University of Zurich[UZH]

URPP Human Reproduction Reloaded | H2R

Franziska Bächler and Anina Meier

An assessment of the current state of interdisciplinary CRISPR research

Report based on the workshop: The Technology and Ethics of CRISPR

H2R Working Paper 01/2024

ZLSR | Zentrum für Life Sciences-Recht

in Kooperation mit dem Zentrum für Life Sciences-Recht

Impressum

Suggested citation: Bächler, Franziska, Anina Meier. 2024. An assessment of the current state of interdisciplinary CRISPR research Report based on the workshop: The Technology and Ethics of CRISPR. URPP Human Reproduction Reloaded | H2R (University of Zurich), *Working Paper Series, 01/2024*. Zurich and Geneva:
Seismo, https://doi.org/10.33058/wpuzh.2024.7110.

Dieses Working Paper wird in Kooperation mit dem Zentrum für Life Sciences-Recht (Universität Basel) publiziert und ist im Rahmen des gemeinsamen Workshops "The Technology and Ethics of CRISPR" (3.–6. März 2024) entstanden.

Seismo Verlag, Sozialwissenschaften und Gesellschaftsfragen AG
www.seismoverlag.ch, buch@seismoverlag.ch

DOI 10.33058/wpuzh.2024.7110

H2R Working Papers Contacts and Information

University of Zurich
URPP Human Reproduction Reloaded | H2R
Law Institute
Rämistrasse 74/71
CH-8001 Zurich
info@humanreproduction.uzh.ch
https://www.humanreproduction.uzh.ch/en.html

Editorial Board

Table of contents

H2R Working Paper (1), 2024, 1–35

An assessment of the current state of interdisciplinary CRISPR research
Report based on the workshop: The Technology and Ethics of CRISPR

Dr. iur. Franziska Bächler* and MA Anina Meier**

Abstract: CRISPR/Cas genome editing is a dynamic field of biotechnology that is evolving and establishing itself in diverse fields such as agriculture and human medicine. The rapid development of this technology is accompanied by public debate about its various applications. This article sets out the opportunities and risks of CRISPR/Cas9 technology from an interdisciplinary perspective. The occasion and inspiration for the article was a workshop entitled 'The Technology and Ethics of CRISPR', which was organised in collaboration between the University of Zurich's Human Reproduction Reloaded (H2R) research programme and the University of Basel's Centre for Life Sciences Law (ZLSR) and was held in spring 2024 with presentations by renowned experts from various scientific disciplines.

The article outlines the current state of research on CRISPR with an overview of the natural and social sciences, legal and patent law as well as ethical aspects that appear to be essential for the interdisciplinary negotiation of the technology. This review of the application of CRISPR in medicine highlights the first approved CRISPR-based gene therapy for sickle cell anaemia and addresses the challenges of access and regulation that such medical breakthroughs face. The somatic application of gene editing is contrasted with its use in the human germline. The technological uncertainties and open ethical and socio-political questions regarding the latter are also summarised.

Key findings from the workshop presentations are embedded in a discussion and analysis of the CRISPR ecosystem, which is characterised by public-private partnerships and a complex patent situation.

Keywords: CRISPR, patent landscape, issue complexity, societal debate, transformative technology, access, guardrails

Une évaluation de l'état actuel de la recherche interdisciplinaire sur CRISPR
Rapport basé sur le workshop : The Technology and Ethics of CRISPR

Résumé : L'édition du génome par CRISPR/Cas est un domaine dynamique de la biotechnologie qui évolue et s'impose dans divers domaines tels que l'agriculture et la médecine humaine. Le développement rapide de cette technologie a été accompagné d'un débat public sur ses diverses applications. Cet article vise à présenter les opportunités et les risques de la technologie CRISPR/Cas dans une perspective interdisciplinaire. Il a été rédigé à l'occasion d'un workshop intitulé

* Franziska Bächler is a PostDoc researcher and the Scientific Manager at the Centre for Life Sciences Law (ZLSR) at the University of Basel.

** Anina Meier is a PhD candidate at the URPP Human Reproduction Reloaded | H2R, University of Zurich.

« The Technology and Ethics of CRISPR », organisé en collaboration avec le programme de recherche Human Reproduction Reloaded (H2R) de l'Université de Zurich et le Centre for Life Sciences Law (ZLSR) de l'Université de Bâle.

Il présente l'état actuel de la recherche sur CRISPR sous la forme d'une vue d'ensemble des sciences naturelles et sociales, des aspects juridiques, du droit des brevets et des aspects éthiques qui semblent essentiels pour la négociation interdisciplinaire de la technologie. Cette analyse de l'application de CRISPR en médecine met en lumière la première thérapie génique basée sur CRISPR approuvée pour l'anémie falciforme et aborde les défis de l'accès et de la réglementation auxquels sont confrontées de telles percées médicales. L'application somatique de l'édition de gènes est mise en contraste avec son utilisation dans la lignée germinale humaine. Dans ce dernier cas, les incertitudes technologiques et les questions éthiques et sociopolitiques en suspens seront présentées.

Les principales conclusions des présentations du workshop sont intégrées dans une discussion et une analyse de l'écosystème CRISPR, qui se caractérise par des partenariats public-privé et une situation complexe en matière de brevets.

Mots-clès : CRISPR, patent landscape, issue complexity, societal debate, transformative technology, accès, cadre juridique

Eine Bewertung des aktuellen Stands der interdisziplinären CRISPR-Forschung Bericht auf der Grundlage des Workshops: The Technology and Ethics of CRISPR

Zusammenfassung: Die Genomeditierung mit CRISPR/Cas ist ein dynamisches Gebiet der Biotechnologie, das sich in verschiedenen Bereichen wie der Landwirtschaft und der Humanmedizin entwickelt und etabliert. Die rasante Entwicklung der Technologie wird begleitet von gesellschaftlichen Debatten über ihre verschiedenen Anwendungen. Dieser Beitrag widmet sich der Einordnung der Chancen und Risiken der CRISPR/Cas9-Technologie aus interdisziplinärer Perspektive. Anlass und Inspiration für den Artikel war ein Workshop mit dem Titel «Technology and Ethics of CRISPR», der in Zusammenarbeit des Universitären Forschungsschwerpunkts Human Reproduction Reloaded (H2R) der Universität Zürich und des Zentrums für Life Sciences Recht (ZLSR) der Universität Basel organisiert und im Frühjahr 2024 mit Referaten von renommierten Expert:innen aus unterschiedlichen wissenschaftlichen Disziplinen durchgeführt wurde.

Der Beitrag skizziert den aktuellen Stand der Forschung zu CRISPR in Form eines Überblicks über natur- und sozialwissenschaftliche, juristische, patentrechtliche und ethische Aspekte, die für die interdisziplinäre Aushandlung der Technologie wesentlich erscheinen. Der Überblick über die Anwendung von CRISPR in der Medizin beleuchtet die erste zugelassene CRISPR-basierte Gentherapie für Sichelzellanämie und thematisiert die Herausforderungen des Zugangs und der Regulierung, mit denen medizinische Errungenschaften wie diese konfrontiert sind. Die somatische Anwendung der Geneditierung wird der Anwendung in der menschlichen Keimbahn gegenübergestellt. Für letztere werden die technologischen Unsicherheiten und die offenen ethischen und gesellschaftspolitischen Fragen dargestellt.

Die Schlüsselergebnisse der Vorträge sind eingebettet in eine Darstellung und Analyse des durch Public-Private-Partnerships geprägten CRISPR-Ökosystems und der komplexen patentrechtlichen Situation.

Schlüsselwörter: CRISPR, Patentlandschaft, Problemkomplexität, gesellschaftliche Debatte, transformative Technologie, Zugang, Rechtsrahmen

1 Introduction

This assessment of the current state of interdisciplinary CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) research is a response to suggestions from two speakers at the workshop, 'The Technology and Ethics of CRISPR', held in March 2024 in Monte Verità, Ascona, Switzerland. Prof. Claudia Wiesemann (Director of the Department of Ethics and History of Medicine, University Medical Centre Göttingen)[1] began her lecture in the 'Balint Room', named after the Hungarian-British psychiatrist Dr. Michael Balint. His life's work consisted of passing on his expertise from psychotherapeutic consultations to general practitioners, thus benefiting a large number of people in need of therapy. The speaker saw a similarity between this approach and the workshop, which was about communicating findings from the laboratory to other disciplines. We owe the suggestion to write a more detailed conference report to Prof. Dieter Egli (Associate Professor of Developmental Cell Biology at Columbia University)[2], who jokingly suggested that many of his colleagues in faraway Silicon Valley would benefit from hearing the insights revealed through our interdisciplinary exchange on the mountain of truth – Monte Verità.

This three-day workshop, lasting from 3 to 6 March 2024, brought together around 35 participants including leading scientists, ethicists, lawyers and practitioners from Switzerland, Europe and across the Atlantic. Following Prof. Andrea Büchler's (former Chair of Private and Comparative Law at University of Zurich and former Director of the University Research Priority Programme Human Reproduction Reloaded (URPP H2R) of the University of Zurich) initiative, the workshop was jointly conceived and organised by URPP H2R of the University of Zurich and the Centre for Life Sciences Law (ZLSR) at the University of Basel.

1 https://www.uni-goettingen.de/en/537520.html (08.08.2024).
2 https://www.eglilab.com (08.08.2024).

The workshop had three objectives:

1. To place the focus on interdisciplinary networking around the technology, in contrast to many conferences where the scientific aspects of CRISPR technology take centre stage
2. To ensure that young scientists would have their say, in addition to established experts.
3. To make a clear distinction between germline gene editing (Costa et al. 2023) and heritable gene editing[3] on the one hand and somatic gene editing[4] on the other hand, to do justice to their specific ethical, legal and social consequences.

To achieve these three goals, we took the following approach:

- We deliberately dispensed with discussion rules and restrictions on speaking time, to prevent hindering the exchange of ideas. In addition to expert presentations, moderated plenary discussions and roundtables were scheduled.
- Young scientists were given the opportunity to present and discuss their current research work in a poster session.
- A clear distinction was made between somatic gene therapy and germline therapy.

