



# Statement on the scientific and translational impact of genome editing and arising ethical, legal and societal issues

MAX PLANCK SOCIETY

## CRISPR-Cas fueled acceleration of genome editing methods

Genome editing, a set of techniques to directly and efficiently modify DNA at specific chromosomal sites, allows for intentional changes to the genomes of living cells or organisms. Until recently, genome editing was cumbersome and thus only rarely applied. The CRISPR-Cas based technology has made genome editing much simpler, not only for research purposes but also for medical therapy and plant breeding as well as other applications.<sup>1</sup> Moreover, CRISPR-Cas has turned

out to be a highly versatile platform for precise alterations of genome activities that do not require permanent changes to the DNA itself, e.g. such as targeted changes of gene expression without DNA sequence modifications.<sup>2</sup> Genome editing has an enormous potential both for understanding biological principles and for improving human, animal and plant health. The technology has been rapidly taken up throughout the life sciences.

## Scientific and translational impact of genome editing

A brief sample of actual and potential applications of genome editing includes:

- Desired genetic changes can be introduced into a specific genetic background within a single generation, greatly accelerating the construction of new animal or plant models for basic research, as well as the construction of new disease models for drug development and testing. Within a few years of its discovery, the CRISPR-Cas technology has already driven many major scientific advances in different fields. Moreover, the relative simplicity of CRISPR-Cas methods puts the technology into reach even for small laboratories, or ones with modest equipment, anywhere in the world.
- Human, patient-derived stem cells can be gene-edited to create disease models in cells or organ-like structures (organooids) in the petri-dish (*in vitro*) to study human pathology and develop new therapeutics (e.g. colon cancer, cystic fibrosis, cardiomyopathy and brain malformations).

- New therapies for genetic disease such as sickle cell disease, beta-thalassemia, muscular dystrophy and for infectious diseases such as AIDS are already being developed.
- Crops with traits that are of interest to the consumer, such as reduced gluten content, have already gone beyond the proof-of-principle stage.
- The introduction of multiple mutations into animals such as pigs that eliminate immune incompatibility can make them suited to serve as organ donors for human patients.

Potential benefits of genome editing with CRISPR-Cas thus include acceleration of basic research, new approaches to transgene-free breeding of crops and the more rapid development of new therapies and cures for genetic diseases. In addition, there are highly controversial applications, such as human germline modification, and the elimination or alteration of populations of insects.

<sup>1</sup> Doudna JA, Charpentier, E. The new frontier of genome engineering with CRISPR-Cas9. *Science* 346: 1258096 (2014). DOI: 10.1126/science.1258096

<sup>2</sup> Dominguez AA, Lim WA, Qi LS. Beyond editing: repurposing CRISPR-Cas9 for precision genome regulation and interrogation. *Nat. Rev. Mol. Cell Biol.* 17, 5–15 (2016).



## Ethical and legal questions raised by genome editing

The ease of CRISPR-Cas methods makes discussions about its ethical, legal and societal implications inevitable. Some of the potential applications that can be implemented are without doubt challenging current normative systems. Examples that are of particular importance include i) release of genome edited plants and animals relevant for ecological research and agriculture, ii) genome editing in humans, and iii) gene drives in insects.

i) Biologists are increasingly realizing that a true understanding of genetic effects requires that their research subjects are studied under natural, outdoor conditions. An obvious question is therefore the legal treatment of genome edited plants and animals that researchers wish to grow or raise outdoors. This question is closely related to that of genome edited crops and animals in agriculture.

Because the European legislative on gene technology from 2001 (Directive 2001/18/EC)<sup>3</sup> did not foresee transgene-free genome editing, the European Court of Justice (ECJ) was asked to interpret the law. The ECJ ruled that genome edited organisms cannot benefit from the exemption that applies to genetically modified organisms (GMOs) generated by conventional mutagenesis techniques such as chemical treatment or irradiation. The ECJ based its ruling on the 2001 Directive, which exempted mutagenized organisms because decades-old experience had proven at the time the Directive went into effect that such organisms did not pose any particular risks. While the ECJ ruling bases on the 2001 Directive, and the precautionary principle, scientists find it difficult to understand why the law should make a distinction whether small mutations such as single basepair substitutions, deletions or additions are the result of spontaneous errors in DNA replication or whether they are the result of CRISPR-Cas based engineering. Such spontaneous mutations occur naturally every generation in every newly germinated plant or newly born animal. As these conflicting views show, there are good reasons to argue that Directive 2001/18 requires revision and updating to account for the major progress of gene technology, in particular in the field of targeted mutagenesis.

