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Ethical Issues in Cell and Gene Therapy Using CRISPR/Cas9 System

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Abstract

The CRISPR/Cas9 system has revived many safety issues with our living system and all organisms such as environmental pollution, ecological calamity, risk assessment and genome editing in germline. The new concern is the simplicity, rapidity, accuracy and economics of CRISPR/Cas9 for cell and gene therapies, with the possibility of ethical issues. These issues may include evaluation of benefits and risks, compatibility of private interests and the public good, random manipulation of genes, and commercialization of human therapy. CRISPR/Cas9 has multiple advantageous applications, but hazards are unavoidable. A scientific evaluation system is needed to assure that benefits are greater than risks. There have been many disputes and frictions among companies over patenting CRISPR/Cas9 for human therapy because many commericial interests are involved. An agreement to regulate patent holders and licensees to consider the public good is required. Altering a gene may produce new or undesired species, and lead to unknown or unpredictable diseases. The use of CRISPR/Cas9 in gene editing should be deliberately evaluated and strictly controlled, especially in human germline. CRISPR/Cas9 has been demonstrated promising for many diseases treatment; however, cell and gene therapies usually require a long course of treatment and cost much. The therapy should be affordable for all patients to avoid being privileged or prioritized for some people. Ethics is not a barrier to science but to allow science to develop long term and perfectly. It is necessary to have a public communication over the social, legal and ethical implications with the policy/regulatory needs of the system.

Keywords: CRISPR, Ethics, Genome editing, Cell and gene therapy, Risk assessment.

Introduction

Cell therapy is a kind of treatment in which live whole autologous or allogeneic cells are introduced into a human body to replace, repair, reconstruct, or supplement damaged cells/tissues. Autologous or allogeneic cells that are engineered and cultured *in vitro* are not the same as the original cells. Cell therapy products (CTPs) are biomedicines containing cells/tissues that have been manipulated to change their biological characteristics, and these cells/tissues can be used to diagnose, treat or prevent diseases [1]. Gene therapy is a kind of treatment to make genetic improvement through the repair, deletion, insertion or substitution of mutated genes or site-specific modifications for target therapies [2]. This therapy has become possible through the advances of genetic engineering technology that enabled the manipulation of genome and the development of delivery tools such as lipoids, viruses, nanoparticles, or gene guns to transport normal genes to target cells. Gene therapy products (GTPs) are biomedicines containing normal genes to diagnose, treat or prevent diseases by the gene targeting or recombination of an abnormal gene responsible

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for a certain disease. At the outset, CTPs are used to treat rejection during organ transplantation and GTPs are used for treating genetic diseases, respectively; furthermore, both of them are being developed to treat cardiovascular diseases, metabolic diseases, neurodegenerative diseases and cancers. Currently, CTPs and GTPs, referred as advanced therapy medicinal products (ATMP), have opened a new era for human therapy and widely used in clinical applications for treating a variety of human diseases.

There have been many biotechnologies applied to manipulate cells and genes for CTPs and GTPs such as zinc finger nucleases (ZFNs), transcription activator-like effectors nucleases (TALENs), bacterial artificial chromosomes (BAC), and clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR associated nucleases 9 (CRISPR/Cas9) system. Among them, CRISPR/Cas9 is the most popular one due to its efficiency, precision, simplicity, versatility and economics compared with other approaches. CRISPR/Cas9 has been shown to work as a successful genome engineering or editing tool in bacteria, animals and human cells [3]. For example, chimeric antigen receptors T cells (CAR-T) which receptors are grafted an arbitrary specificity for cancer immunotherapy can be engineered by CRISPR/Cas9. Indeed, CRISPR/Cas9 offers the potential to facilitate both safe and effective CTPs and GTPs for human diseases [4].

In this review, we discuss some of the major ethical issues including evaluation of benefits and risks, compatibility of private interests and the public good, random manipulation of genes, and commercialization of human therapy for clinicians, regulators, legislators, policy-makers, researcher, bioethicists and human ethics committees in the clinical translation of CRISPR/Cas9 mediated cell and gene therapies.