The workshop agenda was divided into three parts[5]. The first part was about the science of CRISPR/Cas9, its potential, possible applications, limitations and risks. Secondly, some of the speakers addressed ethical concerns, sociological implications, legal philosophical and legal regulatory aspects of gene editing. Thirdly, the workshop intended to shed light on somatic gene editing, to demonstrate the commercial and clinical breakthroughs achieved, discuss the patent landscape and the real-world problems hindering access to gene therapy for patients in need. These three aspects were discussed in an associative manner, in line with

3 Heritable gene editing refers to germline gene editing for reproductive purposes, where the edited embryo is implanted, resulting in a pregnancy. If heritable gene editing were to be carried out, it would be done using IVF technologies, meaning the mother would have to take hormones to produce multiple eggs. The eggs would be removed surgically and then fertilised outside the body in a laboratory. If the eggs were successfully fertilised, the genetic editing of the DNA would take place at a very early stage, before the cells started to divide. If the early embryo survived this, then in theory all the cells that were then created within that embryo would contain the edited DNA (Costa et al. 2023).

4 Somatic gene editing refers to gene editing in specific types of cells of an individual – an adult or even a baby in utero – that affects only that person and cannot be passed on to any future children that person may have, meaning that the changes are non-heritable (Costa et al. 2023).

5 Detailed programme: https://www.humanreproduction.uzh.ch/en/News-and-Events/Events/workshopCRISPR_03-06032024.html (08.08.2024).

the workshop's aim to explore and discuss the topic in an interdisciplinary way. This conference report is structured accordingly and is not based on the workshop agenda. Thereby, we focus on seven insights that emerged from the discussions on Monte Verità and put them into the current context and literature of the interdisciplinary debate on CRISPR.

2 Rapid development of CRISPR tools in a broad range of fields

CRISPR/Cas allows the precise[6] modification of genetic material and can be used in any cell type that has DNA. CRISPR/Cas intersects with a lot of different technologies. This means that a wide range of applications are being investigated, both in basic research and for practical use – from plant breeding to somatic applications in medicine, as well as applications in the human germline or human embryos. The technology can be used as either a research tool, a therapeutic agent or in a double function.

The first commercial breakthroughs in 2023 came just over 10 years after Prof. Martin Jinek et al.'s first publication on CRISPR's potential applications for gene editing in the laboratory in summer 2012 (Jinek et al. 2012). When Casgevy®, co-developed by Vertex Pharmaceuticals and CRISPR Therapeutics for use in patients aged 12 years and older suffering from severe sickle cell disease (SCD) or transfusion-dependent β-thalassemia (TDT), was approved by the UK's Medicines and Healthcare products Regulatory Agency (MHRA) (Kolata 2023), the National Health Regulatory Authority (NHRA) Bahrain (WHQ 2023), the US Food and Drug Administration (FDA) (FDA 2023), the Saudi Food and Drug Authority (SFDA) (Vertex 2024) and the European Medicines Agency (EMA) (EMA 2024), the world's first CRISPR-based therapy left experimental status in late 2023 / early 2024. In April 2024, Health Canada accepted Casgevy® for priority review (CISION 2024) and approves it in September 2024 (Stansfield 2024).

Prof. Gerald Schwank (Professor of Neuropharmacology at the University of Zurich)[7] discussed two technological advances of CRISPR systems, where double-strand breaks in the DNA no longer occur. In the first case, known as prime editing, only one double-strand break is induced. A guide RNA (pegRNA = prime editing guide RNA) combined with a Cas9 enzyme (nuclease) steers to the correct position in the DNA. Since only one strand is cut, off-target effects[8] might

6 Prof. Tanja Krones emphasised that the fact that there are off-target effects shows that CRISPR is not absolutely 'precise'.

7 https://schwanklab.org/ (08.08.24).

8 Discussions at the conference also focused on what terms should be used in relation to CRISPR. For example, Prof. Tanja Krones noted that 'off-target' is a term that originated in war rhetoric.

be reduced.[9] In the second case, known as base editing, there is no DNA strand breakage; instead, the guide RNA used only splits the DNA.[10]

Artificial intelligence programs can play a crucial role in further expediting the process, programming the system, calculating the efficiency and risk of editing, as Prof. Michael Krauthammer (Chair of Medical Informatics at the University of Zurich)[11] explained in his presentation. He described for example how his lab has developed a machine learning tool that uses an attention-based deep learning algorithm to make predictions from base editing results.

3 Significance of research in human embryo gene editing

In CRISPR/Cas, the Cas9 protein cuts the double-stranded DNA at the site where it is to be edited. In his talk on CRISPR/Cas9 in human embryos, Prof. Egli shared his observation that human embryos do not appear able to efficiently repair spontaneous or CRISPR/Cas9-caused DNA double-stranded breaks.[12] Based on these data, he concluded that CRISPR/Cas9 (for the moment) is not a suitable tool for gene editing in the human germline, because the double-strand DNA breaks caused by the application of CRISPR/Cas9 could lead to genetic abnormalities. Prof. Egli raised the question of how human embryos would repair base and prime editors' nicks compared to double-strand breaks.

During the conference participants discussed that research using CRISPR systems in human embryos could be highly relevant as part of basic research to study double-strand breaks, which occur frequently in nature (without being observable). Furthermore, such research could help to understand what does not work with CRISPR-Cas when applied to the human embryo. As in any drug development research, animal models play a central role in the development and research of gene editing. For example, Prof. Ben Davis' (Head of GeMS at The Francis Crick Institute)[13] lab has had significant success in using CRISPR to 'treat' albinism in mouse models by electroporation, as opposed to the pronuclear microinjection approach used previously. Prof. Tommaso Cavazza (Professor of Reproductive Medicine and Genome Editing at the University of Zurich)[14] uses bovine embryos in his research because they share some characteristics with human embryos that are not common to mouse embryos. For instance, bovine

9 Cf. https://www.transgen.de/lexikon/2778.prime-editing.html (08.08.2024).
10 Cf. https://www.transgen.de/lexikon/2686.base-editing.html (08.08.2024).
11 https://krauthammerlab.ch/authors/michaelkrauthammer/ (08.08.2024).
12 See on repair mechanism also the work of molecular biologist Maria Jasin, e.g. Jasin 2018.
13 https://www.crick.ac.uk/research/find-a-researcher/ben-davies (23.08.2024).
14 https://www.reproendo.uzh.ch/en/CavazzaLab.html (08.08.2024).

embryos have similar rates of embryonic aneuploidy and failure. Recent works indicate that bovine zygotes are as inefficient at DNA repair as human zygotes.

Nevertheless, the presentations by Dr. Norah Fogarty (Group Leader / Lecturer at King's College London)[15] and Prof. Egli highlighted the importance of research on human embryos compared to animal models.[16] During her postdoctoral training in the laboratory of Prof. Kathy Niakan Dr. Fogarty researched the application of CRISPR/Cas technology to human embryos in order to better understand key molecular events in the human embryo, which in turn might contribute to the further development of assisted reproductive technologies, reduce the risk of miscarriage and improve pregnancy outcomes. While UK law is one of the few jurisdictions that allows gene editing research on human embryos, it prohibits the commercial use of gene editing tools on human embryos (Global Gene Editing Regulation Tracker 2020). Dr. Fogarty asserted that their work on human embryos is relevant compared to animal embryos because, despite their fundamental biological and clinical importance, the molecular mechanisms that regulate initial cell fate decisions in the human embryo are not yet well understood. Based on a consensus that research using CRISPR systems in human embryos could be highly relevant both to study the specific cell development of the human embryo in more detail and to better understand such development in contrast to the animal model, the participants agreed that it is important to distinguish between research and clinical applications of germline interventions.

4 Demystifying the technology

4.1 Transformative technology?

At the DNA level, CRISPR/Cas9 has a disruptive effect by breaking a DNA strand, but it can undoubtedly also be understood as disruptive from a technology assessment perspective, as Prof. Fateh-Moghadam (Professor of Fundamentals of Law and Life Sciences-Law at the University of Basel)[17] explained as a first step in his talk. This is in the sense that, due to its accuracy, CRISPR/Cas has replaced preceding gene technologies such as zinc finger nucleases (ZFNs) and transcription activator-like effector nucleases (TALEN) on the market. In a second step, Prof. Fateh-Moghadam pursued the question of whether CRISPR is also a transformative technology. He defined transformative technologies as those which are 'capable of influencing and changing normative concepts'. He noted that this classification raises the question of whether CRISPR is changing the self-image of humanity?

15 https://www.kcl.ac.uk/research/trophoblast-and-human-embryo-lab (08.08.2024).

16 Research on human embryos is currently permitted in only a few countries around the world, including the US and the UK. See Section 7.1 below.

17 https://ius.unibas.ch/de/personen/bijan-fateh-moghadam/ (08.08.2024).

Answering that question may depend on both the technological future of CRISPR and what humanity chooses to do with it. From a scientific perspective CRISPR/Cas somatic applications will need to be monitored with respect to: their editing efficacy, targeting range (PAM constraints), precision (off-target or bystander edits with base editors), genotoxicity (on-target rearrangements), delivery (large cargo incompatibility) and immunogenicity.

The anthropologist Prof. Eben Kirksey notes in his monograph that 'CRISPR has no power. The molecule only becomes powerful in the hands of individual humans' (Kirksey 2020). This may also reflect what the historian Prof. David Edgerton has been able to show, that it is ultimately the use of innovations that determines their relevance and the status they achieve in societies (Edgerton 2006). Based on the philosopher Thomas Kuhn's observation that scientific progress does not occur through a continuous growth of knowledge but through revolutionary leaps (1962), this means that only the application of a (biomedical) invention at a local level determines its scope and relevance for a society (Gammeltoft 2014: 166). Therefore, in terms of societal relevance, how groundbreaking an innovation is in itself is of secondary importance. It is recognised that breakthrough inventions always represent a point of rupture along which actors from heterogeneous backgrounds negotiate positions (Long and Long 1992). In other words, whether CRISPR is accepted or rejected by society may well determine the future of the technology – and thus its reputation as a transformative technology.

