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Review on gene therapy and its application in veterinary medicine

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Abstract

The discovery of gene therapy is a pillar of contemporary science and has turned into a revolution in medical treatment. While there are some limitations associated with this approach, its advantages continue to grow. Gene therapy is a therapeutic approach that involves transferring DNA into an individual to correct defective genes and treat conditions not responding to conventional medication. Over time, the scope of gene therapy has expanded from a primary focus on treating monogenetic disorders to a more complex approach that includes induction of cell death in disease management. However, efficient delivery of enough genetic material to target cells or tissues and maintaining gene expression for the desired duration are the challenges in gene therapy. There are numerous ways to transfer genetic material to specific cells or tissues. They can be broadly categorized into viral and non-viral techniques. Among viral vectors adenovirus (AV), adeno-associated virus (AAV), herpes simplex virus (HSV), lentivirus (LV), and poxvirus have been extensively studied. Non-viral delivery methods include extracellular vesicles, bacteria, nanoparticles, and direct injection of naked DNA. Advancements in genetic engineering have enabled the development of species-specific gene therapies for animals, while reducing risks of unintended consequences and adverse effects. In addition, of providing new and modern choices of treating a variety of animal ailments, gene therapy can potentially address the issues such as pet overpopulation. Numerous animal health issues, including hemophilia, cardiovascular disorders, diabetes, muscular dystrophy, lysosomal storage disorders, eye problems, cancer, and infectious diseases have recently been treated by gene therapy. Though considerable success have been achieved in human medicine, gene therapy still remains underutilized in veterinary medicine. Therefore, broader application across different species and targeted veterinary research is essential to fully realize its potential in animal health care.

1. Introduction

Theodore Friedmann and Richard Roblin were first to put forth the concept of gene therapy as a means of treating human diseases in 1972. This idea was preceded by Stanfield Rogers' suggestion in 1970 to correct inherited abnormalities by substituting functional deoxyribonucleic acid (DNA) for defective DNA (Athanasopoulos et al. 2017). However, for decades, the idea of gene therapy was not realized because of the lack of effective techniques for introducing foreign DNA into cells. In 1981, a major breakthrough occurred when Shimotohno and Temin (1982) reported the first successful viral recombination of foreign DNA in mammalian cells using retroviruses. However, wider adoption of this technique remained limited because of inefficiency in the synthesis of these retroviruses. Gene therapy has the potential to successfully treat the underlying causes of monogenic and other genetically determined diseases by targeting defective genes (High and Roncarolo 2019). It is a therapeutic approach which circumvents disease symptoms by delivering foreign genes into specific cells to either complement or rectify defective genes, or induce targeted cellular death. The four main strategies used in gene therapy are gene replacement, augmentation, blockade, and gene modification (Navarro et al. 2016).

Currently, there are two main types of gene therapies – *in vivo* or *ex vivo*. In *in vivo* gene therapy, therapeutic genes are specifically injected into target organs or directly infused into the patient's bloodstream (Doudna 2020). However, in *ex vivo* gene therapy, also known as cell therapy, the target cells from the patient are extracted, cultured in the laboratory, and genetically modified by using vectors that carry therapeutic or corrective genes. These modified cells are then reintroduced into the patient (Sorrentino 2020). Viral vectors are the most effective vectors for delivering genes. Commonly used viruses in gene therapy are retroviruses, lentiviruses (LVs), adenoviruses (Ads), and adeno-associated viruses (AAVs) (Ramsey et al. 2021). Despite their effectiveness, viral vectors have significant drawbacks, such as limited gene loading capacity, immunogenicity, and potential toxicity. These drawbacks have prompted the development of non-viral vectors, which provide nontoxic and effective systems for delivering genes because of their flexible manufacturing, simple chemistry, and safe toxicity profiles (Mintzer and Simanek 2009). These carriers condense DNA/RNA molecules into nano- to micron-sized complexes through electrostatic interactions, shield the payload from enzymatic/nonenzymatic degradation, and improve cellular communication through electrostatic interactions.