Evaluation of Benefits and Risks

Recent research of cell and gene therapies including the discovery, production, applications and prospects has gained fruitful outcome and had a great impact over the humans. Innovative CTPs and GTPs mediated by CRISPR/Cas9 are developing rapidly and have brought great therapeutic benefits. They have been applied to treat a variety of diseases for which no other drugs, medical devices or therapeutic methods are available. In addition, these products are potentially more beneficial than chemotherapy, which usually lacks selectivity and may cause nonspecific toxicity [5]. However, CRISPR/Cas9 may be risky since it may generate off target mutations which are deleterious. A high frequency of off target effects has been found in human cells. CRISPR/Cas9 may also cleave the unintended sequences which are identical or highly homologous to intended target DNA to cause cell death or transformation. Though many efforts have been tried to reduce off target effects, it is still necessary to make further improvement especially for precise modifications needed for therapeutic interventions. Another important problem is that efficient, safe and specific delivery tools of CRISPR/Cas9 are hard to find or develop [6]. In spite of significant progress, several risks still should be noted in the clinic application such as mutation, nonspecific expression, low efficiency delivery and deficiency in biosafety (Table 1).

The important ethical issue in cell and gene therapies is that benefits must be greater than risks (Figure 1). The risks may damage living beings or pollute the environment, so greater attention should be placed on them. Consequently, a scientific evaluation system is needed to assure that benefits are greater than risks. Risks and benefits can be quantified and qualified through the analysis of statistics and classification, respectively. Quantifying the possible risks and benefits of cell and gene therapies is considerably uncertain, though qualifying them is feasible. It is possible to develop a formula to evaluate risk-benefit ratio for cell and gene therapies provided that we have enough data in trials and clinical applications. Within the permissible extent of CRISPR/Cas9 mediated activities, rigorous regulatory approaches for risk assessment will be essential. For variable CTPs and GTPs, it is recommended for the policy-maker to establish a national system for evaluating whether a given intervention has adequate risk–benefit. Jurisdictions may legitimately set different thresholds for an acceptable risk–benefit ratio [4].

Policy and regulation must be science and evidence-based. Regulatory processes should be based on adequate scientific expertise and take into account technological and social risks. It will be challenging for clinicians or regulatory agencies to navigate the risks and benefits of translating genome editing into the clinic only by expert judgement, and thus broader consultation is required. United States Food and Drug Administration (US FDA), European Medicines Agency (EMA), Japanese Pharmaceuticals and Medical Devices Agency (PMDA), and the Australian Therapeutic Good Administration (TGA) are open to public participation in the course of their risk assessment. Human research ethics committees, which are in charge of approving and monitoring clinical trials, show an opportunity for broader engagement. Trials of CRISPR-mediated cell and gene therapies present broader stakeholder engagement in risk assessment, including physicians, patients, patent holders

Table 1: Potential risks of cell and gene therapies based on CRISPR/Cas9.

Risk	Reason
Mutation	INDEL induced by off target effects of CRISPR/Cas9
Nonspecific expression	Incorporation of foreign genes into recipients' genome to produce unpredictable or unknown proteins; Toxic effects of CAR when healthy tissues express the same target antigens as tumor cells, leading to GVHD
Low efficiency delivery	Lack of efficient delivery tools for CRISPR/Cas9
Deficiency in biosafety	Toxic or biohazardous delivery tools; Delivery to non-target cells

Abbreviations: insertion and/or deletion (INDEL), chimeric antigen receptors (CAR), graft-versus-host disease (GVHD), clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR associated nuclease 9 (Cas9) (CRISPR/Cas9).

and product manufacturers, to determine the acceptable thresholds for risk and benefit [7]. This indicates not only to evaluate what magnitude of risk is acceptable, but also to discuss which outcomes are considered, and what counts as risk or benefit, and to whom [4]. Though broader stakeholder engagement is advantageous to set an acceptable threshold for risk and benefit, it may raise the complexity and difficulty in determining the threshold. Therefore, a dialogue platform for all stakeholders to have freedom of information, negotiation, and communication are essential (Figure 2).