4.2 The difference between the potential and perception of CRISPR germline gene editing

From a societal perspective, there seems to be a disconnect between the potential of CRISPR and the public's perception of what science is currently doing, or could do, with CRISPR in germline gene editing. Prof. Egli's example of CRISPR/Cas9-induced DNA double-strand breaks, in which the natural replication mechanism in human DNA causes anomalies, shows that CRISPR/Cas9 is today not even a suitable tool for gene editing in the human germline. Accordingly, as the clinical application of germline gene editing is not allowed in countries that have clinicians with the technical capacity and expertise to perform it, so far no clinical trials for germline gene editing have been approved (Costa et al. 2023).

Nevertheless, there are already widespread public visions of the possibility of CRISPR/Cas9 gene-edited children (so-called 'designer babies') (Haberman 2018). This has been fuelled not least by the first case of gene-edited babies in China, which has been internationally recognised as premature and therefore unethical (Normile 2019).

Such a difference between the potential and perception of CRISPR germline gene editing raises the question, which was also broached in the workshop by participant Prof. Tanja Krones (Head of Clinical Ethics at University Hospital

Zurich)[18], of whether the hype surrounding CRISPR in human reproduction is currently exaggerated.

4.3 Mode of action of Exagamglogene autotemcel

In the workshop presentations and discussions, the experts highlighted some remarkable facts about the newly-approved CRISPR/Cas9-based therapy *Exagamglogene autotemcel* (approved in several jurisdictions under the registered trademark Casgevy®) for the treatment of SCD and TDT, that shed light on the current possibilities and limitations of somatic gene therapies:

- The clinical severity of SCD and TDT means that, under the standard care, it can only be cured by a stem cell or bone marrow transplant from a donor, which has significant risks.
- To date CRISPR Therapeutics and Vertex have shared data from 30 patients with SCD and 35 patients with TDT from two phase 3 trials in both adults and adolescents with severe SCD or TDT. The results are dramatic and durable.[19] Regarding durability, workshop participants noted that, due to the rapid development of CRISPR-based therapies, long-term data are not yet available.
- *Exagamglogene autotemcel* takes advantage of human biology having two separate sets of genes to make haemoglobin. In SCD and TDT patients, symptoms start to show after foetal haemoglobin (HbF) levels decrease in the first months after birth. In *Exagamglogene autotemcel,* CRISPR/Cas9 is used to deactivate the erythroid-specific enhancer-region of the BCL11A gene which is responsible for silencing the foetal haemoglobin (HbF) by preventing blood stem cells from making HbF. By turning HbF back 'on', the symptoms are eliminated (Genomics Education Programme 2023). By silencing a gene without repairing the mutations that cause the diseases, *Exagamglogene autotemcel* can be considered a functional treatment which makes a smaller change to the genome than gene therapies that insert a whole working copy of a gene into the cell's genome (Henderson 2024). Notably, Bluebird Bio, Inc.'s competitor traditional gene therapy, Lovotibeglogene autotemcel, which is marketed under the brand name Lyfgenia™ that was approved by the US FDA in December 2023, also works via a knock-out mechanism. Moreover, epigenome editing as an emerging, promising new strategy, is based on silencing genes in mice without altering their primary DNA sequence (Grinstein 2023).
- *Exagamglogene autotemcel* is a personalised, cell-based gene therapy medicinal product manufactured using CRISPR/Cas9 technology to edit the patient's

18 https://www.ibme.uzh.ch/en/Biomedical-Ethics/Team/Research-Fellows/tanjakrones.html (08.08.2024).

19 See two publications released after the workshop: (Frangoul et al. 2024; Locatelli et al. 2024).

bone marrow stem cells collected from the blood after mobilisation. The stem cells are edited *ex-vivo* and modified cells are infused back into the blood once edited. Such a highly personalised, time and resource-intensive bone marrow transplant-based approach comes with some limitations, such as transplant toxicity, oligoclonal engraftment, graft failure and limited access to particular cell types and genetic targets (Wagners 2024). This is due to the significant challenge in somatic gene editing of delivering the edited genes so that they work in the right cells and tissues.

- In the case of *Exagamglogene autotemcel,* CRISPR/Cas9 is the tool used *ex-vivo* to produce advanced therapeutic medicinal products (ATMPs) in the form of genetically modified therapeutic cells. An ATMP is a genetically modified autologous CD34+ cell enriched population containing haematopoietic stem and progenitor cells (HSPCs) edited at the erythroid-specific enhancer region of the BCL11A gene. This applicability of CRISPR/Cas9 technology as both an enabling technology and a therapeutic agent is an important distinction from a patent perspective from other breakthrough research technologies such as polymerase chain reaction (PCR)[20].
- Before having *Exagamglogene autotemcel* patients need myeloablative conditioning. The chemotherapy required before administering *Exagamglogene autotemcel* is tough on patients and carries the risk of serious side effects.
- Treatment with *Exagamglogene autotemcel* requires a significant amount of healthcare infrastructure, which is not available in most countries in the global South.

The value of this information for interdisciplinary discourse is to understand exactly what we are talking about when we speak about a revolution in healthcare through gene editing, and where we actually are on such a journey. This is particularly important when engaging in technology assessment and legislative processes.

5 Disagreement on the most promising field of application

A discussion on the most likely applications of CRISPR/Cas9 continued throughout the workshop.

Somatic therapies:

Looking at the current state of development of somatic gene therapies, the following picture emerges: of the more than 150 CRISPR-based ongoing clinical

20 PCR: a process in which a particular piece of DNA is copied many times in a laboratory so that the DNA can be examined in detail (https://dictionary.cambridge.org/dictionary/english/pcr) (08.08.2024).

trials by indication, trials in haemoglobinopathies (SCD, TDT) are the most advanced, having an approved drug on the market (see Section 3.3 above). Trials in chronic bacterial infections (UTI) and protein folding disorders (hATTR) are in phase 3, those in inflammatory diseases (HAE) and cancers are in phase 2, while those in cardiovascular diseases, HIV/AIDS, diabetes and autoimmunity (lupus) are in phase 1 (Henderson 2024). It remains to be seen what results these trials will bring.

This means that CRISPR medicines could be used to treat various diseases, including rare single-gene disorders such as muscular dystrophy, sickle cell disease and cystic fibrosis. Regarding rare single-gene diseases, Prof. Egli highlighted in his presentation that gene editing could in the field of heritable single-gene disorders, and, in combination with in vitro fertilisation (IVF), be used as a tool to improve embryo selection and increase the number of embryos eligible for implantation. However, Prof. Egli reasoned that the most promising field, not only from a scientific but also from a financial point of view, is the treatment of polygenic diseases (such as diabetes, heart disease, dementia, infectious diseases and cancer), because they are common diseases that are difficult to prevent, costly to treat and impractical to avert through embryo selection.

Two of the participants, Prof. Tanja Krones and Prof. Alice Margaria, raised the following objections regarding gene therapies for the treatment of obesity as a polygenetic disease: obesity has a genetic background, which is, however, only partially understood due to its complexity and multi-genetic character. Instead, the participants emphasised that the food industry was largely to blame for the 'obesity epidemic', which is often associated with type 2 diabetes, due to the marketing of products high in sugar and fat. They also pointed out that social class plays a crucial role in the transmission of obesity across many generations, including through poor diet and other poverty-related circumstances. Against this background, instead of imposing a sugar tax on the food industry, they argued that a risky germline therapy is an aberrant idea triggered by certain industries.

Embryonic gene editing:

Recognising the ethical controversy surrounding embryonic gene editing, Prof. Egli argued that it would nonetheless have a number of promising advantages, including for polygenic disorders. Gene editing in early human development could potentially prevent disease before irreversible damage occurs and could reach all the cells in a body before a defect was amplified through cell division. In other words, editing genes in an embryo may be a way to get around the major challenge of somatic gene editing, which is to deliver the edited genes so that they work in the right cells and tissues, since all cells would have the altered gene. In polygenic diseases risk factors could be reduced by modifying protective or resistance alleles. Prof. Egli compared this effect to the publication of a book, where the aim would be to correct an error before printing it. He added that editing in

embryos would also overcome some of the problems we face with somatic editing: it would be simpler than gene editing in adults because only one cell would need to be targeted; it could avoid the delivery problems and associated mosaicism of immune responses to viral vectors in adults, which can be lethal[21]; the effects would be permanent; and it would prevent propagation through reproduction. In addition, Prof. Egli argued that embryonic gene editing would have much lower costs than somatic gene therapy.

However, Prof. Egli also stressed that this should not create an overly positive image, as another problem arises at this point in the context of gene editing in human embryos: he raised the concern that editing for the benefit of others (who do not bear the risk of the editing) could be a problem. Editing for the benefit of others would be, for example, to enable same-sex or uniparental reproduction (e.g. to bypass the need for sexual reproduction by altering genetic imprinting) or to create a genetically matched person to serve as an organ or cell donor.

Regardless of these cases, the problem remains that germline editing is always associated with risk and that in vitro fertilisation is mandatory. Since gene editing in an embryo is only allowed for research purposes in some countries, but not for reproductive purposes, edited embryos cannot currently be legally implanted and lead to the birth of a baby. Therefore, we cannot know the potential benefits or additional risks of heritable versus non-heritable gene editing.

