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# Gene Therapy of Some Genetic Diseases by Transferring Normal Human Genomic DNA into Somatic Cells and Stem Cells from Patients

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## 1. Introduction

### 1.1 Viral vectors for gene therapy

Gene therapy is a way to correct mutated genes in vivo by transferring normal genes into cells of patients with genetic diseases or cancers, or to introduce new genes into cells to express therapeutic proteins. Several viruses like adenoviruses (Nayak & Herzog, 2010; Raper et al., 2003), alphaviruses (Lundstrom, 2001, 2005), retroviruses (Aiuti et al., 2009; Bordignon et al., 1989, 1995; Cavazzana-Calvo et al., 2000; Ferrari et al., 1991; Halatsch et al., 2000), lentiviruses (Dupré et al., 2004; Mortellaro et al., 2006; Nayak & Herzog, 2010), adeno-associated viruses (AAV) (Jayandharan et al., 2011; Nayak & Herzog, 2010; Terzi & Zachariou, 2008), herpes simplex viruses type 1 (HSV-I) (Epstein, 2009), have been used as vectors to deliver normal genes into cells of patients for gene therapy. However, there were limitations and hurdles in using these vectors. Some viruses like retroviruses, lentiviruses might integrate into human genomic DNA and cause cancers (Dave et al., 2004; Du et al., 2005; Hacein-Bey-Abina et al., 2003a, 2003b; Z. Li et al., 2002; Modlich et al., 2005; Seggewiss et al., 2006). Most viruses can infect both normal cells and defective/cancer cells of patients, as long as the cells have receptors of the viruses (Antar et al., 2009; K. Holmes et al., 1997; Norkin, 1995; L. Song, 2010; L. Song et al., 2009; van den Wollenberg et al., 2008; van Houdt et al., 2008), and this might lead to serious infections, inflammatory responses, and immunological reactions (Nayak & Herzog, 2010).

### 1.2 Highly pathogenic (virulent) viruses, moderately pathogenic viruses, and lowly or mildly pathogenic viruses

Some viruses like rabies virus, Lassa fever virus, smallpox virus, Eastern equine encephalitis virus, Ebola virus, Marburg virus, and human immunodeficiency virus are highly pathogenic and dangerous; they can cause very severe to fatal diseases in humans. For example, 399 patients had Marburg hemorrhagic fever in Angola in 2005, and 335 of them dead of the fatal disease. The human fatality rate of Ebola virus infection ranged from 50% to 89% (Balter, 2000; Peters, 2005; Rouquet et al., 2005; L. Song & Chen 1995, 1996; Virgin, 2007). Some viruses like some serotypes of seadornavirus isolated from mosquitoes in China have moderate pathogenicity, and they can cause clinical and subclinical infections.

Seadornavirus can cause mild encephalitis and fever. Multisegmented RNA viruses like influenza virus (Garten et al., 2009; E. Holmes, 2005; Karasin et al., 2000; Sun et al., 2011), rotavirus (Matthijnssens et al., 2010; Maunula & Von Bonsdorff, 2002), bluetongue virus (Batten et al., 2008), kemerovo virus (Nuttall & Moss,1989), Thogoto virus (C. Davies et al., 1987; Jones et al., 1987) are able to reassort their genomic segments in vivo, if a cell is infected by two or more different strains of a virus. This is the major reason why these viruses have multiple serotypes and subserotypes. As seadornavirus genome consists of 12 distinct segments of double-stranded RNA, it is easy to create new genotypes of seadornavirus through the reassorment event among different strains of the virus in nature. There are at least 6 different genotypes of seadornavirus in China, and there are various serotypes and subserotypes within the Chinese isolates (Q. Li et al., 1992; L. Song et al., 1995; L. Song & Chen, 1995, 1996; Tao et al., 1999; L. Xu et al., 2003; P. Xu et al., 1990; You et al., 1990). Similar seadornaviruses were isolated from mosquitoes collected in Indonesia (Brown et al., 1993) and Vietnam (Nabeshima et al., 2008). The virus was classified as a probable member of the genus Coltivirus previously, and later it was renamed as a member of a novel genus-Seadornavirus within the family of Reoviridae (Mohd Jaafar et al., 2005). Some viruses like M14-a nonpathogenic twelve-segmented double-stranded RNA virus isolated from mosquitoes in China (C. Huang et al., 1985, Liang et al., 1985) are lowly or mildly virulent viruses. The majority of viruses like hepatitis A, B, C, D, and E virus, polio virus, measles virus, mumps virus, West Nile virus, influenza virus, Coxsackie A virus, enterovirus 71, rhinoviruses, coronaviruses, norovirus, rubella virus, and the newly isolated member of bunyavirus which caused severe fever and thrombocytopenia syndrome in China (X-J. Yu et al., 2011), have moderate pathogenicity. There are very few human viruses are truly nonpathogenic viruses in nature, except some animal viruses that mainly infect animals but not humans. These mildly virulent viruses cannot cause obvious infections in humans (Csatary et al., 1985).

We should be aware that even some mild viruses which do not cause serious infections in normal people still can be dangerous to those with weakened immune systems, like late stage cancer patients, very elderly or critically ill patients, and patients with immunodeficiency disorders. Most viruses were modified and attenuated before being used as vectors for gene therapy, but in very rare situations, even those modified viral vectors can cause problems. An 18-year-old young man with partial ornithine transcarbamylase deficiency died after a clinical trial of gene therapy, even though the vector used in that trial was a modified human adenovirus type 5 virus (Raper et al., 2003).

### 1.3 Reovirus is not an oncolytic virus

There are Some scientists in the world have been trying to use a few so-called oncolytic viruses to cure cancers (Pennisi, 1998). One of the major problems of these therapies is that it is hard to find an ideal wild-type oncolytic virus, which only target cancer cells but not normal cells.

Normal rhesus monkey kidney LLC-MK2 cell line was established in 1955 (Evans et al., 1959; Hull et al., 1956, 1962). Normal mouse L929 cell line was first described by Stanford et al. in 1948. The L929 cell line was a cloned strain of its parental mouse cell strains L. L cell strain was made from the normal subcutaneous areolar and adipose tissue of a male mouse (Earle, 1943; Stanford et al., 1948). These two cell lines were widely used to isolate, grow, and multiplicate many types of viruses including reoviruses.