Compatibility of Private Interests and The Public Good

There have been many disputes and frictions among researchers, institutions and companies over patenting CRISPR/Cas9. In the United States, the developing patent battle between Jennifer Doudna (University of California, Berkeley) and Feng Zhang (Broad Institute, Harvard & MIT) has led to rifts and several institutions are embroiled in the legal dispute over the patent rights to CRISPR/Cas9 technology [8]. The small community of researchers is fractured by concerning about private interests such as intellectual property, academic credit, geographic reputation, media coverage, conceit, personal profit, loyalty and even Nobel Prize [9]. The institutions controlling CRISPR/Cas9 patents have delegated them to surrogate companies which determine who will be capable of taking advantage of them; particularly, exclusive licenses are usually surrogated for human therapeutics [10]. The institutions and companies seem to devote themselves to pursuing commericial interests. The patent fight reminds us that research universities have abandoned their public focus, and everyone is trying to jockey himself and minimize what others do. The tendency is obvious that private interests are over the public good.

It is important to keep the compatibility of private interests and the public good (Figure 3). The research and development (R&D) of cell and gene therapies using CRISPR/Cas9 is perhaps risky, costly, and time-consuming; thus, researchers, funders and product manufacturers must have enough incentives to develop CTPs and GTPs. Patents and licenses are good incentives for geting suitable revenue (Figure 4). In addition, patents can be used as tools to minimize social harm and maximize social benefit if holders are able to negotiate ethical terms into patent license agreements. The benefits of researchers, funders and manufacturer must be encouraged, but the public good should also be considered in that most private interests are from the public. To promote the public good, any exclusive licenses should be narrowly down to specific genes, and the competition in the development of CTPs and GTPs based on CRISPR/Cas9 should be maximized. It is recommended to wind up with some patent rights and finally result in cross licenses among competitive parties or institutions. Regulators have to establish a complete patent system including application process, protective period and extent to assure the intellectual property of inventors and patent holders. It is encouraged to reach an agreement to regulate the right and duty of inventors, patent holders and product manufacturers, respectively (Figure 5).

Random Manipulation of Genes

CRISPR/Cas9 is a powerful and specific tool to target human cell genome, and thus making precise genetic modification at one's will possible [6]. In CAR-T cell therapy for cancer treatment, CARs are genetically engineered receptors that combine the specific binding domains from a tumor targeting antibody with T cell signaling domains to allow T cell activation [11]. Current gene therapies predominantly exist in research laboratories and their applications are still experimental. Most clinical trials are conducted in the United States, Europe, and Australia. However, some GTPs have recently been approved by US FDA such as Kymriah (tisagenlecleucel) and Yescarta (axicabtagene ciloleucel). CRISPR/Cas9 is broadly used for the potential treatment of diseases caused by recessive gene disorders such as cystic fibrosis, α-1 antitrypsin deficiency, β-thalassemia, muscular dystrophy, and sickle cell anemia, acquired genetic diseases such as cancers, and

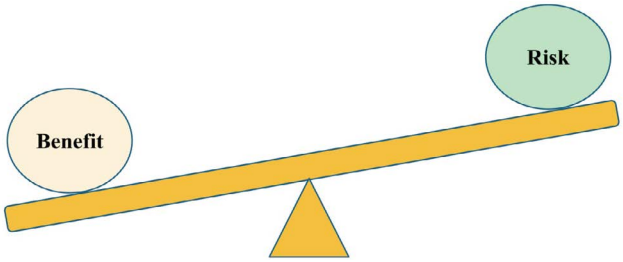

Figure 1: Benefits outweigh risks: In cell and gene therapies, therapeutic benefits for patients must be greater than possible risks.