In his presentation, ethicist Prof. Michael Coors posed the questions: 'How do you ethically measure the risk of germline gene editing in humans?' and 'How do you measure whether the safety issue is resolved?' For him, leaving open the ethical question of a future clinical application of the technology, there are cases that could justify research into germline gene editing. To study the risk that editing a gene in an embryo might pose to the development of the person who will be born from that embryo (developmental risk), one needs to bring a gene-edited embryo to term and observe how the person living with the edited gene develops. Prof. Coors argued that the exposure of these future human beings, who would be part of an experiment to which they had not given their consent, to such an unknown risk could only be justified under two conditions: 1) if the biotechnological risks (e.g. off-target effects) were reduced to the minimum of the always remaining possibility of failure; or 2) if the alternative to the unknown developmental risks the person would be exposed to meant that person had to live a life of severe suffering or a high risk of early death if the genome was not edited. In line with these two premises, Prof. Coors saw the first relevant ethical

21 The first death associated with a CRISPR clinical trial took place during Biotech's non-profit Care Rare Disease clinical trial, with personalised treatment for an individual with Duchenne Muscular Dystrophy (DMD). The treatment aimed to increase production of an alternate form of the dystrophin protein. The participant was dosed in 2023 and died after the treatment was administered. An autopsy showed that the participant's cause of death was acute respiratory distress syndrome (ARDS) that was triggered by an immune response to the (AAV6) used to deliver the CRISPR components.

question as being what is already known about the influence of genetic variants on the development of a human organism over the course of its life. And secondly, he concluded that, based on these two premises, research into the introduction of new genetic traits (so-called 'enhancement') is not justifiable on ethical grounds.

6 Negotiation of CRISPR futures

6.1 The problem of potentialities of CRISPR

We would like to thank Agnes Kandlbinder for her very valuable input, the literature references and the enriching discussion on which the remarks in the following paragraphs are based.

Using the case of Dr. Jiankui's experiment, Prof. David Archard (Emeritus Professor of Philosophy at Queen's University Belfast) opened up the debate on the tensions in CRISPR research between the hope of curing previously incurable (genetic) diseases through germline gene editing and concerns about eugenics. In his presentation, Prof. Fateh-Moghadam raised the question of the role of future individuals and the transformation of the time horizon of legal responsibility in the normative thinking of germline gene editing. Following the moral-philosophical analysis of Karnein (Karnein 2012), he assumed that the special structure of interventions in the human germline makes it necessary to evaluate them in anticipation of the future people who will be created through the use of reproductive procedures. According to Prof. Fateh-Moghadam, the anticipatory personal rights of these future individuals include a fundamental right to a non-manipulated genome, which sets strict limits on the permissibility of germline interventions. If – and only if – the aim of a germline intervention was to correct a genetic defect that would result in that future person being unable to lead an independent and autonomous life, could it be justified by way of exception (Fateh-Moghadam 2023).

- Against this backdrop, the following areas of ethical friction emerged: with regard to germline gene engineering, there is a prevailing view in parts of the population that the human germline is not ours to change.
- Gene editing might involve the manipulation of human embryos, which can be highly controversial in society.
- Some people fear that the possibility of correcting disease-causing genes could lead society to be less accepting of disease and disability in general.
- There are concerns that, due to costs, the technology would be out of reach for many, meaning that only wealthier countries or individuals could benefit from it.

Prof. Archard concluded by stating that it is essential to take on the task of involving society as a whole in the debate on future uses of germline gene editing. This point about societal involvement was echoed by Prof. Wiesemann in her presentation on the German Ethics Council and the legitimacy of germline interventions. Focusing on reproductive justice, Agnes Kandlbinder (PhD candidate at the University of Zurich's URPP H2R)[22] emphasised the need to give affected people[23] a 'seat at the table' when debating potential uses of germline gene editing. It is particularly important to including perspectives that have traditionally been marginalised, such as those of disabled (see more in section 6.3), racialised and socioeconomically disadvantaged people (see also Kandlbinder 2024). Prof. Alice Margaria (Assistant Professor of Legal Issues in Reproduction and Human Genetics at the University of Zurich's URPP H2R)[24] also stressed the importance of qualitative research on germline research with potentially affected people, such as parents at risk of passing on a disease to the next generation.[25]

As several participants in the workshop seemed to agree that public audiences should be included in conversations about the application of the CRISPR/Cas9 technology and affected people should be involved in the discussion, we would like to take a closer look at arguments on public involvement in the following section and situate them within current scientific and political debate.[26] In a second step, we look in detail at the argument for the active participation of affected people.

6.2 Public input into science policy on germline gene editing

A number of reasons are given to argue why public engagement is necessary and important:

. The involvement of different actors helps to ensure that the widest possible range of knowledge and perspectives is considered in the opinion-forming process (see also Kandlbinder et al. forthcoming 2025). This is based on the

22 https://www.humanreproduction.uzh.ch/en/About-us/Academic-Staff/Agnes-Kandlbinder.html (08.08.2024).

23 Affected people are those with a genetic condition, their loved ones as well as people in their immediate environment with caring responsibilities.

24 https://www.ius.uzh.ch/de/staff/professorships/alphabetical/margaria/alice-margaria/person.html (08.08.24).

25 Qualitative, ethnographic research has the potential to delve into the 'dreamworlds' of patient communities and to address the fears and hopes of different actors involved in the negotiation, from biotechnology entrepreneurs to affected parents, from an emic perspective (Kirksey 2023: 455). An advantage of anthropology and anthropological studies or qualitative data collection on reproduction and human gene editing in this contemporary moment is the possibility of reflection and 'disrupting the things we take for granted' (Edu 2023: 263).

26 Other polarising ethical topics where public participation in politics in the form of citizen juries have been important tools for governments in the UK include debates on abortion, gay marriage, Brexit and climate change.

fact that the CRISPR technology has potential to have a far-reaching impact on different areas of human life (Burall 2018; Deutscher Bundestag 2022: 85) and possibly on human self-understanding[27] (Deutscher Ethikrat 2017: 4; Deutscher Bundestag 2022: 85).

. The importance of involving citizens in conversations about how the technology should be used stems from the risk that if scientists make decisions about how to use ethically complex new technologies without consulting the public, it can lead to a loss of public trust in the technology (Scheufele et al. 2021).

. Involving people with first-hand experience of genetic diseases in policy discussions about the technology can help policymakers guide their actions by ensuring that scientific progress is in line with societal values and expectations. Further, the inclusion can help bridge the gap between scientific innovation and societal interests when discussing legislation.[28]

. Scholars of science and technology studies, as well as some commentators, point out that the further development of gene editing should also involve different population groups and scientific disciplines, so that the development is not left only to the goals and logics of science, medicine and industry (Jasanoff 2019; Deutscher Bundestag 2022: 85; Lanphier et al. 2015).

As the last two points make clear, the demand for societal involvement implies a desire on the part of society to control, or at least influence, the direction of research and development. Why is this? Sheila Jasanoff, a Harvard University-affiliated professor[29] known as the founder of Science and Technology studies,[30] writes together with Benjamin Hurlbut and Krishanua Saha with regard to CRISPR that national science academies tend to see the world through a narrow lens because they are inherently stakeholder-oriented, committed first and foremost to the advancement of research and the associated benefits of rapid commercialisation (Jasanoff et al. 2019: 268). They continue: 'Consequently, they are not in the best positioned to frame the right questions for ethical deliberation or to decide who should be at the table to discuss them' (Jasanoff et. al. 2019: 268). This means that research will ultimately develop in the direction in which it is assumed that the technology could potentially be used and exploited. This statement gives rise to the argument for including people who have certain physical health conditions,

27 German: 'menschliches Selbstverständnis'.

28 Professor Anna Middleton (Director of the Kavli Centre for Ethics, Science, and the Public, Faculty of Education, University of Cambridge) came to this conclusion after experiencing how her session at the Second International Summit on Human Genome Editing in Hong Kong in 2018, in which she had planned to present her research on public trust in genomics, was overshadowed by an announcement by Chinese scientist He Jiankui, who claimed to have successfully edited the genomes of twin girls.

29 https://hls.harvard.edu/faculty/sheila-s-jasanoff/ (08. 08. 2024).

30 https://www.hks.harvard.edu/faculty/sheila-jasanoff (08. 08. 2024).

which is analysed in more detail below. For an example of what citizen science involvement could look like, see the example of a citizen jury in the UK (Costa et al. 2024).

6.3 Involving those potentially affected by germline gene editing

The disability rights/justice movement demands that the views of disabled people be included and play a central role in the design and strategy of research, development and marketing of pharmaceutical products and medical therapies. This activist-policy demand is not limited to gene therapies, and even less so to germline interventions. However, the demand made by disability studies is accentuated in the case of germline gene editing. This is because those potentially affected by gene editing are future people who are unable to express themselves today (see also Kandlbinder 2024). Disability rights advocates therefore argue that involving affected people in the form of 'representatives' is all the more urgent for those affected in the future, as such prenatal interventions are raising concerns about eugenics. People with disabilities are more effective in exposing eugenic bias, as this bias might go unnoticed by people who do not experience disability-related discrimination in their daily lives.

Discussions with people affected by rare diseases are characterised by a very heterogeneous discourse with different opinions and demands. One of the concerns is that a liberalised use of germline gene therapies would promote the social assumption that disability is always harmful and should be prevented (voices of participants at National Convening on Disability Rights and Genetic Technologies in Benjamin 2016). De-valuing disabled life experiences further bleeds into the problem of a blurred line between concepts of therapy as opposed to enhancement (Tang 2023: 5). This is because there is no robust consensus between 'normal' variation and disability, even though this distinction has become ubiquitous in coverage of genome editing (Benjamin 2016; Shakespeare 2015). In other words, social perceptions of disability play a central role in the marginalisation of people with disabilities. With regard to the concern of eugenics in the context of human gene editing, the argument is made that market logic and commercialisation places the responsibility for 'racial suitability' in the hands of the consumer (Benjamin 2016). While traditional eugenics relied on state policies and governmental interventions, neo-eugenics describes individual consumer choice without government pressure to utilise testing that is aimed at excluding disability (Ginsburg and Rapp 2023: 283). Conflict emerges due to the economic interest of private actors in the commercialisation of germline interventions, as well as ableist economic considerations regarding the reduction of healthcare costs by means of germline interventions. An interdisciplinary discourse uncovers the problems of market logic in biotechnology development, in light of all these social and ethical concerns.