Reovirus (Respiratory Enteric Orphan Virus) is a member of the family Reoviradae. It got the name originally because it was often isolated from human respiratory and enteric systems but no obvious human disease was associated with it. Reovirus can cause cytopathic effect (CPE) in many normal cell lines like rhesus monkey kidney LLC-MK2 and MA-104E, African green embryonic monkey kidney Vero, baby hamster kidney BHK-21, Buffalo green monkey kidney BGM, African green monkey kidney BS-C-1, Madin-Darby bovine kidney (MDBK), Madin-Darby canine kidney (MDCK), human embryonic intestinal (intestinal 407), human embryonic lung (HEL), and mouse L929 cells. After a few days of cell culture, like most other viruses, reovirus will destroy and lyse the cells it infected eventually in vitro (McClain et al., 1967; Nibert et al., 1991; Ridinger et al., 1982; Rozee & Easterbrook, 1970; Schiff et al, 2007; L. Song et al., 1995, 1999b, 2000, 2009). Reovirus can infect and kill both normal cells and human tumor cells in vitro, as long as the cells have reovirus receptor-junctional adhesion molecule (Antar et al., 2009; L. Song et al., 1999b, 2000, 2009; van den Wollenberg et al., 2008; van Houdt et al., 2008). If a small number of reoviruses are injected into tumor tissues directly, the virus will infect and kill some tumor cells locally. In the meantime, the human immune system will fight with the virus, a lot of immune cells, such as T cells, B cells, natural killer cells, neutrophils, and macrophages will be recruited to the infection site, and the immune cells will produce antibodies, chemokines, and cytokines like interferons, interleukins; and after a few days, before the virus spreading to other parts of the body, the virus will be killed, and be cleared from the human body. If a large number of reoviruses are injected into the tumor body, the viruses will infect tumor cells and nearby normal cells, and spread to other organs of the body and cause systemic infection. This could be fatal for some cancer patients, as we know that many cancer patients have unbalanced, weakened, and dysfunctional immune systems. A great number of cancer patients are treated with radiation and immunosuppressive anticancer drugs, these anticancer therapies can damage immune cells further. Cancer patients with weakened immune systems have more chances to have opportunistic infections (Baggiolini et al., 1997; Bodey, 1986; Dunn et al., 2002, 2004; Locati & Murphy, 1999; Lodish et al., 2008; Luster, 1998; Murdoch & Finn, 2000; Nibert et al., 1991; Pitisuttithum et al., 2001; Schiff et al, 2007; Sutlu & Alici, 2009; Swann & Smyth, 2007; Virgin, 2007). This is the same problem we are facing when a patient has chemotherapies nowadays; there are rare drugs that only specifically and selectively target cancer cells but not normal cells. Over doses of anticancer drugs will kill both normal cells and tumor cells of patients, and lead to serious side effects and deaths; normal doses or small doses of anticancer drugs will not kill all the cancer cells, and the remained cancer cells will overexpress a membrane protein-P-glycoprotein, and be able to resistant to the cell kill effects of multi-anticancer drugs (Arkin et al., 1989; Croop et al., 1988; De Rosa et al., 2008; Debenham et al., 1982; Deuchars et al., 1987; Endicott & Ling, 1989; Goldstein et al., 1989; Juliano & Ling, 1976; Kobayashi et al., 1994, 1998; Moscow & Cowan, 1988; Pastan & Gottesman, 1987; Riordan et al., 1985; L. Song et al., 1999a).

Most people were infected by reovirus without significant symptoms, but L-H. Song et al. isolated a reovirus from the throat swabs of a patient of severe acute respiratory syndrome (SARS) in Beijing in 2003, and the virus can cause clinical symptoms similar to SARS in guinea pigs and macaques (L-H. Song et al., 2008). Antarasena et al. isolated some avian reoviruses from chickens with sudden death in Thailand (Antarasena et al., 2002). Chua et al. reported that a reovirus of bat origin could cause acute respiratory disease in humans (Chua et al., 2007). Given the fact that more than 50% of people were infected by reovirus in their lifetimes, and many of the infections occurred in the early childhood (Selb & Weber,

1994; Tai at el., 2005), and there are increasing evidences indicating that reovirus can infect normal human cells in vivo and cause some mild to serious diseases like upper respiratory illnesses, meningitis in humans (Johansson et al., 1996; Schiff et al., 2007; Tyler et al., 2004); the old concept that reoviruses were "orphan" viruses, and they were not associated with any human diseases, is not true anymore, and it should be revised.
Wild-type reovirus should not be considered as an oncolytic virus, and it is unlikely that reovirus could be an effective and practical anticancer agent (L. Song, 2010).

### 1.4 Non-viral vectors for gene therapy

Non-viral vectors such as peptide, polymer mediated gene therapy can only produce transient expression of genes, and the transfection efficiency is much lower compared to viral vectors (Al-Dosari & Gao, 2009; Cartier & Reszka, 2002; X. Gao et al., 2007; Niidome & Huang, 2002).

## 2. A possible approach for gene therapy of some genetic diseases

It is well known that a bacterium can obtain foreign DNA from another bacterium through a process of bacterial conjugation (Lederberg & Tatum, 1946). In this process, DNA is directly transferred from one cell into another cell via direct cell-to-cell contact or via a bridge-like structure between two cells. By this way, a bacteium's genomic DNA could be changed by homologous recombination with another bacterium's genomic DNA.
As above pointed out, multisegmented RNA viruses like influenza virus can reassort their genomic segments in vivo, if an animal is infected by two or more different strains of a virus in the same time period. This can create new strains of the virus, and the new strains carry the gene segments of their parental strains. There are some triple reassorted influenza virus strains in nature (V. Gregory et al., 2001; Ma et al., 2010; Octaviani et al., 2011; Rambaut et al., 2008; Smith et at., 2004; Vincent et al., 2006; Webby et al., 2000; X. Xu et al., 2002, 2004; Zhou et al., 1999).
Complementation test was used to study genetic subtypes (complementation groups) of a genetic disease like Fanconi anemia. If cells from two patients with Fanconi anemia were from two different complementation groups, the defective genes could be repaired after fusion of the two genetic complementation cells; and the hybrid cells were able to resist the attack of DNA cross-linking agents such as mitomycin C and diepoxybutane. Whereas, if the cells of two patients were from the same complementation group, the hybrid cells would still be sensitive to the attack of DNA cross-linking reagents (Buchwald, 1995; Duckworth-Rysiecki et al., 1985; Fanconi Anaemia/Breast Cancer Consortium, 1996; Giampietro et al., 1997; Joenje et al., 1995; Joenje & Patel, 2001; Levitus et al., 2004; Tischkowitz & Hodgson, 2003; Whitney et al., 1995). 14 different complementation groups of Fanconi anemia have been discovered, and 14 distinct Fanconi anemia genes have been identified (FANCA, FANCB, FANCC, FANCD1, FANCD2, FANCE, FANCF, FANCG, FNACI, FANCJ, FANCL, FANCM, FANCN, FANCP) (Alderton, 2011; Kim et al., 2011; Levitus et al., 2006; Reid et al., 2007; Smogorzewska et al., 2007; L. Song, 2009; Stoepker et al., 2011; Taniguchi & D'Andrea, 2006; Tischkowitz et al., 2008).
It is very interesting that a number of patients with some genetic diseases were cured or improved naturally later in their lives. Somatic mosaicism was involved in this form of miracle "natural gene therapy" process. Somatic mosaicism means that there are genetically different somatic cells exist in a given organism resulting from in vivo reversion of a