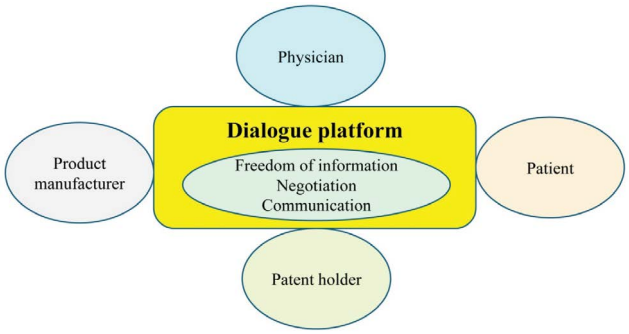

Figure 2: A dialogue platform for all stakeholders: Physicians, patients, patent holders and product manufacturers have freedom of information, negotiation, and communication to determine an acceptable risk-benefit threshold.

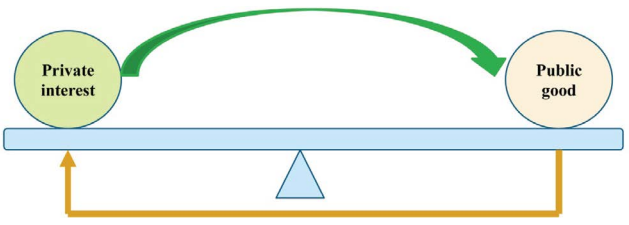

Figure 3: Balance between private interests and the public good: Private interests contribute to the public good and then the public good reimburses to private interests.

certain viral infections such as acquired immunodeficiency syndrome (AIDS) [2]. During the CTPs or GTPs therapeutic period, foreign genes may be introduced into patients and remain inside the body. In some cases, foreign genes are incorporated into host genome to alter genetic traits or even lead to mutations and cancers. Not everyone is adequate to be treated by cell and gene therapies, individual diversity must be considered. Consequently, deliberate evaluation for the adaptation of CTPs and GTPs for individuals by preliminary genome analysis to avoid off targets is needed. It is also required to regulate prophylactic measures such as prognosis monitor and post-market surveillance to prevent side effects and sequelaes caused by cell and gene therapies (Figure 6).

Another important issue is the random manipulation of genes, especially in human germline cells. Scientists have successfully edited the DNA of viable human embryos using CRISPR/Cas9 [12]. This is the first step to gain the ability to edit human DNA to allow scientists to prevent babies from being born with incurable diseases or disabilities by gene therapy. Comparative studies, fueled by recent technological advances in single-cell analysis, have allowed profound analysis and functional genetic studies of the human embryo [13]. Altering an embryotic gene can treat inherent diseases, but it is likely to produce new or undesired species, and lead to other unknown or unpredictable diseases. Consequently, further success with these kinds of research may raise the concerns on the ethical implications of genetically altering human embryos. It is essential to have a deliberate evaluation and strict control mechanism for cell and gene therapies on human embryos using CRISPR/Cas9. We do not advocate any application of genome editing on the human germline until a rigorous assessment and approval process is undertaken by the global research communities and ethics committees [14]. Positioning CRISPR/Cas9 on the manipulation of human embryos within the context of the regulatory framework is crucial to understand the social and political context that has facilitated the support to human embryo research based on CRISPR/Cas9 in the world [15].

Commercialization of Human Therapy

Cell and gene therapies based on CRISPR/Cas9 are highly scientific, specific and customized therapeutic approaches. CTPs and GTPs are expensive due to their high development cost and application for personalized and precise medicine. Additionally, cell and gene therapies usually require a very long course of treatment and have high medical costs; thus, CTPs or GTPs have potentially high profits. Recently, cell and gene therapies based on CRISPR/Cas9 have become a business. Many pharmaceutical plants and biotechnological companies use this technology to produce CTPs and GTPs. Along with the rapid biotechnology development, CTPs and GTPs for the treatment of most diseases may come to fruition very soon. CTPs and GTPs are promising in developing a profitable industry. However, human right for therapy is basic and common value in the world, CTPs and GTPs interventions should be developed to deliver economic value to patients, payers, and healthcare systems. Developers, funders, clinicians and payers should work to ensure that