7 Further engagement needed regarding access-related topics

While the curative potential of CRISPR gene editing has been established with the approval of Casgevy®, there are issues around patients in need gaining access to gene therapy treatments. This was one of the core topics discussed at the workshop, from diverse aspects.

7.1 Cost of somatic gene therapy

The focus on somatic gene therapy has sparked a debate about its high prices, which are particularly important in the context of the burden on healthcare systems. The cost of a single Casgevy® treatment for a patient with sickle cell anaemia is USD 2.2 million. Bluebird Bio, Inc.'s gene therapy costs USD 3.1 million. Novartis gave its gene therapy Zolgensma™ for the treatment of muscular atrophy a price tag of USD 2.1 million, while Sarepta's Duchenne Muscular Dystrophy gene therapy Elevidys™ is priced at USD 3.2 million. The gene therapy Lenmeldy™, approved by the FDA on 18 March 2024 to treat children with the ultra-rare neurodegenerative disease metachromatic leukodystrophy (MLD), has become the most expensive drug in history, at up to USD 4.25 million. Just these prices of both CRISPR-based gene therapies and traditional gene therapies give an idea of their immense cost.

In his presentation, Prof. Egli outlined how somatic gene therapy constitutes a tremendous economic opportunity for a commercialising company. However, this lucrative market could be imploded by viable products stemming from germline editing that might come along with much lower Research and development costs. Germline gene editing should therefore be seen as a competing solution to existing authorised procedures, not only in terms of efficacy and safety, but also cost to the consumer. An opinion was given from the audience that, as long as CRISPR treatments are targeted at small groups of patients with rare diseases, their sales potential will remain limited. However, in this context concerns were raised about the use of CRISPR technology in polygenic diseases, arguing that it could lead to an unfair division of the market, with only wealthy patients being able to afford gene therapies, and the social causes of these diseases risking becoming neglected.[31]

The high prices of gene therapy are justified by the need to recover the costs of developing and manufacturing the treatments, and by the fact that the one-off curative nature of the treatments provides savings to the healthcare system and other societal benefits. In response to this argument, experts at the workshop pointed to the uncertainty about the long-term efficacy and safety of the therapy, with only one year of follow-up clinical trials in the case of Casgevy®. As this

31 Questions were also raised about the phenomena of attenuated phenotypes and repurposing – inventing a drug for rare diseases and then using it for minor variations with fewer symptoms than other more or less similar diseases, while keeping the price tag the same. So, participants asked if rare diseases are the new blockbusters for the pharmaceutical industry?

discussion continues, it is clear that the Swiss healthcare system is not prepared to reimburse these very high prices, which are not based on annual costs but on a one-off basis.

7.2 Equitable access to treatment

Parallel to discussions on the prices of somatic gene therapy and controlling healthcare costs, gaining access to treatment was also discussed at the workshop. CRISPR technology has been heralded as the 'democratisation of gene targeting'[32] and a revolution in healthcare. However, the high prices and the complex healthcare infrastructure required to deliver the therapy threaten this vision, and accessing CRISPR treatments remains a major challenge for patients in need, as Dr. Guzman explained in his presentation. The reason for this limited access lies in the fact that gene therapies are difficult to produce, and there are only a few places in the world with the technical capability and expertise to do so. Dr. Guzman observed how striking it is that about 75% of the approximately 6 million people with SCD live in sub-Saharan Africa. However, he noted that the issue of access is not unique to low-income countries, as these treatments are also challenging to deliver in high-income countries. Accordingly, in high-income countries there is a debate about how to approach routine care for rare diseases, and what infrastructure and processes are needed to identify genetic diseases, find the patients and connect them to the technology (Merelli 2024).

8 Guardrails

Gene therapies harbour a number of risks related to their innovative nature and the current state of the regulatory framework. New manufacturing processes and challenges in ensuring consistent quality and safety contribute to these risks. In addition, the lack of appropriate animal models through which to assess biodistribution and toxicology generates questions about the predictability of responses in humans. Gene therapies also raise environmental concerns, particularly the risk of unintended mutations that could have unforeseen effects on ecosystems and biodiversity. Besides these scientific challenges, the ethical considerations and the nature of CRISPR as potential transformative technology emphasise the need for normative orientation on the topic.

During the workshop, the various regulatory instruments and techniques that our society has developed over time and that are available to us when dealing with CRISPR were addressed. In addition to legal regulation and self-regulation, these include social norms, ethical guidelines and nudges.

32 Dana Carroll from the University of Utah spoke at the event about the 'democratisation of gene targeting' due to the unprecedented simplicity and efficacy of CRISPR technology.

8.1 General legal framework for research and clinical applications

We thank Dr. des. Marie-Hélène Peter-Spiess for her very valuable input, literature references and the enriching discussion which have contributed to this section.

In her presentation, Peter-Spiess (Postdoctoral research fellow at the URPP H2R, University of Zurich)[33] examined the legal landscape of germline gene editing in Switzerland from comparative perspectives. She explained that, in Switzerland, all forms of human germline editing are banned. The prohibition is enshrined in the Constitution, among other legal sources. The constitutional norm reads as follows: 'All forms of cloning and interference with the genetic material of human reproductive cells and embryos are unlawful'.[34]

Thereby, Peter-Spiess proposed that the ban should be interpreted broadly to include all interventions in the human germline, encompassing also foetuses, gonads and all germline cells (including sperm cells and ova, impregnated ova and embryonic cells whose genetic material can be passed on to offspring). However, the Swiss notion of the human germline should not cover the placenta and the umbilical cord blood (Büchler and Peter Spiess 2022: 254–255). The prohibition exists regardless of the purpose of the intervention, e. g. research, therapy or enhancement. Consequently, both research and clinical applications in the human germline remain equally prohibited (Büchler and Peter-Spiess 2022).

In practice, the modification of humans' germline genome is expressly prohibited in several jurisdictions and strictly regulated in others.[35] As Peter-Spiess explained, taking a global comparative perspective shows that regulatory frameworks on germline gene editing differ significantly. For example, some countries allow embryo gene editing in research with restrictions (e. g. a 14-day limit for embryo research).[36] Other countries do not explicitly regulate embryo gene editing in research.[37] Some jurisdictions do not explicitly regulate embryo gene editing for clinical applications,[38] while others do not explicitly prohibit it

33 https://www.humanreproduction.uzh.ch/en/About-us/Academic-Staff/mspiess.html (08. 08. 24).

34 Art. 119 para. 2 lit. a of the Federal Constitution of the Swiss Confederation. See also art. 35 para. 1 of the Reproductive Medicine Act, 3 para. 1 lit. b of the Stem Cell Research and Art. 13 of the Oviedo Convention.

35 Concerning Europe, for example, the restriction imposed by Article 13, Council of Europe Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine (CETS no. 164). Only 28 countries have ratified this, and those who have not ratified it, include the EU as an institution and the following EPO member states: Ireland, Italy, the Netherlands, Poland, Sweden and the UK.

36 Including EU countries such as Belgium or the Netherlands, several Asian countries such as China or South Korea (although often through non-binding guidelines), as well as Australia, Israel and the UK.

37 For example, Argentina, Russia or the USA – although in the USA no public funds can be used for embryo gene editing in research.

38 For example, Argentina, Russia, USA.

in their national regulations,[39] or do so with exceptions.[40] Moreover, in these different legal frameworks some factors have an important impact on the use of the technology. For example, because there is no consensus on the definition of an embryo, jurisdictions around the world use the term to refer to different concepts (Büchler and Peter-Spiess 2022: 258).

Concluding on the topic, Marie-Hélène Peter-Spiess spoke in favour of international legal harmonisation regarding germline gene editing. However, she pointed out that unresolved technical issues and serious ethical concerns should be addressed in advance before human germline editing is possibly liberalised. Prof. Wiesemann, who presented the 2019 statement of the German Ethics Council (Deutscher Ethikrat 2019) calling for an international moratorium on the clinical use of germline interventions, reiterated the need to agree on a global legal standard for germline gene editing, adding that the time of this moratorium should be used to initiate discussions and evaluate processes that are useful for developing the instruments of such international regulation.

Like any other therapeutic modality, somatic gene editing is governed by a number of laws (Fateh-Moghadam 2010). In addition, many jurisdictions have regulations that apply specifically to genetically modified material. However, despite this diversity of national regulations governing somatic gene editing, there are no national laws that specifically prohibit somatic gene editing. Nevertheless, there are some difficult legal and ethical boundaries associated with somatic gene therapy. For example, the sometimes unclear concept of therapy and the distinction between prevention and enhancement must be taken into account when dealing with somatic gene editing (Büchler and Peter-Spiess 2022: 259).

8.2 Tools of governing human gene editing

In an insightful speech, Professor Duncan Matthews (Professor of Intellectual Property Law and Director of the Queen Mary Intellectual Property Research Institute)[41] highlighted the governance of CRISPR technology as a multifaceted challenge that needs to be addressed, and that this requires a better understanding of the relationship between the role of patents and licensing (Matthews et al. 2021). This endeavour includes the study of both public and private governance instruments.

Public governance of human gene editing involves patents and related governance tools to balance the rights of patent holders with the public interest in achieving public health goals. Instruments for public government are either pre-grant limitations on what may be protected by a patent (referred to as 'exclusions' and 'exceptions') or post-grant limits limiting the reach of to the protection

39 For example, Belgium, Israel, Italy.
40 The UK for example allows mitochondrial replacement therapy.
41 www.qmul.ac.uk/law/people/academic-staff/items/matthews.html (08.08.2024).

conferred by a patent (referred to as 'limitations'). The latter include the exemption of activities (e.g. research exemptions) or the restriction of the patent owner's contractual freedom, e.g. compulsory licenses (Matthews et al. 2021: 23). National legislators or international institutions such as the WHO make decisions about public governance tools. Prof. Matthews asserted that private governance refers to discussing patent pools and licensing models, as these tools are developed by private companies, research funding agencies, research institutions, academic and scientific self-governing bodies and other stakeholders (Matthews et al. 2021: 51).