mutated allele to wild type. Somatic mosaicism has been found in several genetic disorders, such as hemophilia B, tyrosinemia type I, Bloom syndrome, adenosine deaminase deficiency, epidermolysis bullosa, Wiskott-Aldrich syndrome, androgen insensitivity syndrome, T-cell immunodeficiency, leukocyte adhesion deficiency type 1, Duchenne muscular dystrophy, atypical X-linked severe combined immunodeficiency, and Fanconi anemia. The mechanism of somatic mosaicism is complicated; it might be due to epigenetic alterations of DNA, copy number variations, back mutation, gene conversion, frame-restoring mutation, DNA polymerase slippage, and compensatory mutation in cis. Homologous genetic recombination between paternally and maternally derived chromosomes also plays a vital role in somatic mosaicism (Darling et al., 1999; J. Jr. Gregory et al., 2001; M. Gross et al., 2002; Hirschhorn, 2003; Lo Ten Foe et al., 1997; Mankad et al., 2006; Müller & Williams, 2009; Notini et al., 2008; Piotrowski et al., 2008; L. Song, 2009; Wada et al., 2001, 2003; Waisfisz et al., 1999; Youssoufian & Pyeritz, 2002).

Homologous genetic recombination was first discovered in bacterium *Escherichia coli* strain K-12 in 1946 by Joshua Lederberg (May 23, 1925 – February 2, 2008), winner of the 1958 Nobel Prize in Physiology or Medicine (Lederberg & Tatum, 1946; Lederberg, 1947, 1987a, 1987b; Tatum & Lederberg, 1947).

Homologous recombination happens when two homologous DNA molecules meet in vivo. They pair up and exchange some sequences. Homologous genetic recombination occurs in the processes of mitosis and meiosis. Gene recombination takes place between two nonsister chromatids of the two homologous chromosomes by crossover during meiosis. Homologous recombination happens much more often in distal regions of chromosomes and on shorter arms of chromosomes. Crossover occurs at least one time per chromosome in each of the process of meiosis. Gene sequences are exchanged during the process of meiosis by crossover (Creighton & McClintock, 1931, 1935; Holliday, 1974; International Human Genome Sequencing Consortium, 2001; Weil, 2002; Whitby, 2005).

Crossover during the process of meiosis is really a smart and fair way to let a female's eggs or a male's sperms to have genetic information from both of her/his parents; and when an egg and a sperm form a new life in the womb, the new baby carries the genetic information from both of his/her grandparents on his/her father's side and grandparents on his/her mother's side; so a baby's genetic traits are inherited from his/her four biological grandparents, this could make the baby more diversity, flexible, and fit.

Radioactive materials like radon gas in some basement rooms, ultraviolet (UV) light, toxic chemicals, reactive-oxygen compounds, polluted air, and smoking, some viral infections all can damage human genomic DNA, cause mutations, and lead to cancers. Human cells are able to cope with outside and inside challenges, and to repair the damaged DNA molecules by several ways. One of the DNA repair mechanisms is homologous recombination to repair DNA gaps, DNA double-stranded breaks, and DNA interstrand crosslinks. A damaged chromatid can be repaired by its undamaged sister chromatid or its homologous nonsister chromatid through homologous recombination during mitosis. Sister chromatids are the preferred templates over homologous or heterologous chromosomes for recombination repair in yeast and mammalian cells. Instead of crossover, gene conversion is the major result of homologous recombination. Cells seem reluctant to crossover their chromatids unnecessarily to maintain their genome's integrity and stability (Hope et al., 2007; Jackson & Bartek, 2009; Johnson & Jasin, 2001; Kadyk & Hartwell, 1992; X. Li & Heyer, 2008; Lorenz & Whitby, 2006; Willers et al., 2004).

Gene targeting (gene knockout) is a technique that a vector is used to deliver a fragment of mutated DNA into embryonic stem cells and to target its homologous DNA in the genome by homologous genetic recombination. Thousands of genes in mice were knocked out by using this method. Mario R. Capecchi, Martin J. Evans, and Oliver Smithies were awarded jointly the Nobel Prize in Physiology or Medicine in 2007 for their discoveries of principles for creating knockout mice (Bradley et al., 1984; Bronson & Smithies, 1994; Capecchi, 1989a, 1989b; Koller & Smithies, 1992; Kuehn et al., 1987; Robertson et al., 1986).

It was assumed that plant tissue grafts did not have gene exchange, but this is not true. A recent discovery found that even in plant tissue grafts, some of their genes were exchanged (Stegemann & Bock, 2009).

Based on the above observations and experiments, I proposed a possible approach for gene therapy of some genetic diseases as indicated in figure 1 (L. Song, 2009).

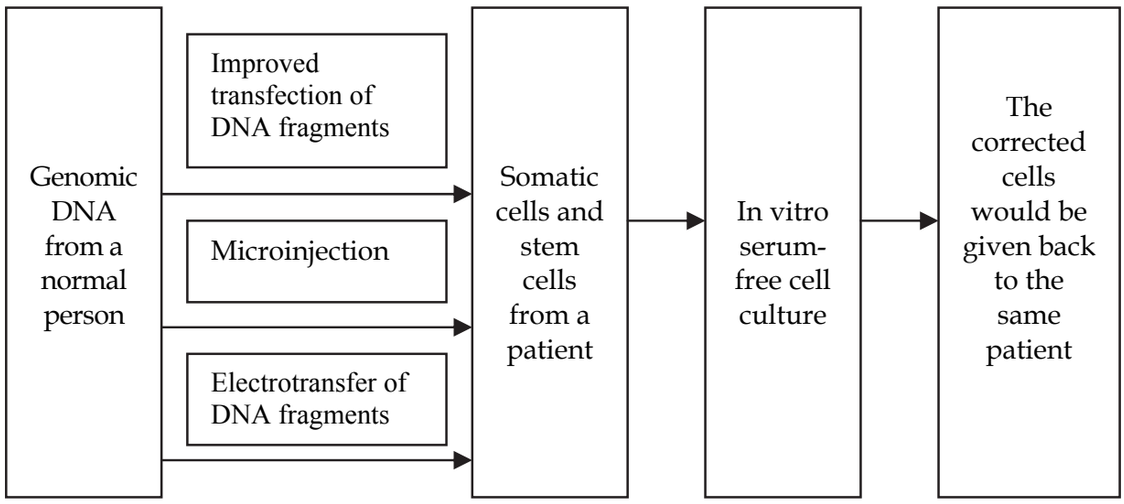



Fig. 1. Gene therapy of some genetic diseases by transferring normal human genomic DNA/DNA fragments into cells from patients.