The primary challenge in effective gene therapy lies in the efficient delivery of the therapeutic genes to the targeted tissue or cell (Palffy et al. 2009). The successful execution of gene therapy relies on two

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essential factors - firstly, identification of an appropriate gene capable of alleviating disease symptoms, secondly, precise delivery of that gene to the location where the gene expression product is needed for effective treatment and with minimum off-target effects (Acland et al. 2005). Human-grade pharmaceuticals are routinely employed in modern veterinary medicine, and large animals are often used as models in the medical research to develop novel treatment approaches. Advances in genetic manipulation in veterinary medicine makes it possible to develop species-specific therapies; which can be tailored to the animal's immune system or the unique metabolic characteristics of the animal to ensure improved therapeutic outcomes with minimum adverse effects. While, regenerative medicine and gene therapy are predominantly concerned with treating human disease conditions, animals are still generally considered as models for testing human-targeted drugs. Hence, the objectives of this review are: a) to describe the different types and principles of gene therapy, b) to describe the current and potential applications of gene therapy in veterinary medicine.

2. Types of gene therapy and steps

In both *in vivo* or *ex vivo* types of gene therapy, identifying an effective technique for transfecting genetic constructs into curative cell lines that ensures sustained and safe expression of the target gene is a significant challenge for gene therapy. For sustained expression successful transport of genetic material across the nuclear membrane is required, which adds another layer of complexity in addition of crossing plasma membrane. Therefore, an optimal delivery method must therefore account for both cytoplasmic and nuclear entry. Preventing unintended interference with endogenous gene expression is another problem, which may otherwise lead to off-target effects, genomic instability, or other adverse outcomes (Naldini 2011).

2.1 In vivo gene therapy

In situ gene therapy involves injection of genetic material directly into a target organ or into the patient's circulation. In *in vivo* gene therapy, a vector is often required to pack and deliver the therapeutic gene to the target cells. Genetically modified viruses are essential vectors in modern medical research due to their efficient gene transfer (Doudna 2020). Targeting organs *in vivo* is particularly appealing because *ex vivo* gene therapies, which involve collection, culture, genetic modification, and transplantation, presents complex practical and regulatory concerns. However, immunological susceptibilities to vector components and unintended germline modifications are problems with *in vivo* approaches (Dunbar et al. 2018). Further disadvantages of *in vivo* gene therapy are its relative imprecision, inefficiency, and possibility of systemic exposure to the transfer vector. Such systemic exposure may result in cancer and inflammation (Smith 2008). Some of these difficulties have been overcome, opening the door for future advancements that target other body tissues like the musculature and nervous system. Hence, such encouraging clinical results, particularly in delivery of genes to the liver and the pigment epithelium of the retina, have demonstrated the feasibility of *in vivo* gene therapy and expanding therapeutic scope of this technology (Dunbar et al 2018).

2.2 In vitro gene therapy

In *ex vivo* gene therapy, cells are genetically altered outside the body and subsequently transplanted, either temporarily or permanently, into the target patient. This process is utilized to produce therapeutic proteins or replace damaged or dysfunctional cells (Naldini 2011). Without exposing the recipient directly to the gene transfer agent, this therapeutic approach allows for a comprehensive characterization of the modified cell products before administration. Typically, *ex vivo* gene therapy process involves the isolation of patient's cells followed by autologous reintroduction after genetic modification. Furthermore, allogeneic cell lines, derived from donors, can be genetically modified and stored for future therapeutic use (Mangraviti et al. 2015).

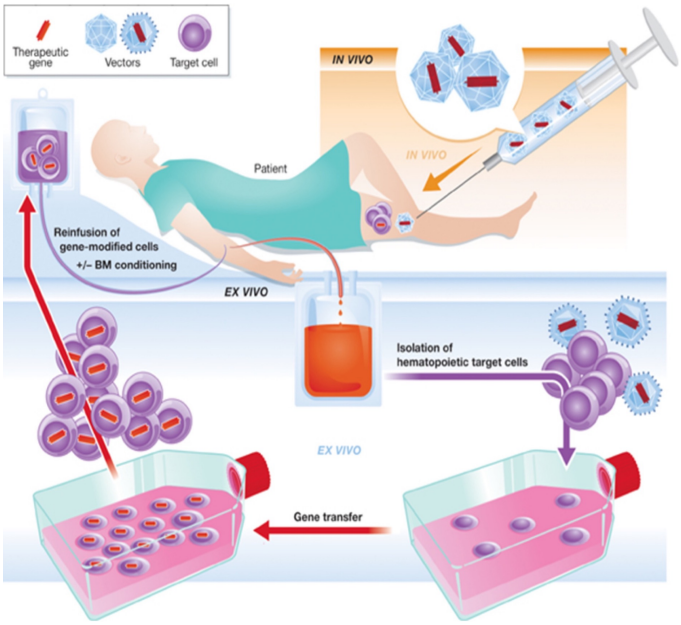

Fig. 1. *In vivo and ex vivo gene therapy (Aiuti et al. 2012)*

2.3. Gene transfer steps

From identifying the faulty gene to administering a modified foreign gene into patient's body, genetic engineering or the gene therapy procedure consists of three stages. The first step is to identify the mutated or defective gene that is responsible for a disease or disorder. The second step is synthesizing a functional DNA copy that matches

