Recommendation

Genome Editing Technology in Medical Sciences and Clinical Applications in Japan

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Science Council of Japan

The original was written in Japanese and SCJ provides English version for non-Japanese readers.

Committee on Genome Editing Technology in Medical Sciences and Clinical Applications, of Science Council of Japan.

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This recommendation is published as a result of deliberations held by the Committee on Genome Editing Technology in Medical Sciences and Clinical Applications of Science Council of Japan (SCJ).

Abstract

1 Background of the recommendation

Genome editing, a new genetic engineering technology, enables the addition of exogenous genes, the correction of mutations, and the induction of deletion or insertion mutations at specific sites in a human genome with 3.1 billion base pairs. It has become an indispensable technique in the medical sciences because it is significantly more accurate and efficient compared to conventional recombinant DNA technologies. In the fields of medical sciences and clinical applications, therapies for a variety of diseases using genome editing are being developed, and some of them have already entered the stage of clinical development abroad.

2 State of play and issues

In 1990, long before the emergence of genome editing, the clinical development of gene therapy using recombinant DNA technology began in the United States. Initially, the efficacy was confirmed in clinical trials involving the transfer of a functional copy of a gene into patients with congenital enzyme-deficiency disorders. However, in a clinical trial conducted in France, gene insertion at an unexpected site caused the onset of leukemia, resulting in the patient's death. In Japan, against a backdrop of uncertainties surrounding gene transfer, guidelines for clinical research on gene therapy[1] were established, which required both the research institution and government to review research protocols. Today, nearly 30 years after the event, there are not many approved gene therapy products worldwide. Recently, gene therapy products have increasingly been approved outside Japan, whereas there has been no approved product yet in Japan.

Although genome editing enables us to conduct various forms of genetic modification in human somatic cells and stem cells, it is faced with technological challenges such as unintentionally introducing a mutation at sites other than at the target sequence (off-target mutation). In this context, expectations for the future clinical development of genome editing therapy in Japan pose a challenge on how to make fruitful use of its various genetic modification capabilities, which are not exclusive to gene

[1] "Guidelines for Gene Therapy Clinical Research" MHW: Ministry of Health and Welfare Notice No. 23). Published in 1994 (last amended in April 2017).

addition, in therapies for a variety of diseases while securing patient safety. Meanwhile, a paper by researchers in China attempting to genetically modify human zygotes (one-cell stage embryos) using genome editing has stirred a worldwide controversy over its ethical and social implications. We should be cautious about the clinical use of genome editing in human embryos because the rough-and-ready use of such a clinical application may lead to off-target mutations and could affect every cell in the resulting child. Moreover, in countries where reproductive medicine is not strictly regulated, some people fear that it might be abused by prospective parents to attain a desired trait, such as appearance, for their child. Furthermore, some people are concerned about genetic modification of human embryos, considering them as "the emerging potential of human life,"[2] while molecular biological research on human germ cells and embryos using genome editing is expected to produce significant scientific knowledge regarding human reproduction and development.

With these situations in mind, this committee has organized an open symposium in 2017, and taken into account opinions expressed by citizens at the symposium in deliberations on the use of genome editing technologies primarily in medical sciences and clinical applications in Japan. The committee now summarizes this recommendation as the result of these discussions.

3 Content of the recommendation

(1) Somatic genome editing therapy – Protection of the rights of research subjects and development for regulation on clinical research

Somatic genome editing-based therapy, which is expected to offer promising treatments for intractable diseases, is divided into ex-vivo genome editing therapy and in-vivo genome editing therapy. The former is subject to the Act on the Safety of Regenerative Medicine[3], and the latter is subject to the Guidelines for Gene Therapy Clinical Research. Somatic genome editing therapy must be cautiously developed based on each of these regulations with the protection of the rights of the research subjects in mind. As the current Guidelines for Gene Therapy Clinical Research does not cover clinical studies on in-vivo genome editing therapy not involving gene transfer,

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[2] In Japan, there is no provision of the law to give the status of a human being to human embryos. As the result of examining the handling of human embryos by the Council for Science and Technology Policy based on the Act on Regulation of Human Cloning Techniques (Article 2 of the supplementary provision), a report called "The Basic Concept of Handling of Human Embryos" was submitted. The report states that even though human embryos may not be "human beings" themselves, they should be particularly respected in order to maintain the fundamental values of society for "human dignity," and they are considered to be "the emerging potential of human life" in this sense.