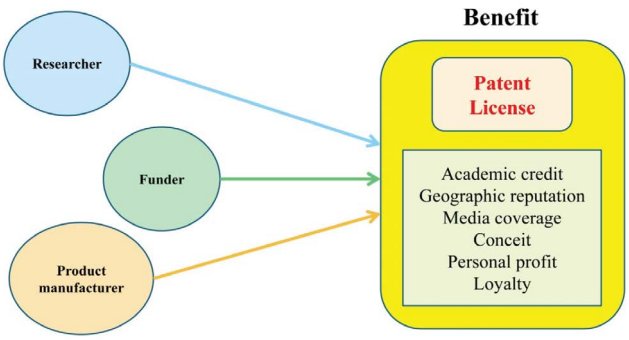

Figure 4: Encouragement of the development of cell and gene therapies for researchers, funders and product manufacturers: Patents and licenses are the best incentives for getting suitable revenue, in addition to other benefits such as academic credit, geographic reputation, media coverage, conceit, personal profit and loyalty.

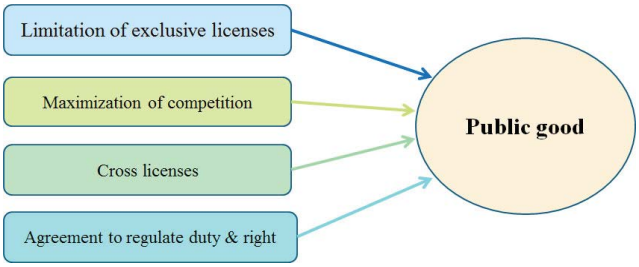

Figure 5: Promotion of the public good: The public good must be considered in that most private interests are from the public. Licensing and an agreement among inventors, patent holders and product manufacturers should be regulated.

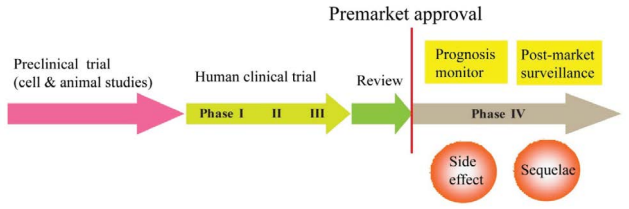

Figure 6: Prophylactic measures: To regulate prognosis monitor and post-market surveillance to prevent side effects and sequelaes is required.

cost of treatment does not prevent patients from accessing these interventions for life-threatening or seriously debilitating medical conditions [16]. It is imperative that cell and gene therapies equitably cover all persons and that it is affordable for all patients. The regulators have to establish a specific insurance and payment system to regulate cell and gene therapies to avoid CTPs and GTPs being privileged or prioritized for only some people (Figure 7).

CTPs and GTPs have the trend to be commodified; many manufacturers are aiming at pursuing commercial interests. Commercial promotion of unsupported therapeutic uses of CTPs and GTPs is a global problem that has proven resistant to regulatory efforts. Some unapproved or unproved CTPs

and GTPs are tried on patients only according to their indefinite perspective. Some CTPs and GTPs which clinical trials or data are still incomplete are prematurely released on the market only due to significant interests. A coordinated approach at the national and international levels focused on engagement, harmonization and enforcement must be implemented to reduce the risks related to direct consumer marketing of unapproved or unproven CTPs and GTPs [17]. Though some CTPs or GTPs have not yet completed their efficacy validation, they have enough data to verify their safety and estimate their efficacy. For the therapy of patients who are in serious conditions or unmet medical needs, specific CTPs or GTPs can be accessible to these patients with adaptive licensing [1]. The regulator should establish a conditional approval system with deadline, a fast-track review and communication mechanism to have patients in urgent need use specific CTPs or GTPs as soon as possible.