Many scientists are worried about the recent ECJ decision, since it effectively makes field research and crop breeding that take advantage of genome editing impossible in Germany. Many MPG scientists strongly advocate a European

political process aiming at updated Genetic Engineering legislation that is compatible with progress in gene technology and innovation in Europe and that distinguishes between genome editing applications that mimic natural mutagenesis processes and ones that require more oversight. In either case, transparency should be the guiding principle with regard to genetic changes that have been introduced to organisms through genome editing.

ii) For treatment of a range of human diseases, genome editing in somatic cells - all cells besides the germ cells that give rise to gametes, e.g. egg and sperm cells - has enormous potential. Examples include the treatment of hereditary genetic defects, of cancer, which is due to somatic mutations, and of certain infectious diseases such as HIV, which can be inactivated with CRISPR-Cas methods. Clinical trials are indeed already ongoing. There are no new ethical or legal issues concerning somatic gene editing beyond conventional gene therapy in adults.

Genome editing in human embryos has already been attempted.<sup>4</sup> Notably, He Jiankui in China, has claimed to have gene-modified an HIV susceptibility gene in at least two or three embryos that were recently born, sparking much debate about the ethics of heritable gene edits among the public, ethics councils, regulatory bodies and scientists alike.<sup>5</sup> In Germany, the law is very clear and human germline editing/ germline therapy or the use of human embryos for scientific research are prohibited by law, as they are in 13 other European countries. Such legislation is, however, not universal. There is agreement in large parts of the international scientific community that clinical use of genome editing in human embryos remains irresponsible, given the current state of the technology, the lack of clinical indications and the uncertainty about the ethical permissibility of such clinical use.<sup>6</sup> At the same time, opinions about future therapies for genetic diseases through heritable gene editing vary widely in different cultures, and within.

In agreement with the vast majority of their colleagues, MPG scientists currently do not see a justification for genome editing in the human germline, since safety issues as well as ethical concerns are not resolved. In addition, much safer alternatives already exist (e.g. preimplantation diagnostics). For germline editing of humans to be implemented, very difficult ethical conflicts would have to be resolved, including

<sup>3</sup> Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms.

<sup>4</sup> Liang P, Xu Y, Zhang X, Ding C, Huang R, Zhang Z, Lv J, Xie X, Chen Y, Li Y, Sun Y, Bai Y, Songyang Z, Ma W, Zhou C, Huang J. CRISPR-Cas9-mediated gene editing in human triploid zygotes. *Protein Cell* 6: 363–372 (2015).

<sup>5</sup> Dennis Normile, *Science*, 29 November 2018: Organizers of gene-editing meeting blast Chinese study but call for 'pathway' to human trials. *Deutscher Ethikrat*, Pressemeldung 26 November 2018; Anwendung von Keimbahn Eingriffen derzeit ethisch nicht vertretbar. *Christiane Nüsslein-Volhard*, *FAZ*, 8. Dezember 2018: Grenzen der Menschheit.

<sup>6</sup> <http://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=11282018b>. On Human Genome Editing II. Statement by the Organizing Committee of the Second International Summit on Human Genome Editing. November 29, 2018.



the trade-off between potential patient benefit and possible harm through off-target effects, unexpected effects in following generations. A further complication is where the line is to be drawn between curing a disease and enhancement of cognitive or other traits, which poses extremely difficult ethical questions. As long as there is no clear path for resolving such issues, genome editing in the human germline should not be pursued in the Max Planck Society.

iii) CRISPR-Cas methods can be applied to wild species with the goal of changing or eliminating entire populations of insects, in particular in combination with gene drive technology. The combination of both can potentially enable an enhanced frequency of inheritance that within a few generations can lead to an entire population being taken over by individuals having an introduced gene of choice. Such genes might prevent the vectors from transmitting diseases such as malaria, or maybe lead to collapse of the population due to sterility. The

application of the technique leads to ethical and legal problems that have to be responded, including the assessment of potential benefit and possible harms through off-target effects, cross border effects, and the need of informed consent by the potentially affected individuals and groups.<sup>7</sup>

In Europe, research and release of such modified insect vectors would fall under EU Directive 2001/18, which regulates the release of genetically modified organisms, while internationally the Cartagena Protocol will be applicable in many countries.<sup>8</sup> However, because not all problems are resolved by these rules and there are states where neither applies, MPG scientists deem it necessary to observe this field of research. The MPG intends to adopt an active advisory role in Germany and internationally regarding opportunities and risks of this technology, as the MPG is convinced that it is necessary to develop universal ethical and legal standards with regard to gene drives.

## Responsible research of the MPG with special consideration of the transformative power of genome editing

The MPG stands for free and responsible research<sup>9</sup> and thus requires its scientists to reflect on the ethics of experiments that use genome editing. It supports them in difficult ethical decisions through its institutional mechanisms (e.g. its Ethics Council).

