Charter	Merck KGaA, Darmstadt, Germany
Genome Editing Principles	
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Genome Editing Principles
Our Position

Merck KGaA, Darmstadt, Germany, recognizes the potential benefits of conducting properly defined research with genome editing because of the therapeutic potential for the treatment of a variety of diseases, conditions, and injuries. Therefore, certain research with genome editing is allowed with careful consideration of ethical and legal standards. We have established the MEAP to provide oversight and guidance on research we conduct involving genome editing.

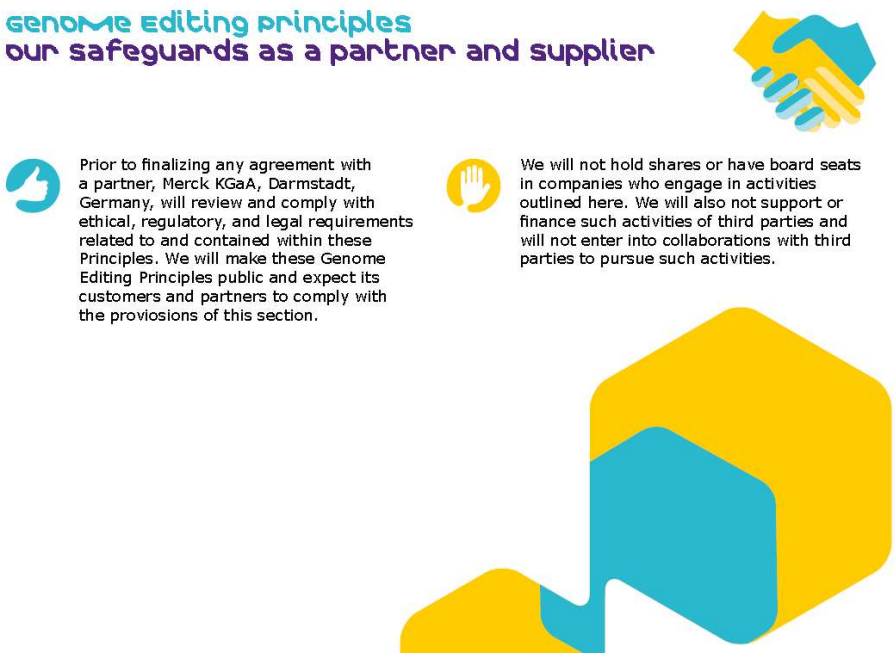
Genome Editing Principles
Our Safeguards for Research and Applications

In accordance with the German Embryo Protection Act and consistent with current guidelines, Merck KGaA, Darmstadt, Germany, will not engage in the use of genome editing in human embryos and clinical applications of germline interventions in humans. We recognize that there may be value of responsibly conducted research in these areas.

For genome editing research involving stem cells, careful ethical and legal assessments are also made in accordance with our Stem Cell Principles.

For genome editing research with animals, careful ethical and legal assessments are also made in accordance with our Policy on Animal Welfare.

Merck KGaA,
Darmstadt, Germany



1. Objective

Recent discoveries in the area of genome editing have resulted in major positive advancements in biological research and medicine. However, the potential of using genome editing technologies in the human germline, amongst others, has opened up scientific, legal and societal concerns while the regulatory framework has not adapted to the new possibilities. Research, clinical and commercial activities in the field of genome editing thus needs careful evaluation of ethical and legal concerns and requires a clear ramework within the Merck KGaA, Darmstadt, Germany, Group. Therefore, Merck KGaA, Darmstadt, Germany, has developed the following company Principles.

2. Scope

These company Principles provide Merck KGaA, Darmstadt, Germany, employees with background information on genome editing technologies and with the current position of the company on the use of such technologies.

All Merck KGaA, Darmstadt, Germany, employees using, or otherwise working with genome editing technologies are responsible for understanding and abiding by these Genome Editing Principles. In addition, Merck KGaA, Darmstadt, Germany, expects that third parties are up to date with respect to the on-going deliberations regarding the ethical aspects of genome editing.

New Merck KGaA, Darmstadt, Germany, technologies, services and therapies as well as collaborations in this area undergo regular internal review, in close relationship with, seeking and taking advice, from the Merck KGaA, Darmstadt, Germany, Ethics Advisory Panel for Science and Technology (MEAP), formerly Merck KGaA, Darmstadt, Germany, Bioethics Advisory Panel for Science and Technology (MBAP).