Briefly, normal human genomic DNA or genomic DNA fragments from a healthy donor can be transferred into somatic cells and stem cells from a patient by microinjection, gene electrotransfer (electroporation), and improved transfection. After in vitro serum-free cell culture, the defective genes could be repaired by homologous genetic recombination, since the genomic DNAs of the two persons are considerably similar, although there are deletions, insertions, rearrangements, loss-of-function variants, and copy number variations (CNV) (Fujimoto et al, 2010; Levy et al., 2007; H. Park et al., 2010; The 1000 Genomes Consortium, 2010, 2011; J. Wang et al., 2008; Yim et al., 2010).

## 3. Discussion

### 3.1 Stem cells, somatic cells

Stem cells were first discovered by Ernest Armstrong McCulloch (April 27, 1926–January 20, 2011) and James Edgar Till in 1963 **(**Becker et al., 1963; McCulloch et al., 1964; Siminovitch et al., 1963; Till et al., 1964; Weissman & Shizuru, 2008). Stem cells have the ability to self-renew and to differentiate into different cell types. Early stage embryonic stem cells can

form all types of cells. Adult stem cells only can differentiate and generate specialized cells, like bone cells, liver cells, blood cells, skin cells. The stem cells that produce all the blood cell types are called hematopoietic stem cells (Bordignon, 2006; Spangrude et al., 1988; Thomson et al., 1998; Weissman & Shizuru, 2008).
Stem cells and their differentiated cells (somatic cells) maintain a balance-homeostasis. When under stress, stem cells are activated, and start to produce more differentiated cells (Jiang et al., 2009; Martinez-Agosto et al., 2007; Till et al., 1964; Wilson et al., 2004).
Somatic cells are the end products of stem cells, they are unable to self-renew.

### 3.2 Induced pluripotent stem cells

In recent years, a few transcription factors (genes) were introduced into somatic cells by lentiviral or retroviral vectors, to reprogram somatic cells into pluripotent stem cells (Liao et al., 2008; I. Park et al., 2008; Takahashi et al., 2007; J. Yu et al., 2007).
Some of the genes like c-Myc that used to form induced pluripotent stem cells are oncogenes, and as above revealed, retroviral or lentiviral vectors might integrate into genome DNA randomly, these risk factors might lead to producing cancer cells. A recent study revealed that human induced stem cells were easier and faster to form tumors than human embryonic stem cells (Gutierrez-Aranda et al., 2010).
Some recently published papers disclosed that induced pluripotent stem cells could induce more immune responses and immunological rejections in the recipient mice, and had more protein-coding point mutations, more abnormal epigenomic reprogramming, and more copy number variations than normal somatic cells and normal embryonic stem cells (Gore et al., 2011; Hussein et al., 2011; Laurent et al., 2011; Lister et al., 2011; Zhao et al., 2011).

### 3.3 Cell membrane and nuclear envelope

Both a eukaryotic cell and a prokaryotic cell have a flexible lipid bilayer plasma membrane that controls movement of molecules in and out of the cell. A eukaryotic cell has a nucleus, while a prokaryotic cell does not have a nucleus; this is the characteristic difference between a eukaryotic cell and a prokaryotic cell.
The eukaryotic cell nucleus is surrounded by a nuclear envelope with nuclear pores. The nuclear envelope has two layers: the out nuclear membrane which faces the cytoplasm, and the inner nucleic membrane which faces the nucleoplasm. The nuclear pores are formed by nuclear pore complexes (NPCs) that span the double lipid bilayer of the nuclear envelope. The NPCs are formed by about 30 proteins. NPCs are gatekeepers of the nucleus (Alber et al., 2007; D'Angelo et al., 2006; D'Angelo & Hetzer, 2008; Devos et al., 2006; Fernandez-Martinez & Rout, 2009; Lam & Dean, 2010; Terry et al., 2007; Theerthagiri et al., 2010; E. Tran & Wente, 2006).
Ions and small molecules and DNA smaller than 200 bp can diffuse through the nuclear pore freely; while the transport of DNA molecules between 310 bp and 1500 bp from the cytosol to the nucleus is through an active transport process. DNA greater than 2 kb can rarely be seen in the nucleus (Cartier & Reszka, 2002; Hagstrom et al., 1997; Ludtke et al., 1999).
A foreign DNA molecule has to go through the human cell membrane, cytoplasm, and the nuclear envelope to reach the genomic DNA in the nucleus. This process can be performed and prompted by microinjection, electroporation, and transfection.

### 3.4 Microinjection

Microinjection technique has been used in transgenic animals for many years (Bishop & Smith, 1989; Chan & Yang, 2009; Charreau et al., 1996; Filipiak & Saunders, 2006; Ménoret et al., 2010; Tesson et al., 2005; Yang et al., 2008). Microinjection technique also has been used as a tool to clone animals-first, an unfertilized egg's nucleus is removed; then a nucleus of a somatic cell is microinjected into the denucleated egg; now the egg contains a whole copy of the diploid genomic DNA from the somatic cell and can be cultured in vitro to form a blastocyst; and the blastocyst is implanted into the womb of an animal; eventually a cloned animal is born (Campbell et al., 1996; Vajta & Gjerris, 2006; Willadsen, 1986; Wilmut et al., 1997).

Several different genes inserted into plasmids were microinjected into cultured mammalian somatic cells, and some genetic defective genes were corrected by homologous recombination (W. Anderson et al., 1980; Capecchi, 1980; Folger et al., 1982; Yamaizumi et al., 1983).