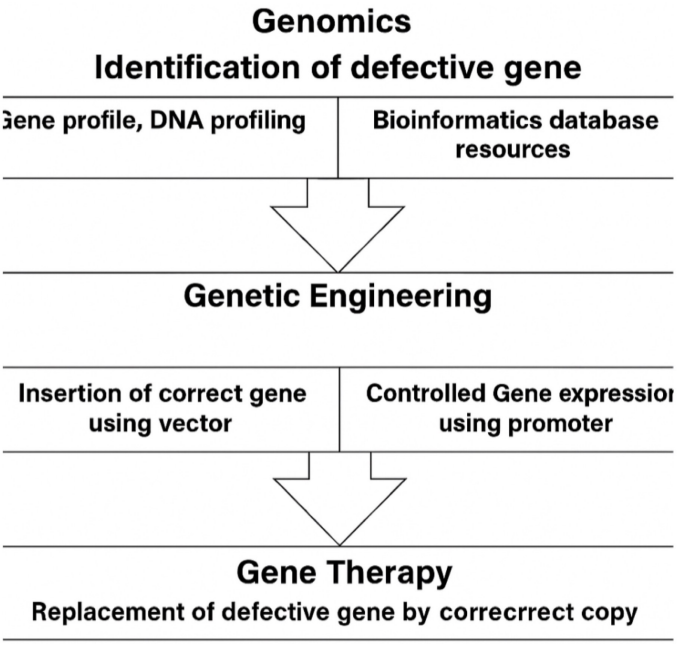

Fig. 2. *Stages in basic process of gene therapy (Alnasser 2021)*

the faulty gene. The final step is to develop an efficient delivery mechanism that can transfer the therapeutic gene into a patient's body to ensure adequate expression at the target site (Naso et al. 2017).

3. Gene delivery system

Gene transfer has been achieved using two main categories of vectors – viral and non-viral vectors. Common viral vectors include retroviruses, Ads, AAVs, and LVs. On the other hand, non-viral vectors can be classified into physical, mechanical, and biological vectors. While each vector type have specific advantages, but no vector has yet been found that meets all the criteria of an ideal vector (Parker and Brereton 2010). The development of an effective, safe, and purpose-specific delivery system is at the core of successful gene therapy. For gene delivery systems to be considered ideal, they must exhibit various desirable properties. Firstly, they should have broad gene insertion capacity and a high transfection rate coupled with a non-invasive delivery method. Secondly, they should ensure gene expression for an extended length of time within the target cells. Thirdly, they must demonstrate target-specific selectivity, especially in applications such as tumor-targeted therapy. Fourth, they should exhibit safety-related properties such as biocompatibility, stability, and minimal immunogenicity. Lastly, these systems should be readily available for widespread use. Although a wide variety of vectors have been developed and tested in clinical trials, the search for a truly optimal delivery system continues (Ginn et al. 2005). The comparison between a viral vector, such as adenovirus vector, and a non-viral vector, such as Lipofectamine Plus revealed stark difference in gene transfer efficiency. It was reported that Lipofectamine Plus is 1,000 times less potent than the viral vector with an efficiency in the range of 0.1% to 10% of viral vector (Hama et al 2006)