3. Executive Summary

Merck KGaA, Darmstadt, Germany, acknowledges the ethical controversies surrounding various applications of genome editing. These safeguards stipulate that consistent with current guidelines, Merck KGaA, Darmstadt, Germany, will currently not engage in the use of genome editing in human embryos and clinical applications of germline interventions in humans, while recognizing the potential value of responsibly conducted research in these areas. This includes collaborations or grants involving such research. Prior to finalizing any agreement with a partner, Merck KGaA, Darmstadt, Germany, will review and comply with ethical, regulatory, and legal requirements related to and contained within these Principles. Merck KGaA, Darmstadt, Germany, will not deliver any of its genome editing products and related services, if Merck KGaA, Darmstadt, Germany, becomes aware of any projects by customers, partners or institutes directed at research, clinical and commercial activities that are prohibited by Merck KGaA, Darmstadt, Germany, as specified here (see. 5.2 below).

4. 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. In 2021, the World Health Organisation's (WHO) Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing has issued a framework for governance and a set of accompanying recommendations (WHO 2021).

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

4.1. Fundamental research

- Basic biology (e.g., mechanisms of hereditary diseases)
- Genome editing methodologies (e.g., new targeted CRISPR-Cas9 techniques)

4.2. Research for clinical purposes

- 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.

5. Merck KGaA, Darmstadt, Germany, Position

Merck KGaA, Darmstadt, Germany, recognizes the potential benefits of conducting properly defined research with genome editing because of the therapeutic potential for the treatment of a variety of diseases, conditions, and injuries. Therefore, certain research with genome editing is allowed with careful consideration of ethical and legal standards. Merck KGaA, Darmstadt, Germany, has established the MEAP to provide oversight and guidance on research Merck KGaA, Darmstadt, Germany, conducts involving genome editing.

5.1. Current Engagement

Merck KGaA, Darmstadt, Germany, is a user of genome editing technologies in basic and clinical research as well as a supplier of custom targeted nucleases and genetically modified cell-lines. Merck KGaA, Darmstadt, Germany, uses its reasonable diligence to only sell to purchasers affiliated with recognized institutions and companies. Merck KGaA, Darmstadt, Germany, will not dispatch any purchase without a label license that outlines the licensed use of our material (see: https://www.sigmaaldrich.com/DE/de/life-science/legal/product-licenses/crispr-use-license-agreement).

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.

5.2. Safeguards for genome editing research and applications

Merck KGaA, Darmstadt, Germany, acknowledges the ethical controversies surrounding genome editing. In doing so, Merck KGaA, Darmstadt, Germany, complies with the following:

- In accordance with the German Embryo Protection Act and consistent with current guidelines, Merck KGaA, Darmstadt, Germany, will not engage in the use of genome

editing in human embryos and clinical applications of germline interventions in humans. Merck KGaA, Darmstadt, Germany, recognizes that there may be value of responsibly conducted research in these areas.

- For genome editing research involving stem cells, careful ethical and legal assessments are also made in accordance with Merck KGaA, Darmstadt, Germany,'s Stem Cell Principles.
- For genome editing research with animals, careful ethical and legal assessments are also made in accordance with Merck KGaA, Darmstadt, Germany,'s Policy on Animal Welfare.
- Prior to finalizing any agreement with a partner, Merck KGaA, Darmstadt, Germany, will review and comply with ethical, regulatory, and legal requirements related to and contained within these Principles. Merck KGaA, Darmstadt, Germany, will make these Genome Editing Principles public and expect its customers and partners to comply with the proviosions of this section.
- Merck KGaA, Darmstadt, Germany, will not hold shares or have board seats in companies who engage in activities outlined here. Merck KGaA, Darmstadt, Germany, will also not support or finance such activities of third parties and will not enter into collaborations with third parties to pursue such activities.

6. Outlook

Merck KGaA, Darmstadt, Germany, will periodically review this position according to latest scientific, ethical, and legal insights. The MEAP regularly advises on important topics with ethical and legal impact related to genome editing.

7. Glossary

Abbreviations	Definition
ZFN	Zinc Finger Nucleases
TALEN	Transcription Activator-Like Effector Nucleases
CRISR	Clustered Regularly Interspaced Short Palindromic Repeat
MBAP	Merck KGaA, Darmstadt, Germany, Bioethics Advisory Panel
MEAP	Merck KGaA, Darmstadt, Germany, Ethics Advisory Panel for Science and Technology

8. References

Group Standard "iMS-Document Management" (*ManGo Doc ID* 20043334)

9. Revision History

Version Number	Change short description	Replacement of Document
1.0	First Version	N/A
2.0	Updated according to new ISSCR guidelines; Merck KGaA, Darmstadt, Germany, position unchanged.	First Version