Feng et al. introduced a 110 kb whole human alpha globin gene cluster clone in a bacterial artificial chromosome (BAC) vector into fertilized eggs to generate transgenic mice by microinjection method. The human alpha globin gene cluster DNA was integrated into the mice genome, and human alpha globin mRNA was expressed in 3 transgenic mice (Feng et al., 2001). Similarly, Gao et al. generated transgenic mice carrying a BAC clone of a 116 kb human *apoAI/CIII/AIV/AV* gene cluster and a mutant in which the *apoCIII* enhancer was deleted from the 116 kb gene cluster by microinjection (J. Gao et al., 2005).

I assume that normal genomic DNA without a plasmid or an artificial chromosome can be directly microinjected into the nucleus of somatic cells and stem cells from a patient successfully. This method could have a higher homologous recombination rate and less immunological reactions. It is not a very convenient method, but I think it is worth the effort to try. It only needs 30 purified mouse hematopoietic stem cells to save 50% of lethally irradiated mice (Spangrude et al., 1988). Even one single stem cell transplant can significantly reconstruct the bone marrow function of some irradiated mice (Decker & Nyberg, 2001; Krause et al., 2001; Mankad et al., 2006; Osawa et al., 1996). Therefore, we might need to collect less than one hundred stem cells from a patient, and microinject normal genomic DNA into these cells. Hopefully, less than one hundred of these corrected cells are sufficient to improve a patient's physiological function significantly.

### 3.5 Electroporation

Electroporation or electropermeabilization has been used to transfer foreign plasmid DNA into bacteria, yeast, and mammalian cells (Escoffre et al., 2009; Favard et al., 2007; Golzio et al., 2010; Mir, 2009; Neumann et al., 1982; Somiari et al., 2000). It might be difficult to transfer large genomic DNA molecules into mammalian cells by this method. We might first digest the normal human genomic DNA by restriction enzymes, and then transfer the normal genomic DNA fragments into a patient's stem cells and somatic cells by electroporation in vitro. After a few days of in vitro cell culture in serum free media, the cells can be transplanted into the same patient. Of course, before conducting human clinical trials, this kind of experiment should be performed in animal models first.

### 3.6 Genomic DNA Transfection

Whole genomic DNA molecules are too big to be transfected into cells directly. Normal genomic DNA can be digested by a few restriction enzymes first, and then the purified genomic DNA fragments can be transfected into stem cells and somatic cells from patients.

Molecules commonly used for transfection are smaller than 10 kb; transfection efficiency is very low with plasmids of 12 kb or bigger (Campeau et al., 2001; Cartier & Reszka, 2002). Transfection is a relatively simple, easy, and convenient method to transfer a foreign DNA into a cell, but the current transfection methods cannot satisfy our needs when we want to transfer large DNA fragments. We have to improve the transfection efficiency, and new methods and advanced techniques are needed to transfer large genomic DNA fragments.
A cell culture medium with a little bit lower osmotic pressure can cause cell osmotic swelling, and the cells become bigger, cell membrane permeability is increased, the nuclear pores might become bigger also. Therefore, bigger size of DNA molecules might be easier to enter the swelling cells and reach the genomic DNA inside the nucleus. After transfection, the transfected cells are grown in a cell culture medium with normal osmotic pressure for a period of time, and let the cells to recover to normal. The recovered transfected cells can be transplanted into animal models of a genetic disease.

### 3.7 Genome sequencing and human genetic variation

Human somatic cells are diploid, each somatic cell has 23 homologous chromosome pairs (46 chromosomes), 23 of the chromosomes are from a sperm of the father and other 23 chromosomes are from an egg of the mother. The paired homologous chromosomes are similar in length, except the pair of X and Y chromosomes, an X chromosome is much longer than a Y chromosome. The human sperm cells and egg cells are haploid-each of them has 23 chromosomes.
Different species of animals or plants have different number of chromosomes. A chimpanzee has 48 chromosomes (Young et al., 1960), a dog has 78, a chicken has 78, a pig has 38, a cat has 38, a horse has 64, a cow has 60, a goat has 60, a sheep has 54, a mouse has 40, and a rat has 42 chromosomes separately (O'Brien et al., 1999); and a silkworm has 28 chromosomes (International Silkworm Genome Consortium, 2008; Xia et al., 2004). Wheat has three ploidy levels: diploid wheat (Triticum urartu, Aegilops speltoides, and Ae. tauschii) has 14 (2x), tetraploid wheat (Triticum turgidum ssp. dicoccoides) has 28 (4x), and hexaploid wheat (Triticum aestivum) has 42 (6x) chromosomes respectively; diploid wheat is the ancestor of the tetraploid and hexaploid wheat (Akhunov et al., 2005, 2010; Dvorak & Akhunov, 2005; S. Huang et al., 2002).
Each human gene has two alleles, one allele on each chromosome of the homologous pair. If the 2 alleles have the same sequence, they are called homozygotes; otherwise, they are called heterozygotes.
A specific phenotype (trait) might be determined by two alleles (recessive) or by one allele (dominant). In autosomal recessive genetic diseases like cystic fibrosis, sickle-cell anemia, and fanconi anemia (except FANCB), if a mutant gene appears on both of the paired homologous chromosomes of a person, this person has the genetic disease; if the mutant gene occurs on one of the homologous chromosomes of a person, this person is a carrier of the genetic disease. In X-linked recessive genetic diseases like Fanconi anemia subtype B, Duchenne muscular dystrophy, and Wiskott-Aldrich syndrome, if a male's X chromosome carries the mutated gene, this male has the genetic disease; if one of a female's X chromosomes carries the mutated gene, this female is a carrier; if both of a female's X chromosomes carry the mutated gene, this female has the genetic disease. On the other hand, in autosomal dominant genetic diseases like Huntington's disease, it only needs one mutated allele on any of the two homologous chromosomes to have the related genetic

disease; there is no carrier of a dominant genetic disease, because every person who has the mutated allele gets the disease.

A diploid genome sequence showed that we are genetically more diverse than we have claimed before (International Human Genome Sequencing Consortium, 2001, 2004; Venter et al., 2001) based on the haploid genome sequences, and the difference between two homologous chromosomes of a pair of chromosomes inherited from one's parents is bigger than we thought before. There were more than 4.1 million DNA sequence variants in this new diploid genome. Single-base variations -single nucleotide polymorphisms (SNPs) are the major variants, small fragments insertions or deletions (indels), large fragments deletions and duplications- copy number variations also contribute to the genomic variation significantly (L. Gross, 2007; Levy et al., 2007).