[3] "Act on the Safety of Regenerative Medicine" (Act No. 85 of 2013). Established in November 2014.

we request that the Japanese Ministry of Health, Labour and Welfare (MHLW) develop necessary regulations that adequately cover clinical research of somatic genome editing therapy.

(2) Building a support framework for the development of somatic genome editing therapy products

With regard to the development of products for genome editing therapy within the framework of the Pharmaceutical and Medical Device Act[4], the MHLW and the Pharmaceuticals and Medical Devices Agency (PMDA) should materialize the mechanism for consultation and support by, for example, establishing risk assessment systems for off-target mutations in cooperation with relevant academic societies.

(3) Stringent regulations including prohibition of clinical applications of reproductive medicine involving genome editing

Reproductive medicine which uses genome editing to genetically modify germ cells or embryos poses grave medical and ethical concerns such as side effects on resulting children. In addition, discussion on this issue within Japanese society is still premature. It is, therefore, not appropriate to apply genome editing to reproductive medicine at present; hence, such a clinical application must be prohibited for the time being by governmental guidelines. On the other hand, even when advances in medical sciences resolve safety issues, or when changes in the mindsets of people resolve ethical issues, the permissibility of implementation of reproductive medicine involving genome editing requires careful and ongoing discussions. Furthermore, the need for statutes for regulating experimental manipulation of human germ cells and embryos, including genome editing, must also be considered.

(4) Regulations on basic research involving genome editing of human germ cells and embryos, taking into account social understanding and transparency

Scientific findings obtained through this basic research are expected to contribute to the improvement of assisted reproduction technology by elucidating human reproductive and developmental processes; however, considering people's ethical concerns, a cautious attitude is required on the part of researchers. In view of concerns regarding research reports from China, basic research that clearly aims for applications

4 "Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices" (Act No. 145 of 1960). Amendment of Act No. 50 of 2015.

in reproductive medicine should be withheld at the moment. A framework must be established that cautiously examines whether each basic research should withhold its implementation presently or allow it under stringent conditions while considering advances in medical science, as well as growth in social understanding according to specific research purposes. In case basic research is undertaken, we strongly urge that the existing government guidelines be followed and that the Japanese Ministry of Education, Culture, Sports, Science and Technology and the MHLW take the lead in developing guidelines, including those for screening procedures adequate for this scientific research.

Conclusion

This committee has discussed chiefly genome editing regarding human somatic cells, germ cells, and embryos, and compiled proposals on the use of genome editing in Japan. However, proposing a tangible regulatory framework remains a challenge because our discussion was not comprehensive enough to cover the background and opinions of the general public on this issue, taking into account the close link between this issue and the practices of conventional gene therapy and reproductive medicine. The committee has also discussed how national regulations ought to be and has pointed out flaws in the current regulations. However, a framework outlining the direction for future international cooperation has yet to be established as far as human genome editing is concerned. SCJ must continue discussions on issues presented herein, and positive responses are required from the relevant ministries.

Research on human germline genome editing has caused strong concerns globally since basic research using human embryos by a Chinese team was reported in April 2015. The International Summit on Human Gene Editing was held in the United States in December of the same year, which included the participation of academic representatives from Japan. At that time, however, SCJ had not conducted a full-fledged discussion on genome editing of human germ cells and embryos, while applications of genome editing to agriculture had been discussed from a technical standpoint. It was not until July 2016 that this committee started discussing the matter, so it is hard to claim that our discussion was prompt.

Recent technological progress in biomedicine is moving at a fast pace, and novel scientific achievements may not only provide benefits to society, but also cause serious ethical concerns. If SCJ is to take the initiative in dealing with problems that will arise between science and society, it must develop a framework whereby it continuously keeps

track of the latest life science research and expected problems. The committee may face difficulties if its study framework is sectional or organized by each issue. Its mission should be to track the latest trends by seeking assistance from relevant academic societies and following people's views on certain technologies through public comments and open forums. Furthermore, this committee must set out to discuss, in advance, problems that may arise between science and society. We believe that the development of such a study framework ensures that missing correct timing, as seen in the late start of discussions mentioned above, would be avoided, and that SCJ, as a representative academic organization in Japan, will always lead the latest research. Therefore, we hope to see the council's development. Furthermore, since international cooperation is of crucial importance for regulations concerning genome editing, we hope that representatives from SCJ will attend relevant international conferences, and that the MHLW, PMDA, and pharmaceutical companies will proceed with regulatory harmonization by utilizing the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH).