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Genome Editing Technology - Principle -

Rationale

Genome editing is a type of genetic engineering in which DNA is inserted, deleted or replaced in the genome of living organisms through the use of engineered DNA binding proteins. In recent years, genome editing focused on targeted nucleases such as Zinc Finger Nucleases (ZFN) and Transcription Activator-Like Effector Nucleases (TALEN). The discovery of Clustered Regularly Interspaced Short Palindromic Repeat (CRISPR) associated with Cas-9 has rapidly expanded the availability of genome editing tools and has made genome editing far more accessible and easy to implement. While this has resulted in major positive advancements in biological research and medicine, the growing potential of using genome editing technologies in the human germline has opened up scientific, legal and societal concerns while the regulatory framework has not adapted to the new possibilities. In this environment, a clear ethical framework is needed, within which Merck KGaA, Darmstadt, Germany, and its divisions can operate. To provide clarity, Merck KGaA, Darmstadt, Germany, has developed the following company Principle.

Objective

This Principle provides all Merck KGaA, Darmstadt, Germany, employees with background information on genome editing technology and with the current position on the engagement of the company on the use of such technologies.

This Principle defines the ethical framework and operational boundaries for Merck KGaA, Darmstadt, Germany, and its divisions as a:

- supplier of custom targeted nucleases and genetically modified cell-lines;
- user of genome editing technologies for scientific research.

Since genome editing technology is constantly progressing this Principle undergoes regular review including review by the Bioethics Advisory Panel (MBAP).

Contents

1. Background

There has been a rapid development in genome editing technologies in the last few years. While the programming and use of previously available zinc finger nucleases and TALEN is cumbersome and expensive, the CRISPR-Cas9 method can be used very efficiently, saving time and costs. This opens up a new scope for molecular biological basic research, particularly into organisms that were not previously accessible for molecular genetic purposes, and for elucidating poorly understood gene functions. A publication in March 2014 (Tebas P et al. 2014) demonstrated the clinical use of zinc finger nucleases for the induction of acquired genetic resistance to HIV infection via targeted gene disruption of CCR5 in autologous CD4 T cells and in April 2015 Liang P et al. showed genome editing of non-viable human embryos using CRISPR-Cas9 (Liang P et al. 2018). These publications demonstrate that human therapeutic genome editing as well as germ line genome modification have moved out of the realm of the theoretical to the actual. The first use ZFN *in vivo* in a human clinical trial for somatic cell therapy was initiated by *Sangamo Therapeutics* (Mullard A at al. 2019).

In October 2018, there were reports (but not peer-reviewed publications) of the birth of the first germ line edited humans (Cyranoski D 2019). This breach of law, ethics and academic self-regulation has led to marked global critique. Subsequent discussions have emphasized the need for deep bioethical debate and meaningful governance of genome editing research in the human germline.

The current discussion as it relates to this Principle focuses on the following areas:

1. Fundamental research on:
   - basic biology, e.g. mechanisms of hereditary diseases
   - genome editing methodologies

2. Research for clinical purposes on:
   - Alterations to somatic cells, e.g. genome editing or gene transfer for the treatment of certain diseases (mainly those attributable to one or only a few parts of the genome) or for introducing certain desirable characteristics such as immunity against certain infections. Such cells are generally modified outside the body (ex vivo) and any adverse side effects would be limited to the removed cells. Nevertheless, the potential risk for off-target toxicity and the insufficient specificity and efficiency make these methods only suitable for the treatment of severe diseases. Furthermore, there is still a significant lack of the necessary insight into the complex interplay between human genes and/or individual gene variants and environmental and life-style issues. Cells can also be directly modified within an organism (in vivo), in which case the same risks apply as for ex vivo modification and there is additional care needed to ensure that only the target cells are genetically modified.
   - Alterations to germ cells or embryos. These suffer the same shortcomings and uncertainties as for somatic cells. However, for every change, any unintended alteration, together with the intended alteration, will be passed to the progeny of the treated person.

Even if the questions around efficiency, specificity and safety of genome editing can be resolved, there are also ethical issues to be considered. These issues include the consequences for the individual, their offspring and the potential repercussions for society as a whole.

2. Merck KGaA, Darmstadt, Germany, Position

Merck KGaA, Darmstadt, Germany, as both user and supplier of the necessary technology, has defined a clear operational position taking into account scientific and societal issues while not blocking any promising therapeutic approaches for use in research and application.

Merck KGaA, Darmstadt, Germany, supports the use of genome editing in basic research in hopes of discovering new and actionable biological information leading to novel approaches for disease treatment and prevention.

Merck KGaA, Darmstadt, Germany, supports the clinical use of genome editing and recognizes many potential benefits for correcting genetic diseases via the direct application of targeted nucleases to human somatic cells and tissues.

Merck KGaA, Darmstadt, Germany, does not support the use of genome editing in human embryos and clinical applications of germline interventions in humans in accordance with the German Embryo Protection Act. Merck KGaA, Darmstadt, Germany, recognizes that there may be value of responsibly conducted related research.

Merck KGaA, Darmstadt, Germany, is actively committed to a thoughtful discussion of genome editing issues via the ongoing work of the Bioethics Advisory Panel (MBAP).

Merck KGaA, Darmstadt, Germany, as a user of genome editing technologies in basic and clinical research.

Merck KGaA, Darmstadt, Germany, recognizes the potential benefits of conducting properly defined research with genome editing because of the breakthrough therapeutic potential. Therefore, research with genome editing is allowed with careful consideration of ethical and legal standards. Merck KGaA, Darmstadt, Germany, has established the MBAP to provide continuing guidance for research in which Merck KGaA, Darmstadt, Germany, is involved, including research on or using genome editing.

Merck KGaA, Darmstadt, Germany, as supplier of custom targeted nucleases and genetically modified cell-lines

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3. Outlook

In order to challenge the internal assessment of the genome editing position, this Principle will be periodically reviewed according to latest scientific, legal and ethical insights. To facilitate and support this type of review, Merck KGaA, Darmstadt, Germany, has installed a Bioethics Advisory Panel (MBAP) in 2011. The MBAP consists of a group of external renowned experts from the fields of sciences, bioethics and law. This board advises Merck KGaA, Darmstadt, Germany, on a regular basis on important topics with ethical and legal impact, including embryo technology, stem cell research, and genome editing.

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4. Glossary and Definitions

Abbreviation	Definition
ZFN	Zinc Finger Nucleases
TALEN	Transcription Activator-Like Effector Nucleases
CRISPR	Clustered Regularly Interspaced Short Palindromic Repeat
MBAP	Bioethics Advisory Panel

- **"Principle": Corporate definition**

  A Principle specifies the basic rules for Corporate Governance which needs to be complied with by all subsidiaries of Merck KGaA, Darmstadt, Germany, KGaA ("Subsidaries"). Its purpose is to ensure a consistent corporate governance framework for all Subsidaries worldwide. A Principle defines corporate governance structures and corporate governance responsibilities. It does not address organizational responsibilities.

For reference, link to other Merck KGaA, Darmstadt, Germany, policies:
http://biopharma.merckgroup.com/en/research_development/positions_policies/positions_policies.html