3.1. Viral vectors

The most effective viral gene delivery systems currently available are retroviruses, Ads, AAVs (parvoviruses), herpesviruses (HVs), poxviruses, LVs, and others. These gene delivery systems are manipulated by introducing subtle genetic modifications in their genome and then incorporating a foreign gene that encodes the needed therapeutic protein in the targeted cells or tissues (Huang et al. 2011). However, their clinical use in gene therapy is still limited due to several issues such as immunogenicity, toxicity to cells, insertional mutagenesis, potential oncogenesis, and their inability to maintain long-term transgene expression (Wolde and Toth 2013). The most widely used viral vector for *in vivo* gene therapy applications is AAV, a nonpathogenic parvovirus with a 4.7 kb DNA genome encapsulated in a non-enveloped icosahedral capsid. Since the early 2000s, significant progress has been made in understanding viral vector biology, accompanied with advancements in design and production of AAV. To date, more than 100 AAV variants and 11 natural serotypes have been identified (Wang et al. 2019). For *in vivo* gene transfer, viral vectors are currently the most successful gene delivery technique. A gene transfer vector should ideally have high transduction efficiency, the ability to target a particular tissue, sustained and regulated gene expression, low immunogenicity, and minimal adverse effects. Unfortunately, none of the currently available gene delivery vectors satisfy all these requirements. When a vector is injected locally, the region of action is usually precise but their area of effect is limited. On the other hand, widespread gene expression may occur when a vector is administered systemically. In order to enhance targeted delivery and boost transduction efficiency, both vectors and their delivery systems have been modified (Yla-Herttuala et al. 2018). However, most viral vectors have an inherent affinity for certain cell types or tissues that can be used for therapeutic applications (Coughlan et al. 2010).

3.2. Non-viral vectors

Although non-viral gene transfer techniques are generally less efficient than viral systems in terms of gene transduction, they are still regarded as valuable tools for transgenic DNA and gene delivery. This is because of their affordability, accessibility, lower immunogenicity, enhanced biosafety, and capacity to deliver the required size genetic payloads. Non-viral delivery approaches include chemical ways such as cationic liposomes, cationic polymers, and lipid polymers, biological vectors such as genetically modified bacteria, and physical methods such as electroporation, sonoporation, laser irradiation, microinjection, and gene gun methods (Parayath et al. 2018). Genetic materials are delivered across cell membranes in non-viral gene delivery that is purposefully mediated by physical means. These methods include needle-stamping, ballistic (gene gun) DNA injection, sonoporation (ultrasound-mediated delivery), photoporation (laser-mediated delivery), magnetofection (magnetic field-assisted transfection), and hydroporation (fluid pressure-mediated transfer) (Sung and Kim 2018).

4. Application of gene therapy in veterinary medicine

Currently, the primary focus of regenerative medicine has been the treatment of human disease and animals are usually used as experimental models for testing human medicinal products. Although the therapeutic efficacy of such treatments in many animal models is realized, they cannot be applied directly in veterinary medicine. This is because of genetic differences between humans and animals, which can potentially result in differences in the composition and activity of biopharmaceuticals. These differences can limit the effectiveness of human medicines to treat animal diseases due to incomplete homology (Litvin et al. 2016).

4.1. Gene therapy for diabetic disease

Diabetes is a chronic metabolic disorder for which there is currently no definitive cure. The primary purpose of any treatment for insulin-dependent diabetes is to prevent hypoglycemia and attain normoglycemia. Exogenous insulin treatment does not fully eliminate the long-term complications associated with the disease, which often leads to substantial morbidity, a lower quality of life, and increased mortality. In veterinary medicine, diabetes in dogs is closely associated with aging and dogs older than eight years are at higher risk (Heeley et al. 2020). A single intramuscular injection of AAV serotype 1 vectors carrying insulin and glucokinase transgenes has been used for treatment of canine diabetes. When intracellular glucose levels are high, the enzyme glucokinase, part of this system, reacts by triggering glucose phosphorylation. This system also promotes stable and sustained insulin production, leading to additional metabolic benefits beyond glycemic control (Jaén et al. 2017).

4.2. Gene therapy for cancer treatment

The field of veterinary oncology is expanding quickly, and treatment of cancer in companion animals is becoming more common in clinical settings. Nowadays, radiation therapy remains restricted due to the limited availability of specialized facilities, and thus the primary treatment methods are chemotherapy and surgery. Cancer is still a disease with a high death rate in both human and veterinary medicine,

despite advancements in the use of these techniques, which supports research into alternate therapies. Today, the majority of gene therapy clinical trials in human medicine include cancer patients, and gene therapy technology has turned its attention to cancer. This progress has been made possible by advances in tumor immunology and carcinogenesis, including the identification of oncogenes and tumor suppressor genes (Argyle 1999). There are four primary broad approaches of gene therapy for cancer. The first option is to correct the genetic defect associated with the malignant phenotype by using antisense therapy, gene substitution, or gene editing. Second option is the induction of cancer cell death through the introduction of suicide genes, also known as drug-activating genes, which leads to targeted cell destruction. Third approach is the enhancement of anti-tumor immunity, wherein the suicide genes stimulate the host immune system to recognize and attack the cancer cells. Fourth approach is protection of healthy tissue, such as introducing chemo-protective genes into bone marrow cells, to enable administration of extremely powerful chemotherapies (Yoon et al. 2020).