As a crucial contribution to the public trust in science, the MPG is committed to open and transparent communication of its research using genome editing technologies, including respective procedures and objectives. New knowledge to assess and minimize risks of genome editing technologies acquired in the process of basic research in the MPG will therefore be made openly available, as is the case for other research in the MPG. The MPG will continue to inform policy makers about genome editing and participate in public debates as a contribution to the discourse about choices and decisions concerning issues of societal interest and the future of humankind. Within this process, risks and benefits must be assessed and balanced, and human rights must not be violated. The MPG is committed to ensuring that progress in genome editing technologies and the resulting applications (e.g. therapies for diseases) will be available to all. As part of this, we will ensure license practices coherent with freedom of research. The MPG will observe critical fields of research such as gene drive in wild populations of insects and, whenever possible, adopt an active advisory role in Germany and internationally on opportunities, risks and human rights implications of the respective technology.

In the area of plant and animal genome editing, the MPG calls upon politicians to pursue new and amended legislation that takes into account the differences between conventional genetic modification using recombinant DNA technology and transgene-free genome editing.

In the area of human genome editing, the MPG confirms its commitment to engage in discussions on the use of genome editing in humans, in particular when intended to induce heritable genetic changes. The MPG unequivocally judges that science is by far not sufficiently advanced to proceed safely to germline therapy. The MPG sees the need to discuss where to draw ethical red lines and what image we have of humans in the future. Whether it is possible to "improve" humans by germline modification, especially by introduction of favorable traits, can currently not be answered, given both the ethical challenges and our still limited knowledge about the complexity of human biology in health and disease. In addition, ethical viewpoints about the rights and values of people will differ between individuals, religions and cultures. There needs to be room, also in the future, for a variety of answers, without drawing in question fairness in the use of genome editing technology and respective therapies.

In cooperation with policy-makers, the MPG should play a role in shaping international norms for the responsible conduct of human germline editing.

<sup>7</sup> Cf UN Doc. CBD/COP/14/L.31, 28 November 2018.

<sup>8</sup> <https://bch.cbd.int/protocol/text/>

<sup>9</sup> Guidelines and Rules of the Max Planck Society on a Responsible Approach to Freedom of Research and Risks (Max-Planck-Gesellschaft, Hrsg., Mai 2017)



## Approach in this inquiry

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In 2017, the President of the MPG asked the MPG Ethics Council to provide information and expert advice on ethical issues relating to research that employs genome editing using CRISPR-Cas9 methods. The aim was to initiate a discussion, to inform the public, participate in public discourse, formulate requests to policy makers and ensure freedom of research while respecting legal and ethical limitations.

A working group of the Ethics Council started deliberations in 2017 and assembled a statement covering a wide range of aspects relevant to genome editing in basic science, and ethical, legal and societal implications, with the aim to inform the president. The working group has considered and discussed statements of other organizations.<sup>10</sup> These statements reflect an intense discourse on the implications of genome editing for the scientific community that began in 2015, and has recently culminated in the 2nd International Summit on Human Genome Editing in Hong Kong (November 2018). In a recent publication in *Nature*<sup>11</sup>, a prominent group of 18 scientists and bioethicists has called for a global moratorium on introducing heritable changes into DNA (human in sperm, eggs or embryos) to make genetically modified children. We have taken note of this initiative, but will not comment on it here since it came out after conclusion of the deliberations of our Working Group. We deem further discussions on heritable human genome editing necessary.<sup>12</sup>

Here, key points of the resulting paper<sup>13</sup> are summarized highlighting issues that should be addressed within the MPG and/or by policy makers in the near future. This summary is an initial contribution by the MPG to a discourse within the scientific community and beyond, intended to stimulate discussion on a range of issues relevant to MPG research. The rapid scientific developments based on CRISPR-Cas and other genome editing tools, and their possible applications will continue to raise new questions that call for discussion within the scientific community and the public at large. As an organization engaged at the frontline of basic research in life sciences and biomedicine, we want to continue to contribute our viewpoints to these discussions.<sup>14</sup>

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<sup>10</sup> E.g. <https://www.nap.edu/catalog/24623/human-genome-editing-science-ethics-and-governance>  
<http://nuffieldbioethics.org/project/genome-editing/ethical-review-published-september-2016>  
<https://www.gene-drives.com/gene-drives.pdf>

<sup>11</sup> Lander E, Baylis F, Zhang F, Charpentier E. et al. Adopt a moratorium on heritable genome editing. *Nature* 567: 165-168 (2019).

<sup>12</sup> [http://www.nationalacademies.org/genome-editing/2nd\\_summit/](http://www.nationalacademies.org/genome-editing/2nd_summit/)

<sup>13</sup> Statement (or Discussion paper) on Genome Editing by the Ethics Council of the MPG, 2018

<sup>14</sup> The presented paper reflects the status of January 2019.