Financial imperatives are another complication in the clinical application of CTPs and GTPs based on CRISPR/Cas9, because it is needed to ensure that the financial benefits of clinical delivery outweigh the costs. The development process of CTPs and GTPs including discovery, production, application and marketing usually cost much; however, the revenue is hard to evaluate, that is, reimbursement is an important consideration. Some products failed to be continuously produced after marketing due to low cost recovery, for example, Glybera, the first gene therapy product to get EMA authorization and approval in 2012, has been discontinued by its manufacturers following poor application by physicians [4]. Consequently, any manufacturer plans to involve in the industry of CTPs and GTPs, it is necessary to have a preliminary evaluation plan for finance to verify the returns to make them worth investing. These manufacturers have to try their best to raise the profit but to reduce the expense. One way to reduce the large financial burdens is to facilitate the collaboration of different manufacturers worldwide to allocate their jobs depending on individually specialized fields such as R&D, production, application and marketing. The other way is to harmonize CTPs and GTPs review and approval processes across countries. This means that if a product is approved in one country, the same document can be used for approval in another and perhaps even be automatically granted. Such collaboration or harmonization would permit manufacturers to reach economic scale more quickly, reducing the cost and resulting in more favorable cost-benefit analyses (Figure 8). Although international collaboration and harmonization is difficult to achieve, regulators should make effort to work towards this aim through the exchange of experience in global forums and international conference of harmonization (ICH).

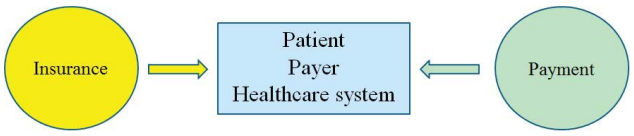

Figure 7: A specific insurance and payment system for patients, payers, and healthcare systems.

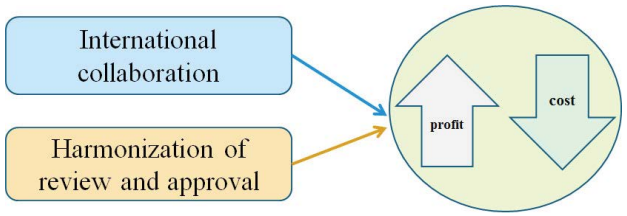

Figure 8: Measures to raise profit and cost down cell and gene therapy products.

Conclusion

The CRISPR/Cas9 system has revived many ethic issues of cell and gene therapies such as risk assessment, consideration of private interest and the public good, genome editing in human embryos and commercialization of therapy. The clinical applications of CTPs and GTPs pose a few ethical issues including costs, access, sustainability, information and consent, the right to unapproved or unproven treatments, scientific evaluation, patents and regulatory aspects [18]. If CTPs or GTPs can meet the requirement of ethics, then they will be approved for clinical application and marketing. However, through the resolution of ethical issues, ethics allow the therapeutic approaches to develop long term and perfectly rather than a barrier to cell and gene therapies based on CRISPR/Cas9.

To foster cell and gene therapy research, the feasibility, efficacy and safety of CRISPR/Cas9 must be assessed such as the benefit-to-risk balance of any potential clinical applications. It is necessary to estimate the impact of mosaicism at the on-target location, potential off-target effects, other adverse reactions and their clinical relatedness in cell and gene therapies by science and evidence based approaches [19]. The diligence of inventors and manufacturers should be encouraged by patent grant and commercial interest acquirement, respectively. The achievement of CTPs and GTPs will benefit the public, and the public good also can be strengthened by the return of private interests when therapy is motivated by market possibilities and opportunity [20]. Cell and gene therapies will contribute to the treatment of genetic or congenital diseases in embryos, but may cause unknown mutation or unpredictable diseases. The genome editing based on CRISPR/Cas9 should be monitored and evaluated strictly by regulation to avoid mutation induced by off targets, especially in human germline. Commodification of cell and gene therapies is an inevitable trend, but privileged or prioritized for only some people can be avoided through the establishment of a social security system. Additionally, the international cooperation and harmonization for the development and application of CTPs and GTPs will reduce the cost.

Cell and gene therapies provide a foresight and new option for incurable diseases using conventional therapeutic approaches such as surgery, drugs and medical devices. The CRISPR/Cas9 technology expedites the development of CTPs and GTPs; however, some ethical issues come with it. A public

communication and discussion over the social, legal, safe and ethical implications with the policy/regulation of CTPs and GTPs based on CRISPR/Cas9 is needed. In this review, we hope to provide a program for establishing a policy and regulation system to facilitate the development of cell and gene therapies but to minimize their ethical concerns.

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Conflict of Interest

The authors have no conflict of interest.

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