8.2.1 Patentability of gene editing inventions and exclusions

In terms of public governance, Prof. Matthews outlined a series of legal rules that set the stage for the role of patents in CRISPR, such as the CRISPR initiative of the National Academies of Sciences, Engineering and Medicine, the Royal Society and the World Health Organisation.

Firstly, it should be noted that inventions in connection with CRISPR are, in principle, patentable. However, under the TRIPS Agreement,[42] a number of countries[43] have introduced flexibility into their national laws for excluding certain subject matter from patentability, on the ground of commercial exploitation being contrary to *ordre public* or morality (Matthews et al. 2022: 562ff.). Accordingly, many national patent laws either exclude germline gene editing as a subject matter from patentability or provide that inventions relating to germline gene editing are not patentable on the grounds that their (commercial) exploitation would be contrary to the social interest, to life or to public health.[44] At present, there is considerable uncertainty about the practice of patent offices and courts in applying patent exclusions. Prof. Matthews emphasised the urgent need to carry out a landscape study to examine how the law is being applied in practice in these countries. Such a study would provide the empirical basis for the necessary public debate on the use of public policy and moral patenting exceptions in the regulation of germline gene editing.

In addition to such patent exceptions in national laws, the European Patent Convention (EPC) of 1973, which is the legal basis for granting European patents,

42 Article 27 para 2 of the WTO Agreement on Trade-Related Aspects of Intellectual Property Rights (the TRIPS Agreement): 'Members may exclude from patentability inventions, the prevention within their territory of the commercial exploitation of which is necessary to protect *ordre public* or morality, including to protect human, animal or plant life or health or to avoid serious prejudice to the environment, provided that such exclusion is not made merely because the exploitation is prohibited by their law'.

43 Cf. World Intellectual Property Organisation, 'Certain Aspects of National/Regional Patent Laws', www.wipo.int/export/sites/www/scp/en/naizational_laws/exclusions.pdf, status as of June 2023 (08.08.24).

44 Article 27.2 of TRIPS; WTO, Canada – Patent Protection of Pharmaceutical Products, Report of the Panel, WT/DS114/R, 17 March 2000, para 7.92 < 7428d.PDF (wto.org)>.

provides for patent exceptions on grounds of *ordre public* and morality policy, in terms similar to the TRIPS Agreement.[45] The implementing regulations of the EPC, adopted in 2006, contain some examples of inventions that are considered to fall within the scope of the provision. As such, 'European patents shall not be granted in respect of biotechnological inventions which […] concern […] (a) processes for cloning human beings; (b) processes for modifying the germ line genetic identity of human beings; and (c) uses of human embryos for industrial or commercial purposes; […]'[46] Regarding the European Patent Office's (EPO) practice in applying these provisions, Prof. Matthews pointed out that the EPO takes a broad view (Matthews et al. 2021: 30).

Prof. Matthews presented the European patent granted to the Broad Institute on CRISPR[47] and the claims filed, in which the applicant excluded what cannot be patented under the EPC.[48] His explanations on patent exceptions due to *ordre public* or morality considerations gave rise to a lively debate. Questions were asked whether the determination of what is contrary to *ordre public* or morality should be made by administrative bodies such as the EPO or national patent offices, especially as such decisions involve ethical normative considerations on which there is no social consensus (Nordberg 2020: 11; EU Commission Expert Group 2016; Sterckx and Cockbain 2012: 75). The existence of moral exceptions *per se* was also challenged, which seems to be in line with the US approach of not having any exclusions from patentability.[49]

In contrast to the legal situation for germline gene editing, neither national nor international rules provide for genome engineering-specific limitations on the patentability of gene editing inventions and exclusions for somatic applications. However, somatic genome engineering may still require an assessment of moral conformity under the general *ordre public* and the morality clause, as there may be objections if these interventions are intended for human enhancement purposes (Nordberg 2020: 14).

45 Article 53a EPC: 'European patents shall not be granted in respect of: inventions the publication or exploitation of which would be contrary to "ordre public" or morality, provided that the exploitation shall not be deemed to be so contrary merely because it is prohibited by law or regulation in some or all of the Contracting States'.

46 Rule 28 of the Implementing Regulations to the Convention on the Grant of European Patents of 5 October 1973 as adopted by decision of the Administrative Council of the European Patent Organisation of 7 December 2006 and as last amended by decision of the Administrative Council of the European Patent Organisation of 15 December 2020.

47 Broad Institute European patent EP2771468.

48 Claim 12 of Broad Institute European patent EP2771468: 'Use of the composition of claim 1, […] for genome engineering, provided that said use is not a method for treatment of the human or animal body by surgery or therapy, and provided that said use is not a process for modifying the germline genetic identity of human beings'.

49 'Anything under the sun that is made by man' is patentable (decision of the US Supreme Court in Diamond v. Chakrabarty, 447 U.S. 303 [1980]).

8.2.2 Private governance

Patent rights give a patent holder the right to make exclusive use of the patented technology and allow the holder to control how and by whom the technology can be used. The right holder controls the technology through licensing models such as exclusive licensing, non-exclusive licensing and collaborative licensing including patent pooling (Matthews et al. 2021: 41ff.). Dr. Wilming's presentation outlined the difficulties of operating patent pools in the CRISPR field, showing that the existing hurdles make it very unlikely that a CRISPR patent pool will emerge in the near future. Thus, licensing models appear to be a more realistic private governance tool that can be used to ensure equitable access to human gene editing interventions.

Prof. Matthews pointed to concerns about the regulatory power of private actors that arise as a consequence of the existing system. Accordingly, public health activists in relation to CRISPR technology observe that such private regulatory power might lead to increasing costs, licensing fees and market prices, leading to uncertainty for third parties. This would endanger the wide dissemination of and access to the technology. Prof. Matthews emphasised the importance of an international initiative, supported by international organisations such as the WHO, WIPO and WTO, to explore with CRISPR patent holders the potential for adopting appropriate ethical licensing requirements. The fact that no internationally coordinated attempt has been made to date may indicate how difficult it is to achieve the goal of ethical licensing models of balancing innovation with protecting higher normative societal values such as equitable access to technology (WHO Expert Advisory Committee 2021).

8.3 Patent landscape and its indications

8.3.1 Market failure caused by CRISPR patents?

As Dr. Martin Wilming (Patent Attorney at Hepp Wenger Ryffel Ltd.)[50] outlined in his talk, there are essentially two major holders of the foundational patents on CRISPR,[51] the CVC cluster (comprising Emmanuelle Charpentier, the University of California and the University of Vienna) and the MIT/Broad cluster (composed of Massachusetts General Hospital, Duke University and the Broad Institute, a cooperation between Harvard University and MIT). He then explained the complexities of the ongoing patent litigation that has been going on for several years in multiple jurisdictions between these two CRISPR technology patent

50 www.hepp.ch/de/about-us/attorneys/name/wilming (08.08.2024).

51 The other patent holders are the University of Vilnius, Toolgen (a Korean company) and Sigma Aldrich. Although the first applications for CRISPR were all filed very close together, the Broad cluster has the earliest filing dates for eukaryotes and the CVC cluster for bacteria. Toolgen has so far tried unsuccessfully to get something out of its first application. See, for example, the judgement from Australia: https://www.spruson.com/patents/toolgen-unsuccessful-in-landmark-crispr-patent-appeal/ (08.08.2024).

holders. While the CVC cluster (largely undisputed) was the first to propose the chimeric RNA for the CRISPR technology, the bone of contention is its transfer into eukaryotes (i.e. inter alia, humans; quite likely the most profitable segment). Interference proceedings in the US are still ongoing. The United States Patent and Trademark Office (USPTO) had ruled in favour of the Broad cluster, but this decision has been appealed, and the Court of Appeal of the Federal Circuit heard the oral arguments on 7. May 2024. Commentators held that the court 'seems wary of Broad's CRISPR inventorship win', i.e. that Broad's transfer into eukaryotic cells was patentably distinct from CVC's earlier invention (in prokaryotic cells) (Storz 2023).[52] Meanwhile, an Opposition Division of the European Patent Office (EPO) had ruled in May 2020 that a CVC patent enabled the invention in eukaryotic cells at the priority date. But the Board of Appeal preliminarily held in July 2024 that it disagreed with that finding. To prevent a precedent, CVC withdrew the patent. The appeal proceedings accordingly ended with a revocation of the patent without a decision being made on the merits by the Board of Appeal.[53] Divisional patent applications are (of course) still pending.

Prof. Alfred Früh (Professor of Private Law, specialising in Life Sciences Law and Intellectual Property Law at the University of Basel)[54] pointed out in his introductory speech that, based on the fact there are only two major patent holders, one could assume that this monopoly situation in the technology market – which gives the patent holders considerable power – could lead to a narrowing of the product market and thus impair inventions in this field. In patent situations where basic technology patents are in one or a few hands, there is a concern that the patent holders will extract monopoly rents or otherwise drive competitors out of business. As a result, the technology would not be diffused as efficiently and widely as an optimal allocation of goods would require. The result would be market distortions or market failure.

However, these questionable scenarios from a competition perspective do not seem to have materialised in the CRISPR field so far. Instead, an active field of research and a large number of new inventions can be observed. It would therefore not be obvious at this stage to legitimise the regulation of CRISPR patents in the form of exclusion or limitation of patentability on the basis of an existing market failure.