J. Wang et al. sequenced a Chinese diploid genome sequence (named YH) and found about 3 million SNPs in YH's genome, of which 13.6% were new compared to the SNP database dbSNP. They compared the 3 known genome sequences and recognized that the genomes of YH, Venter, and Watson shared 1.2 million SNPs, and their unique SNPs were 31.8% (YH), 30.1% (Venter), and 33.0% (Watson) separately (J. Wang et al., 2008).

Koreans and Chinese were historically related, and they might have the same ancestors. The diploid genome sequence of a Korean male (named SJK) was significantly different from the Chinese YH; there were 1.3 million different SNPs between the two persons; even though SJK shared more SNPs with YH than with Caucasians Venter and Watson, and the Nigerian male Yoruba. 420, 083 (12.2%) SNPs of SJK were not found in the dbSNP database before, and 39.87% of the SNPs were SJK-specific (S. Ahn et al., 2009).

More than 99% of the genomic DNA sequences of a Japanese male were same to the reference human genome, but there were still 3,132,608 single nucleotide variations (SNVs) compared to other six reported human genomes (Fujimoto et al., 2010).

### 3.8 Copy number variations (CNV)

We are in a new era of personalized genomic medicine. With the significantly advanced and simplified new DNA sequencing tools and methods available in a few years, we would be able to know the whole genomic DNA sequence of every person in a few hours at an affordable price (less than one thousand dollars) (L. Gross, 2007).

In addition to each person has his /her unique protein-coding sequences, deletions, insertions, and inversions, copy number variations is one of the main reasons that we are different from each other genetically. Copy number variations is a hot topic of research in recent years, the aim of the studies is to disclose some possible diseases caused/or influenced by copy number variations; and how copy number variations might determine, regulate, and affect our genetic traits and social behaviours. Park et al. discovered 5,177 CNVs in 30 individuals of Korean, Chinese and Japanese, of which 3,547 were putative Asian-specific CNVs (H. Park et al., 2010). Every genome has about 40.3 CNVs averagely; the median length of CNVs is 18.9 kb. About 8% regions of the human genome are occupied by CNV regions (Yim et al., 2010).

The current research data revealed that every genetically unrelated person is significantly different from each other on protein-coding sequences, single-base variations –SNPs, small nucleotide insertions and deletions (called indels), and copy number variations.

It is time to compare genomic DNA sequences among family members, relatives, and genetically unrelated persons, to confirm that genomic DNA sequences are much more

similar among family members and relatives than among genetically unrelated persons. For example, we are interested to see if a son's Y chromosome sequence is as same as his biological father's; or how many differences there are between these two if they are not the same. I assume it will be proved that genomic DNA sequences are much more similar among family members than among genetically unrelated persons. A new research showed that chromosomes with insertions or deletions could affect the process of meiosis (J. Wang et al., 2010). Therefore, if a healthy donor is a family member/relative of a patient, their genomic DNAs could be matched much better, and there should be less immunological reactions and rejections.

A gene might only be expressed from a chromosome of the paternal or maternal origin resulting from genomic imprinting effect, and some genetic diseases like Prader-Willi syndrome, Angelman syndrome, Beckwith-Wiedemann syndrome, are due to genomic imprinting (Falls et al., 1999; Hall, 1990; Tycko, 1994). Additionally, some genetic diseases such as X-linked severe combined immunodeficiency, Glucose-6-phosphate dehydrogenase deficiency, Pyruvate dehydrogenase deficiency, Wiskott-Aldrich syndrome, and Becker/Duchenne muscular dystrophy are sex linked. Hence, both genomic DNAs from a healthy male and a healthy female might be introduced into somatic cells and stem cells of a patient, to correct the mutated genes in vitro, so as to get possibly more efficient and effective gene therapy. Finally, the corrected cells would be given back to the same patient.

### 3.9 Human gene's exons are separated by introns

Many of the human genes have a few introns and exons, and the exons are separated by introns in the human genomic DNA. Introns in a gene can be 10 to 100 times longer than the exons. Statistically, the average exon length is about 170 bp, whereas, the average intron size is about 5419 bp; the average human gene has about 8.8 exons and 7.8 introns. The human nebulin gene has 147 introns. Some introns like the human dystrophin gene intron 44 can be more than 250,000 bp in length (Hawkins, 1988; Lodish et al., 2008; Sakharkar et al., 2004; V. Tran et al., 2005). Introns are removed from the gene to form mRNA by a process of RNA splicing (Berget et al., 1977; Chow et al., 1977) during transcription. mRNA exits the nucleus via nuclear pores, and binds to ribosomes. The ribosome moves along the mRNA, and selects the right tRNA by matching an anti-codon on a tRNA to a codon on the mRNA strand. Each tRNA can only carry a specific amino acid by the help of an enzyme called aminoacyl tRNA synthetase. This is the process of translation-an mRNA sequence is translated into a protein sequence (Goldman, 2008; Lodish et al., 2008).

The human dystrophin gene is the largest known human gene. It has more than 2, 400 kb in length, and has at least 79 exons, its intron 44 has 250 kb, its second largest intron-intron 2, is 170 kb long. 99% of the dystrophin gene sequences are present in introns. The human dystrophin gene locates at locus Xp21.2, and is mutated in patients with Duchenne and Becker muscular dystrophies (Dwi Pramono et al., 2000; Golubovsky & Manton, 2005; Koenig et al., 1987, 1988; Nishio et al., 1994; Roberts, 2001; V. Tran et al., 2005; Zhang et al., 2007).

Human hemoglobin is the protein in red blood cells responsible for transferring oxygen from the lungs to the cells of other parts of the human body . Fetal human hemoglobin has two alpha chains and 2 gamma chains; each of the polypeptide chain has a heme. After birth, the gamma globin gene expression was turned off, and two gamma chains were replaced by two β chains. Therefore, in adult human hemoglobin, there are two α chains,

two β chains, and four heme groups (Feng et al., 2001; Groudine et al., 1983; Hardison, 1996; Yin et al., 2007). The human α-globin gene cluster lies on chromosome 16 (16p13.3), and is about 30 kb, it has 7 genes: zeta, pseudozeta, mu, pseudoalpha-1, alpha-2, alpha-1, theta (Barbour et al., 2000; Entrez Gene, 2011; Feng et al., 2001; Higgs et al., 1989). The human β-globin gene cluster is about 100 kb; it locates on chromosome 11 (11p15.5), and has 5 genes in the order of epsilon, gamma-G, gamma-A, delta, and beta. Both of α-globin gene and β-globin gene have three exons and two introns (Higgs et al., 1989; Yin et al., 2007).