4.3 Gene therapy in eye disease

A innovative strategy to possibly cure a range of keratopathies is corneal gene therapy. One novel application of this emerging technique is gene therapy for corneal disorders in horses. Gene therapy has shown promising results in treatment of eye conditions and prevention of permanent blindness, as evidenced by the effective restoration of vision in patients with congenital leber amaurosis (LCA) (Mohan et al. 2021). It may also help in problems including glaucoma in dogs, corneal dystrophy, dermoid, chemical burns, cuts, and corneal degeneration. AVs, LVs, and AAVs containing the target therapeutic genes are among the methods that have been suggested for the delivery of genetic material to cure these corneal condition (Komáromy et al. 2019). When the size of therapeutic gene exceeds the AAV vector's packing capacity, the treatment of inherited retinal disorders (IRDs) becomes more difficult. Although LV vectors are a good substitute for these treatments, their inability to effectively infect photoreceptors has hampered the development of vehicles for big genes like ABCA4 and MYO7A. However, using LV vectors gene therapy has achieved considerable success for both genes in animal models (Hashimoto et al. 2007).

4.4. Gene therapy for hemophilia

The monogenic nature of haemophilia and its readily measured outcomes make it a desirable target for gene therapy. Haemophilia is classified into two kinds, both of which are X-linked monogenic disorders. Mutations in the F8 gene, which codes for coagulation factor VIII, cause haemophilia A, whereas mutations in the F9 gene, which codes for coagulation factor IX, cause haemophilia B (Stonebraker et al. 2010). Gene therapy strategies aimed at both types of haemophilia have reached to preclinical and clinical stages (Batty and Lillicrap 2019). The research indicates that the most promising vectors for haemophilia gene therapy are the AAV and LV vectors (Cantore et al. 2015). In veterinary applications, gene transfer approaches are also being explored for metabolic and cardiovascular disorders, including those that affect the myocardium at a molecular level. Notably, gene therapy has shown potential in the treatment of dilated cardiomyopathy (DCM) in dogs of various etiologies, as well as heart failure in both dogs and cats (Sleeper 2017).

4.5 Gene therapy in lysosomal storage disorders

Hereditary conditions known as lysosomal storage disorders (LSDs) are caused by the intracellular accumulation of macromolecules that are not completely broken down due to defective lysosomal enzymes. Current therapeutic approaches – such as enzyme replacement therapy (ERT), substrate reduction therapy (SRT), and bone marrow transplantation are ineffective treatments for the majority of LSDs, which affect both the peripheral and central nervous systems. Large animal models that naturally develop LSDs closely replicate the lesions, metabolic abnormalities, and clinical phenotypes observed in human patients. These models are especially valuable as their longer lifespans allow for the evaluation of gene therapy's effects on late-onset symptoms, which are challenging to study in small animal models (Bradbury et al 2015). LSDs are an ideal candidates for gene therapy because they are typically monogenetic, and the therapy can be administered as a one-off treatment. In addition, gene therapy can take advantage of a beneficial mechanism of lysosomal enzyme uptake known as cross-correction, wherein functional lysosomal enzymes produced by genetically corrected cells are secreted and subsequently taken up by neighbouring deficient cells (Hurlbut et al 2010).

4.6 Gene therapy for infectious disease

Gene-based therapies for viral diseases in native animals have mostly focusses on nucleic acid immunization. Bridges and Sarver have developed several gene therapy options for treating viral infections such as HIV. Transferring antiviral genes to pluripotent hematopoietic stem cells is one of these strategies to guarantee the patient a steady supply of HIV-resistant cells. Such methods could be used to treat lentiviral infections in other animals, such feline immunodeficiency virus (FIV) in cats (Argyle 1999). During the first two weeks of their lives, newly hatched chickens are particularly vulnerable to diseases. The use of cytokines as treatments in livestock, especially poultry, has increased due to recent cytokine gene cloning and the development of novel delivery platforms, such as B cells and live recombinant vectors. For instance, a live recombinant fowl-pox virus (FPV) that produces chicken myelomonocytic growth factor (MGF) was developed by Lowenthall et al. (2006).