In the product market, the more than 150 clinical trials currently underway using CRISPR, base editing and other emerging modalities, and the remarkable expansion of these trials in terms of number and disease areas of investigation over the past few years (Henderson 2024), are living proof that the field is not suffering from impairment. As Dr. Wilming demonstrated, from a patent perspec-

52 https://www.law360.com/articles/1834383/fed-circ-seems-wary-of-broad-s-crispr-inventorship-win (08.08.2024).
53 https://register.epo.org/application?number=EP13793997&lng=en&tab=main (08.08.2024).
54 https://ius.unibas.ch/en/persons/frueh-alfred/ (08.08.2024).

tive, we have seen a continuous steep curve in the number of patent families and grants related to CRISPR over the last 15 years. Searching for 'CRISPR' in claims of patent publications finds over 13 726 patent families claiming CRISPR, over 48 144 patent applications in the patent families, with around 12 176 granted patents.[55] Because these early CRISPR applications are so new and not additional, they are moving smoothly through the patenting process. The numerous scientific developments in the field of CRISPR and the corresponding expansion of CRISPR-related patents in the CRISPR pipeline also demonstrate a high level of agility in the field of gene editing. These include inventions in the field of delivery systems such as nanoparticles, capsids or CRISPR follow-on inventions like base editing and prime editing. In connection with an analysis of the world's CRISPR patent applications' regions of origin, Dr. Wilming noted that many of these (many in agriculture) are based in China.[56]

8.3.2 Licensing strategies

Dr. Wilming explained the complicated licensing situation in the field of CRISPR. Both the CVC and the MIT/Broad clusters, together with one of their principal investigators, have teamed up with private companies (called 'surrogates') to which they have granted exclusive licenses and outsourced the task of exploiting the technology. The surrogates are free to exploit the technology either themselves or by sublicensing it to partners of their choice. For instance, as one of the surrogates of the CVC cluster which has been granted rights for therapeutic use, CRISPR Therapeutics has granted exclusive licenses under the patents held by Emmanuelle Charpentier to Vertex Pharmaceuticals for use in treating sickle cell disease. The financial benefits of the CRISPR patent holders' licensing activity can be seen, for example, in the fact that the Broad Institute generated over USD 16 million in licensing revenue in the fiscal year 2022 (Broad Institute 2023). In addition, this licensing of the CRISPR technology opens up a lucrative field for the surrogates to exploit the technology. Such a 'surrogate licensing model' is preferable for universities, offering them a substantial share of the profits generated by the technology (through equity stakes in the surrogates and from royalties) with minimal risk. In addition, the principal investigators, who have significant equity in the surrogates, stand to gain much more from such a model than would otherwise be the case (Contreras and Sherkow 2017).

Dr. Wilming further noted that, shortly after receiving the FDA's green light for Casgevy®, Vertex Pharmaceuticals paid USD 50 million upfront in cash, plus USD 50 million in contingent payments (the triggering events were not disclosed) and license fees in the range of USD 10–140 million annually, to be paid up to 2034 to Editas Medicine, the MIT/Broad cluster's license surrogate. These payments were made in exchange for Vertex Pharmaceuticals receiving a non-exclusive

55 The numbers are based on PatBase (patbase.com) as of 21. October 2024.
56 PatBase (patbase.com).

license for the patent rights to CRISPR-Cas9 technology under the control of the MIT/Broad cluster for use in *ex-vivo* gene editing drugs targeting the BCL11A gene in SCD and beta thalassemia (Masson 2023). Participants' interpretations of such moderate license payments from Vertex Pharmaceuticals to Editas Medicine – compared to the USD 2.2 million price tag for Casgevy® – remained open at the workshop (see Regalado 2023). They thought that it could be interpreted as a sign of a well-functioning CRISPR product market that is not impaired by the foundational patents being held by only two institutional clusters who have been in patent litigations for years. Alternatively, it could be interpreted as confirming that public interest in access to therapies outweighs the exclusionary nature of patent rights, which would provide a patent holder with the right to hold third parties liable through patent infringement litigation if they used the patented technologies without the rights holder's permission. However, one participant pointed out that the described licensing practices of the two patent holders of the foundational CRISPR patents and the agreement between Vertex Pharmaceuticals and Editas Medicine may be problematic from an antitrust perspective.

8.4 Regulatory adaptions

Although the number of CRISPR clinical trials and the disease areas in which CRISPR is being studied have expanded rapidly in recent years, the financial pressures on gene editing companies have increased. Development and manufacturing phases are long and costly, the patient base is limited, market forces have reduced venture capital investment in biotechnology, and investors want to see quick returns on their financial input.[57] These realities present real challenges to the development of gene therapies. As a result, developing the pipeline of new treatments and expanding disease areas are at risk. For example, this year there is only one trial happening in a new disease area, autoimmunity (Henderson 2024). Accordingly, there is a growing understanding that innovative regulatory approaches are needed to fully realise the therapeutic potential of CRISPR, especially for rare diseases, and increase the speed of bringing innovative products to patients (Henderson 2024).

Dr. Philippe Girard's (Vice Director at Swissmedic)[58] insightful presentation reassured the audience that Swissmedic, the Swiss Agency for Therapeutic Products, which is responsible for, among other things, granting marketing authorisations for medicines but not setting prices, is aware of these challenges and is ready to guide the adaptation process. He claimed that the real barriers to translation come from the regulatory burden on medicinal products, since the traditional clinical pathway is not suitable for orphan drugs, for which randomised

57 A case in point is Bluebird Bio's struggle to secure new investment, which led to the withdrawal of its products from the EU market (Bashar 2024).

58 www.innovation-office.ch (08. 08. 2024).

controlled trials are not possible to the same extent as for other drugs, due to the small populations involved.[59]

The Swiss Federal Act on Medicinal Products and Medical Devices (Therapeutic Products Act, (TPA))[60] is currently being revised, with the aim of creating legal certainty for advanced therapy medicinal products (ATMPs),[61] including gene therapy products,[62] which, from a legal point of view, are currently categorised at the interface between medicinal products and transplant products. ATMPs will in future be regulated by the TPA, which will entail regulations on authorisation and private market surveillance. This revision will improve the Swiss population's access to safe, effective and high-quality ATMPs and ensure patient safety through regulations on their authorisation procedure and traceability. The revised TPA will contain regulations on authorisation in general[63] and simplified authorisation[64]. The hospital exemption, the temporary authorisations for the use of unlicensed medicines that allow patient-based preparations of gene therapy to be developed in a hospital for use in an individual patient suffering from an ultra-rare disease, is regulated in the current revision of the Transplantation Act.[65]

The revision is intended to harmonise the TPA with the legal situation in the EU, which provides detailed rules for ATMPs in Directive (EU) No. 1394/2007 (Krämer et al. 2023: 9, 16). A specific regulatory challenge consists of the fact that gene therapy products are legally considered genetically modified organisms (GMOs).[66] As such, releases[67] can be granted for a maximum of 10 years.[68] For this, *de lege ferenda*, harmonising the duration of authorisation for a gene therapy

59 Orphan drugs (as defined in Article 4 para 1 lit. a^{decies} TPA) already benefit from a simplified authorisation procedure (Article 14 para 1 lit. f TPA) and 15-year document protection (Article 11b para 4 TPA).

60 Therapeutic Products Act dated as of 15. December 2000 (SR 812.21).

61 ATMPs are innovative therapies that are expected to provide groundbreaking new opportunities for disease treatment, but also have a significant impact on the pharmaceutical budget. See Hanna et al. 2016.

62 In gene therapy products, genetic materials – in particular DNA or RNA – are introduced into a patient's cells in order to repair, regulate or replace defective or missing gene (components). See Hanna et al. 2016.

63 Article 11 para 2ter of the draft revision of the TPA.

64 Article 14 para 1bis of the draft revision of the TPA.

65 Article 2b of the Amendment to the Federal Act on the Transplantation of Organs, Tissues and Cells of 29 September 2023 (https://www.fedlex.admin.ch/eli/cc/2001/422/de); https://www.humanrights.ch/de/stellungnahmen/transplantationsgesetz-menschenrechtliche-perspektive?gad_source=1&gclid=CjwKCAjw9p24BhB_EiwA8ID5Bl97DqqsGhKP_hKU5veeykE6z-1lh9evBNm9HLJWfdHGXW9rwEWqZaRoC8uYQAvD_BwE (10. 10. 2024).

66 Article 3(1)(c) of the Ordinance on the Handling of Organisms in the Environment (Release Ordinance, RO) dated as of 10. September 2008 (SR 814.911) defines genetically modified organisms as 'organisms in which the genetic material has been altered by methods of gene technology in accordance with Annex 1 in a way that does not occur under natural conditions […]'. See hereto Swissmedic Information Sheet Requirements ZL TpP GT GVO valid as of 8 May, 2024, identification number BW313_00 996, version 1.1.

67 German: 'Freisetzung'.

68 Article 44(3) RO.

product, must be sought, and a mechanism provided to demonstrate that the product does not pose an environmental risk due to possible new mutations.

9 Conclusion

Gene editing has entered a new era, driven by the transformative potential of CRISPR. This ground-breaking technology opens up unprecedented possibilities to modify the DNA of living organisms. This means that we are currently faced with the question of what we can achieve with CRISPR – not only what we want to do, but also what we should prevent. An interdisciplinary overview of CRISPR research, the social sciences and humanities, the private research industry, patent expectations and patent analysis reveals the diverse applications of the technology in humans, its potential and its risks.

The diversity of perspectives and questions raised in this paper make it clear that CRISPR is far more than just a biotechnological tool. The opportunities and dangers arising from the use of CRISPR comprise a societal challenge that calls for an interdisciplinary dialogue in which various, sometimes contradictory perspectives, must be taken into account. How should these diverse concerns be evaluated? Should priority be given to those who want to advance CRISPR research, or to those who object to the possibility of modifying the genome at will, or to the patients who could benefit from new therapies, or to the parents of future generations? This endeavour is necessary because a responsible approach to CRISPR can only emerge if all scientific and social perspectives are taken into account, weighing up both the possibilities and the risks of the technology. The expert discussions at the workshop showed that to achieve such a goal, it is important to develop a common understanding of the technology in order to facilitate an evidence-based discussion between the disciplines. To this end, this article contributes an informative basic resource to institutionalise such interdisciplinary exchange and to engage the public in discussions about the future possibilities of CRISPR.

10 References

Bashar, Issa. 25. 01. 2024. Bluebird Bio: Innovative Therapies, Monetary Setbacks. *Seeking Alpha*, www.seekingalpha.com/article/4664945-bluebird-bio-innovative-therapies-monetary-setbacks (08. 08. 2024).

Benjamin, Ruha. 2016. 'Interrogating Equity: A Disability Justice Approach to Genetic Engineering.' *Issues in Science and Technology 32*(3): 51–54.