Typically, in a viral or plasmid vector mediated gene therapy, normal mRNAs are reverse transcribed into cDNAs; and specific cDNAs are amplified by PCR method; the PCR products are purified and digested by restriction enzymes; the digested PCR products are inserted into the viral or plasmid vectors; the viral or plasmid vectors containing the normal genes are transfected/transformed into cells, in order to express normal proteins, or to correct the mutated genes in vivo.

This procedure has a problem. As the above described, the mutated genes might be separated by several introns and located in several places of the genomic DNA, the cDNA clones of the normal genes are too short to match and find the mutated genes, therefore, it is hard to correct the mutated genes in vivo, although the cloned genes might express normal proteins transiently. By transferring normal human genomic DNA into cells from patients, it can overcome this difficulty.

### 3.10 Non-coding sequences of genome sequences, and the miracle silkworm

We are living in an age that many important organisms have been sequenced (S. Ahn et al., 2009; Fujimoto et al., 2010; Holmes et al., 2005; International Human Genome Sequencing Consortium, 2001, 2004; International Silkworm Genome Consortium, 2008; Levy et al., 2007; O'Brien et al., 1999; Venter et al., 2001; J. Wang et al., 2008; Xia et al., 2004). We gained some valuable information from the genome sequence data of these organisms, but we are far away from knowing the secret of lives. A silkworm has a short but magical life cycle, and it proceeds in the following processes: it starts from a tiny egg; in a suitable environment, the egg turns into a small worm (larva); the small worm eats mulberry tree leaves greedily and thoroughly days and nights, and after 4 times of shedding its skin, it grows bigger and bigger; one day it starts to weave a silk house-a cocoon for itself, in about 2 days, a beautiful and perfect white colored cocoon is made by itself; the silkworm pees before weaving a cocoon, this makes its body smaller, so as to let itself be able to fit in the cocoon; inside the cocoon, the worm changes to a pupa, and before this happens, the worm poops, this makes its body further smaller; after about two weeks, the pupa becomes a moth, and it is time to get out of the cocoon; the moth is very smart, it pees inside the cocoon, the chemicals of the urine are so powerful-one of the chemicals is a special enzyme which can break down the cocoon wall, and it makes one end of the cocoon softer, so the moth can get out without trouble; the female moth comes out of the damaged cocoon, and releases sex pheromones to attract males, and mates with a few males, lays eggs after mating; and a new life cycle is started again if the environment is appropriate; or it will go through a period of hibernating.

When you think about this miracle life cycle of a silkworm, you have to believe that these abilities, talents, and skills of a silkworm are not learned from others or from the environment, because actually no one teaches it to do this step by step, especially for the first silkworm who started doing these things earlier than all the others in a group of

silkworms. These natural born skills must have been inherited from its parents, and they are encoded in its genome.

It is estimated that there are only about 20,000-25,000 protein-coding genes in humans; the majority of genome sequences are non-coding sequences (International Human Genome Sequencing Consortium, 2004). We might have ignored some small protein-coding genes, and some alternatively spliced genes. The actual number of protein-coding genes might be bigger than we have claimed. (A. Ahn & Kunkel, 1993; Black, 2003; Dwi Pramono et al., 2000; Muntoni et al., 2003; Nishio et al., 1994; L. Song et al., 2003; V. Tran et al., 2005; Zhang et al., 2007). We do not know the meaning and usefulness of these non-coding sequences clearly so far, only one thing we are almost certain is that: they must have meaning and usefulness. We read many books, newspapers, and journals; we watched hundreds of movies, TV shows; we travelled numerous places, and met a lot of people. We do not know why and how we can remember all these things, and why the childhood memories can be stored in our brains for many years, and the memories can be recalled after so many years. If we can transfer the information from one person's brain to a computer, it might take up millions of gigabyte DVD space. In a human brain cell, only genomic DNA molecules could have such big storage capabilities to store such huge quantities of information. The mechanism of memory is one of the biggest challenges of our human beings; we should be able to uncover the secret of our brains with our own brains if we are on the right track. One day we might be able to know all the secrets of the silkworm and other organisms including humans.

### 3.11 Graft-versus-host disease (GVHD)

It is often hard to find a human leukocyte antigen (HLA)-identical sibling or a well-matched HLA unrelated donor when a patient needs hematopoietic stem cell transplant (HSCT). Sometimes, a patient had to receive a mismatched or partially matched bone marrow transplant and cord-blood transplant, when there was no HLA-matched unrelated donor available, and when a transplant was needed urgently. Acute and chronic graft-versus-host disease is the most severe and common long-term side effect of allogeneic hematopoietic stem cell transplantation (HCT). Acute GVHD was more likely to occur after mismatched marrow transplantation. Chronic GVHD was the major cause of late death of HSCT patients (Eapen et al., 2010; Laughlin et al., 2001, 2004; Mastaglio et al., 2010; Rocha et al., 2004).

Cells seem to be able to tolerate foreign DNA without immunological reactions; this is proved by the animal cloning experiments, transgenic animal models, and human and animal replication phenomena. Therefore, the possible approach I described above might have great benefits and advantages. Hopefully some genetic diseases listed below could be cured or improved by using this gene therapy method.

### 3.12 Fanconi anemia

Fanconi anemia (FA) is a rare chromosomal recessive genetic disease. As above cited, there are at least 14 subtypes of Fanconi anemia, and 14 genes whose mutation can cause FA are cloned. FANCB gene is on the X chromosome, and it is the only one on sex chromosomes, the other 13 FA genes are on autosomes. FA was first described by the Swiss pediatrician Guido Fanconi (1892-1979) in 1927 (Joenje & Patel, 2001; Lobitz & Velleuer, 2006; L. Song, 2009; Tischkowitz & Hodgson, 2003).

There are mouse models of Fanconi anemia available currently; FancA, FancC, FancG, FancD1, and FancD2 genes have been deleted or mutated in the mice (Parmar et al., 2009).

These 5 mouse models of Fanconi anemia will be used to prompt the research of gene therapy of these 5 subtypes of Fanconi anemia, because we can use these mouse models to do animal experiments. Normal genomic DNA or normal DNA fragments can be microinjected/electrotransfered, and transfected into stem cells and somatic cells from a mutated mouse; the corrected stem cells and somatic cells can be transplanted back to the same mouse, to see if the Fanconi anemia mouse model's physiological function is improved by this kind of gene therapy.