4.7 Gene therapy in muscular dystrophy

A group of genetically diverse disorders, known as muscular dystrophies (MDs), are caused by mutations in one of several different genes. Since mutations in a single gene cause nearly all forms of muscular dystrophy, gene therapy, which entails correcting or replacing the defective gene, has become a viable therapeutic strategy. Since muscle tissue accounts for more than 40% of body mass, the widespread delivery of therapeutic gene across the great majority of the body muscles poses a significant challenge. The majority of current research is focused on identifying a suitable gene and developing safe and efficient delivery techniques for systemic muscle targeting (Chamberlain 2002). MD gene therapy demands that a dystrophin expression vector be effectively delivered to the majority of the body's striated muscles. Due to the large size of dystrophin gene (2.4 MB), mini-gene cassettes that can produce therapeutic quantities of a functional protein must be made. Thus, it is necessary to develop a delivery vectors that are capable of efficient transduction in striated muscle and transportation of these expression cassettes, while also minimizing immunological or toxic responses to prevent further muscle damage (Emery 2002). CRISPR/Cas9 technology displayed promising advancement in the correction of dystrophin gene mutation (Amoasii et al. 2018). In canine models, restoration of dystrophin expression in both

skeletal and cardiac muscle was observed following intramuscular or systemic administration of CRISPR components. Despite encouraging results, long-term follow-up is required to evaluate safety and effectiveness of this approach (Wasala et al. 2019).

5. Pros and cons of gene therapy

Gene therapy is an approach which offers a potential for a permanent cure rather than merely a palliative or symptomatic relief. Gene therapy may be the only effective treatment for certain genetic disorders. The cost and risk of multigenerational somatic cell therapy are minimized by preventing the transmission of disease causing genes. Hence, there is a need to address the reproductive health of prospective parents at higher risk of developing serious genetic disorders. Gene therapy provides the possibility of long-term therapeutic advantages without requiring recurrent medication by replacing damaged genes with functional ones. Once effective methods are established, germline gene therapy could help parents and researchers avoid the ethical conundrum of discarding defective embryos during preimplantation genetic diagnosis (PGD) by repairing such genetic defects. However, the refinement of germline gene therapy techniques may surely place some embryos at risk during the laboratory experimentation (McCain 2005).

Despite its promise, gene therapy raises significant scientific, ethical, and social concerns. The long-term risks remain poorly understood and clinical trials of such therapies could modify human characteristics unrelated to diseases such as altering physical and cognitive traits, which would make social discrimination issues worse. The germline modifications would basically create generations of study subjects without consent because it includes early embryos and has consequences for their progeny. The right of future generations to inherit an unaltered genetic composition would be infringed by germline gene therapy. Due of its enormous cost, gene therapy will have limited accessibility, challenging the principle of equitable healthcare and making it difficult to justify broad societal investment (Jafarlou et al. 2019). Moreover, the use of viral vectors for gene delivery faces multiple issues such as immunogenicity, cytotoxicity, insertional mutagenicity, and carcinogenicity, all of which thwarted the advancement in gene therapy is restricted (Jafarlou et al. 2019).

6. Conclusion and recommendations

Gene therapy is a novel and rapidly evolving treatment approach that may continuously promote regeneration. Fundamentally, it involves introduction of small segments of recombinant genetic material, either DNA or RNA, into host cells to reprogram their function. The host machinery transcribes and translates these recombinant genes delivered in the form of bare plasmid DNA, nanoscale complexes, or viral particles, resulting in the manufacture of therapeutic proteins. Instead of repeated administration of conventional drugs or recombinant proteins, gene therapy enables the body to produce its own therapeutic agents in a sustained manner. A number of internationally authorized gene therapy drugs that assist patients limit the progression of their cancer, such as Kymriah, Oncorine, and Gendicine. Despite its introduction in United States in 1972, gene therapy is mostly confined to clinical studies and it has yet to offer treatment options for a number of diseases. Though significant progress has been achieved in human medicine, veterinary medicine still lacks species-specific licensed gene therapies. Current veterinary research primarily employs animal models for the development and testing of human-targeted therapies, rather than focusing on therapeutic applications for the animals themselves. For successful development and application of gene therapy is veterinary medicine several critical directions in veterinary medicine need to be addressed.

- Dedicated research at animal gene therapy be conducted at the species level rather than using animals as models for human medicines.
- Veterinarians must improve their understanding of molecular and cellular mechanisms of diseases to precisely apply such gene based interventions.
- This technology needs to be adopted over a wide range of therapeutics and a variety of species, emphasizing species-specific design and development.
- Due to the high cost of the gene therapy drugs, sponsors are needed for both clinical trials and equitable access to the approved drug.

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