigorous evaluation based on sharia law. The procedure entails a comprehensive and meticulous examination starting from the beginning; this led to the creation of halal status through a MUI fatwa and covered the preparation, ingredients, cooking, serving, kitchen, hygiene, and labeling. The halal mark featured on the product package (7) indicates that a product has passed the MUI halal certification exam.

Beyond national and Islamic borders, the idea of halal is becoming a global concern for manufacturers of drugs, food, cosmetics, and cosmetics as well as for consumers. Moreover, its importance has gone beyond regional and religious connotations, attracting broad interest in the manufacturing and use of diverse goods [1,2]. The 2.4 billion Muslims who shop worldwide are

becoming more conscious of and demanding halal pharmaceutical and cosmetic products [3,4]. Estimates indicate that until 2024, the worldwide halal market will increase at a compound annual growth rate of 6.8% [5]. This idea highlights the necessity of "toyyib," which calls for items to satisfy high standards of quality [4,5,8], and the significance of following authorized Shariah procedures in products that are consumed [6,7].

It is imperative to incorporate a halal assurance system at every stage of the production process to guarantee the provision of products that satisfy quality benchmarks [9]. This idea, as applied to the Islamic context, concerns the permissibility of consuming particular products because non-halal goods have the potential to negatively impact customers' behavior and health [10,11].

The first step towards satisfying the demand for halal products is the approval of halal labeling [21]. Transparent product labeling is necessary to raise customer awareness and boost the demand for halal products. The halal mark, even on over-the-counter medications, can enable customers to make knowledgeable decisions regarding their purchases [21, 22]. Future expansion will depend on the creation of goods that prioritize Muslim customers and follow the "halal-first" approach.

This is so because it is a fundamental human right to have access to medications that align with one's values. The International Pharmaceutical Manufacturing Group (IPMG) has opposed the proposal to make halal labeling on pharmaceutical products mandatory in Indonesia, arguing that the small size of the country's market makes it difficult to attract investors to the halal product manufacturing industry. This calls for cooperation and communication amongst stakeholders in the search for a solution that satisfies the demands of the market and the industry.

When developing halal pharmaceuticals, it is necessary to investigate alternative materials that meet halal standards while reducing the usage of essential chemicals [12, 38–41]. Regulatory agencies may also need halal certification to guarantee that the goods and excipients used meet the needs of particular customers or marketplaces. As a result, drug manufacturers are urged to reveal the source of their ingredients and endeavor to provide substitutes for people whose religious convictions or personal preferences prevent them from consuming pork-derived goods.

Production of halal products adheres to several key principles:

1) All ingredients must be safe to eat and free of ethanol, blood, pork, and animal parts—including human parts—that are carnivorous and omnivorous. Under some conditions, the MUI Fatwa in Indonesia allows the use of non-khamr sources of ethanol, such as synthetic or industrially fermented ethanol. Additionally, it permits a tolerance for beverages with an ethanol level of less than 0.5% when alcohol poses no medical risk. This guideline guarantees that products with halal certification can contain allowed ethanol levels while upholding consumer safety and adhering to Islamic law.
2) Tight hygiene protocols need to be followed in order to reduce the possibility of contamination from potentially hazardous, ritually unclean, or impure substances.
3) All aspects of production, including cultivation and distribution, must abide by halal and Sharia law.
4) To avoid any mixing, halal and non-halal production must be physically isolated from one another.
5) It is imperative to prevent any possible cross-contamination between non-halal and halal materials and products [45].

Islamic dietary regulations stipulate that animals used for food or medicinal purposes must be slaughtered using a certain technique known as halal slaughter. This technique involves making a quick cut to the throat with a sharp knife, disconnecting the carotid arteries and jugular veins without damaging the spinal cord. To be precise, an animal designated as halal has to be alive and in good health when it is slaughtered, and before it is chopped, Allah's name has to be uttered. Muslims can consume

the animal or utilize it as medicine because it complies with these regulations, making it halal. There are notable differences between the normal approach and the halal certification process for pharmaceutical items, despite certain similarities [6,38,46,47].

Because pharmaceutical products are unique and technically complicated, each medicine needs to be evaluated separately based on its intended use case, formulation, and technique [7]. Marine animals are regarded as halal, while synthetic materials are safe for customers and free of dirt (najis). Halal pharmaceutical ingredients are components obtained from plants, soil, water, and animals slaughtered in accordance with Islamic law. Manufacturers should, as a general rule, obtain halal certification from suppliers for every ingredient [5].

An Islamic concept known as istiklah describes how a substance can be changed by combining it with other substances to create new goods that have a different form and content [48]. The Shariah allows for modifications to the controlling rule in cases where a prohibited substance undergoes transformation. For instance, istihalah comes into play when alcohol turns into vinegar either naturally or chemically. Among the many crucial factors are the following: 1) The process is not intrinsically impure; it only makes filthy things pure when converted. On the other hand, wine-based vinegar is regarded as pure. 2) Impurity growth medium processes need to be purified, and 3) substances that come from pigs or their derivatives are usually forbidden. It is important to seek assistance because different scholars may have different interpretations [48–50].

COULD CELL AND GENE THERAPY BE THE HALAL PRODUCT?

Similar with above statement mention that when developing halal pharmaceuticals, it is necessary to investigate alternative materials that meet halal standards while reducing the usage of essential chemicals, as well as several key principles that must be obeyed.

As a therapeutic ingredient, everything is regulated by the US Food and Drug Administration regulations. (FDA.gov) The FDA regulates everything regarding cell and gene therapy, starting from safety testing of human cells, the use of animal material for cell and gene therapy purposes, donor eligibility regulations to testing donors of human cells.

Regarding whether cell and gene therapy can be categorized as halal or not, it can be seen from whether all the procedures and equipment used have met the requirements in the halal certification process or not, for example, whether it involves "haram" materials such as pork, animals that have been slaughtered improperly. mentions the name of Allah, is ethanol free, and the room is not mixed with other experiments that contain non-halal materials.

ANALYSIS OF GLOBAL CGT CLINICAL TRIAL WITH OR WITHOUT HALAL CERTIFICATION

As a result of interviews with several colleagues implementing cell and gene therapy, halal certification is very necessary, but not all cell and gene therapy clinics take care of halal certification for their clinics. In Indonesia, if you meet the standards for opening a clinic from the Ministry of Health, and Licensing Service and fulfill the necessary documents, the clinic can still operate properly.

Apart from Indonesia, several Muslim countries are also concerned about halal cell and gene therapy, such as Malaysia, Brunei Darussalam, UAE, but it is still not really clear how they manage the halal certification of cell and gene therapy clinic.

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Author Contributions

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