### 3.13 Sickle-cell anemia

Sickle-cell anemia is an autosomal recessive genetic disease. It results from a mutation at the sixth codon of the β hemoglobin gene on chromosome 11 (the hydrophilic amino acid glutamic acid is replaced by the hydrophobic amino acid valine). This mutation causes red blood cells to become rigid and inflexible. The patient's red blood cells are difficult to go through small capillaries, leading to stroke, chronic pain, anemia, and infection. This disease affects more than 300, 000 people worldwide (Ataga, 2009; Chang et al., 2006; Ingram, 1956, 1957; Pawliuk et al., 2001; Wu et al., 2006).

### 3.14 Cystic fibrosis

Cystic fibrosis is a common autosomal recessive genetic disease caused by mutations of cystic fibrosis transmembrane conductance regulator (CFTR) gene on chromosome 7 in Caucasian population (Kerem et al., 1989; Riordan et al., 1989; Rommens et al., 1989). CFTR is a cAMP-regulated chloride channel; the CFTR gene mutations lead to the cAMP-induced chloride channel dysfunction, thereby alter the transport of chloride and associated liquid, cause problems in several organ systems including respiratory system, sweat glands, pancreas, intestine, liver and gallbladder. There are more than 1800 CFTR gene mutations in the world. Cystic fibrosis affacts more than 70, 000 individuals worldwide. In 2006, the median survival age for a person with cystic fibrosis was 37 (M. Anderson et al., 1991; Collaco & Cutting, 2008; Collins, 1992; Cutting, 2010; Lee et al., 2005; Rowntree & Harris, 2003; G. Wang et al., 2005; Zielenski, 2000).

### 3.15 Duchenne muscular dystrophy

Duchenne muscular dystrophy (DMD) is the most common form of muscular dystrophy, it affacts about one of every 3500 males. DMD is an X-linked recessive muscle degenerative disease caused by the mutations of dystrophin. As the above stated, the DMD gene is the largest human gene (>2.4 million bp on chromosome X), its cDNA is 14 kb long. DMD gene encodes a single 427 kDa protein-dystrophin. Patient's muscle fibers do not have the 427 kDa dystrophin (Burghes et al., 1987; Campeau et al., 2001; Hoffmanet al., 1987; Koenig et al., 1987, 1988; Kunkel, 2004; Monaco et al., 1986; Nelson et al., 2009).

### 3.16 Huntington's disease

Huntington's disease (HD) was first described by George Huntington in 1872. HD is an autosomal dominant neurodegenerative disease caused by the mutation of the huntingtin (HTT) gene. HTT gene located at 4p16.3; it has longer CAG trinucletide repeats (more than 40 CAG repeats) in the first exon of the HTT gene than the normal gene. There are transgenic mouse, sheep and monkey models available for conducting animal experiments currently (Bates et al., 1997; Beilby, 2007; S. Davies & Ramsden, 2001; Jacobsen et al., 2010; MacDonald et al., 1993; Yang et al., 2008).

### 3.17 X-linked severe combined immunodeficiency (SCID-X1)

X-linked severe combined immunodeficiency (SCID-X1) is caused by the mutations of interleukin-2 receptor subunit gamma (IL2RG) gene. Patients with the disease lack of T cells and natural killer cells, their B cells are functionally impaired; therefore, they are extremely vulnerable to infections (Aiuti & Roncarolo, 2009; Cavazzana-Calvo et al., 2000; Gaspar et al., 2004; Hacein-Bey-Abina et al., 2002, 2010).

### 3.18 Adenosine deaminase deficiency (ADA)-SCID

ADA- SCID is a rare genetic disease caused by a mutation of a gene on chromosome 20; this gene encodes an enzyme called adenosine deaminase (ADA). The mutation can lead to lack of ADA enzyme, and the lack of ADA enzyme causes disorder of adenosine metabolism and severe combined immunodeficiency (Aiuti et al., 2002, 2009; Aiuti & Roncarolo, 2009; Bordignon et al., 1989, 1995; Ferrari et al., 1991; Gaspar et al., 2009; Mortellaro et al., 2006).

### 3.19 Wiskott-Aldrich syndrome (WAS)

Wiskott-Aldrich syndrome (WAS) is an X-linked recessive primary immunodeficiency disease caused by mutations of the WAS protein (WASP) gene. The WASP gene is located on chromosome Xp11.22–Xp11.23. It has 12 exons, and encodes 502 amino acids. Patients with Wiskott-Aldrich syndrome have smaller platelets and lymphocytes, and their platelet counts are decreased; they have bleeding problems, recurrent bacterial and viral infections, and higher risk of autoimmune diseases and cancers. This disease affects about 1-10 in 1 million of live births (Aiuti & Roncarolo, 2009; Bouma et al., 2009; Dupré et al., 2004; Jin et al., 2004; Qasim et al., 2009; Ramesh et al., 1997; Zhu et al., 1997).

### 3.20 Other diseases

This possible gene therapy method also might be used to cure other diseases such as Alzheimer's disease (Rogaev et al., 1995; Sherrington et al., 1995), Parkinson's disease (Terzi & Zachariou, 2008; Veeriah et al., 2010), X-chronic granulomatous disease (CGD) (Aiuti & Roncarolo, 2009; Kang et al., 2010), type I (insulin-dependent) (Efrat, 1998) and type II (non-insulin-dependent) (Freeman et al., 1999) diabetes.

## 4. Conclusion

It is possible that normal human genomic DNA to be used as materials for homologous genetic recombination to repair defective genes *in vivo*. Normal human genomic DNA or normal genomic DNA fragments can be transferred into somatic cells/stem cells from a patient by microinjection, transfection, and electroporation. The corrected cells can be transplanted back to the same patient. Cells seem to be able to tolerate foreign DNA without immunological rejections; thus, the method described above may be an effective, relatively simple gene therapy method, and it may have no or less immunological reactions and rejections. Certainly, this possible approach of gene therapy should be performed only after strict and well-designed cellular and animal experiments and human clinical trials.

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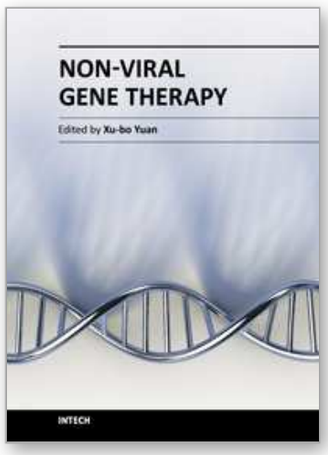
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