The Broad Institute, Inc. 30. 06. 2023. Consolidated Statements of Financial Position June 30, 2023. Boston, Massachusetts: PWC, https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&ved=2ahUKEwjo5LDFqsSHAxUlxQIHHR6rFnoQFnoECB4QAQ&url=https%3A%2F%2Ffdpclearinghouse.org%2Ffile%2Fget%3Fid%3D3601&usg=AOvVaw1YoSGwQUbUgasx0JiR4B_z&cshid=1721984137816806&opi=89978449 (08.08.2024).

Burall, Simon. 2018. 'Rethink public engagement for gene editing.' *Nature* 555(7697): 438–439. https://doi.org/10.1038/d41586-018-03269-3.

Büchler, Andrea and Peter-Spiess, Marie-Hélène. 2022. 'Human Germline Editing: Legal Framework in Switzerland and Abroad.' *Life Science Recht* 4: 251–260.

CISION. 01.04.2024. Vertex Announces New Drug Submission for Exagamglogene Autotemcel (exa-cel) Has Been Accepted for Priority Review by Health Canada for the Treatment of Sickle Cell Disease and Transfusion-Dependent Beta Thalassemia Canada. *CISION*, https://www.newswire.ca/news-releases/vertex-announces-new-drug-submission-for-exagamglogene-autotemcel-exa-cel-has-been-accepted-for-priority-review-by-health-canada-for-the-treatment-of-sickle-cell-disease-and-transfusion-dependent-beta-thalassemia-840383125.html (08.08.2024).

Contreras, Jorge L. and Sherkow, Jacob S. 2017. 'Surrogate licensing, and scientific discovery.' *Science 355*(6326). https://doi.org/10.1126/science.aal4222.

Costa, Alessia, Patch, Christine, Middleton, Anna and Burall, Simon. 2023. *UK citizens' jury on genome editing. Handbook.* Genome Research Limited. https://societyandethicsresearch.wellcomeconnectingscience.org/wp-content/uploads/2021/11/UKCitizensJuryHandbook_20220830_website-version.pdf (08.08.2024).

Deutscher Bundestag. 2022. *Bericht des Ausschusses für Bildung, Forschung und Technikfolgenabschätzung. Technikfolgenabschätzung (TA) Genome Editing am Menschen*, https://dserver.bundestag.de/btd/20/016/2001650.pdf (08.08.2024).

Deutscher Ethikrat. 29.09.2017. Keimbahneingriffe am menschlichen Embryo: Deutscher Ethikrat fordert globalen politischen Diskurs und internationale Regulierung. Ad-hoc-Empfehlung. Berlin: German Ethics Council, https://www.ethikrat.org/fileadmin/Publikationen/Ad-hoc-Empfehlungen/deutsch/empfehlung-keimbahneingriffe-am-menschlichen-embryo.pdf (08.08.2024).

Deutscher Ethikrat. 09.05.2019. Eingriffe in die menschliche Keimbahn. Stellungnahme. Berlin: German Ethics Council, https://www.ethikrat.org/fileadmin/Publikationen/Stellungnahmen/deutsch/stellungnahme-eingriffe-in-die-menschliche-keimbahn.pdf (08.08.2024).

Edgerton, David. 2006. *The Shock of the Old. Technology and Global History since 1990*. London: Profile Books.

Edu, U. 2023. Race, Racism, And Reproductive Justice. In *A Companion to the Anthropology of Reproductive Medicine and Technology*, edited by C. C. Van Hollen and N. Appleton. Place: Publisher, p. 250–265. https://doi.org/10.1002/9781119845379.ch14.

EMA. 21.03.2024. Casgevy. Exagamglogene autotemcel. Amsterdam: European Medicines Agency, https://www.ema.europa.eu/en/medicines/human/EPAR/casgevy#overview (08.08.2024).

Kamperman Sanders, A., Bostyn, S., Iserentant, H., Sattler de Sousa eBrito, C., Taormino, J., Farquharson, A., Jacob, R., Knuth Lethola, S., Pereira, G., Puigdomènech, P., Schneider, I., Czörgö, S., Then, C., Würtz Lindum, P., & Yates, S. 2016. Final Report of the Expert Group on the development and implications of patent law in the field of biotechnology and genetic engineering. European Commission. https://cris.maastrichtuniversity.nl/ws/portalfiles/portal/4753322/Report_of_Biotech_Expert_Group.pdf (08.08.2024).

Fateh-Moghadam, Bijan. 2010. Rechtliche Aspekte der somatischen Gentherapie. Roxin/Schroth, p. 569–602.

Fateh-Moghadam, Bijan. 2023. Fortpflanzungsmedizingesetz (FMedG). In *Gesundheitsrecht. Band VIII/1*, edited by T. Poledna and V. Rumetsch. Basel: Helbing Lichtenhahn, p. 935–996.

FDA. 08.12.2023. FDA Approves First Gene Therapies to Treat Patients with Sickle Cell Disease. Silver Spring MD: FDA U.S. Food and Drug Administration, https://www.fda.gov/news-events/press-announcements/fda-approves-first-gene-therapies-treat-patients-sickle-cell-disease (08.08.2024).

Frangoul, Haydar, Locatelli, Franco, Sharma Akshay et al. 2024. 'Exagamglogene Autotemcel for Severe Sickle Cell Disease.' *The New England Journal of Medicine 390*(18): 663–1676. https//doi.org/10.1056/NEJMoa2309673.

Gammeltoft, Tine. 2014. *Haunting Images. A Cultural Account of Selective Reproduction in Vietnam*. Berkeley: University of California Press.

Genomics Education Programme. 08. 12. 2023. Casgevy – how it works. Bermingham: *Genomics Education Programme*, https://www.genomicseducation.hee.nhs.uk/about-us/#contactus (08. 08. 2024).

Ginsburg, Faye and Rapp, Rayna. 2023. Cripping Reproduction. The Intersections Of Pregnancy And Disability. In *A Companion to the Anthropology of Reproductive Medicine and Technology*, edited by Cecilia Coale Van Hollen and Nayantara Appleton. Place: Publisher, p. 282–297. https://doi.org/10.1002/9781119845379.ch16

Global Gene Editing Regulation Tracker. 2020. United Kingdom: Germline/Embryonic. Atlanta: Genetic Literacy Project. Science not ideology, https://crispr-gene-editing-regs-tracker.geneticliteracyproject.org/united-kingdom-germline-embryonic/ (08. 08. 2024).

Grinstein, Jonathan. 2023. Rhapsody in B: Tune Therapeutics Presents Data for Hepatitis B. Epigenetic Silencer. *GENEDGE*, https://www.genengnews.com/topics/translational-medicine/rhapsody-in-b-tune-therapeutics-presents-data-for-hepatitis-b-epigenetic-silencer/ (08. 08. 2024).

Haberman, Clyde. 10. 06. 2018. Scientists Can Design 'Better' Babies. Should They? *The New York Times*, https://www.nytimes.com/2018/06/10/us/11retro-baby-genetics.html (08. 08. 2024).

Hanna, Eve, Rémuzat, Cécile, Auquier, Pascal and Toumi, Mondher. 2016. 'Advanced therapy medicinal products: current and future perspectives.' *J Mark Access Health Policy* 4(1): 31036. https://doi.org/10.3402/jmahp.v4.31036.

Henderson, Hope. 2024. CRISPR Clinical Trials: A 2024 Update, https://innovativegenomics.org/news/crispr-clinical-trials-2024/ (08. 08. 2024).

Jasanoff, Sheila, Hurlbut, Benjamin J and Krishanu, Saha. 2019. 'Democratic Governance of Human Germline Genome Editing.' *The CRISPR journal* 2(5): 266–271. http://doi.org/10.1089/crispr.2019.0047.

Jasin, Maria. 2018. 'Under the Influence: Cas9 Ends and DNA Repair Outcomes.' *The CRISPR journal* 1(2): 123–134. https://doi.org/10.1089/crispr.2018.29014.jas.

Jinek, Martin, Chylinski, Krzysztof, Fonfara, Ines, Hauer, Michael, Doudna, Jennifer A. and Charpentier, Emmanuelle. 2012. 'A Programmable Dual-RNA–Guided DNA Endonuclease in Adaptive Bacterial Immunity.' *Science* 337: 816–821. https://doi.org/10.1126/science.1225829.

Kandlbinder, Agnes. 2024. 'A critical view on using "life not worth living" in the bioethics of assisted reproduction.' *Medicine, Health Care and Philosophy* 27(2): 189–203. https://doi.org/10.1007/s11019-023-10191-7.

Kandlbinder, Agnes, Peter-Spiess, Marie-Hélène, Leeners, Brigitte, Mollaysa, Amina, Cavazza, Tommaso, Meier, Anina, Braunschweig, Michael, Ioannidi, Eleonora, Coors, Michael, Schwank, Gerald, Krauthammer, Michael. Forthcoming manuscript 2025. Strategies for Guiding Interdisciplinary Human Gene Editing Research.

Karnein, Anja. 2012. *A theory of unborn life: from abortion to genetic manipulation.* Oxford: Oxford University Press.

Kirksey, Ebben. 2023. CRISPR Enters the Fertility Clinic. In *A Companion to the Anthropology of Reproductive Medicine and Technology*, edited by Cecilia Coale Van Hollen and Nayantara Appleton. John Wiley & Sons, p. 444–457. https://doi.org/10.1002/9781119845379.ch26.

Kirksey, Ebben. 2020. *The Mutant Project: Inside the Global Race to Genetically Modify Humans*. New York: St. Martin's Press.

Kolata, Gina. 16. 11. 2023. Sickle-Cell Treatment Created With Gene Editing Wins U.K. Approval. *The New York Times*, www.nytimes.com/2023/11/16/health/casgevy-sickle-cell-crispr.html (08. 08. 2024)

Krämer, Florentin, Möhr, Thomas, Keller, Tabea, Picecchi, Dario. 2023. Regulierungsfolgenabschätzung zu ausgewählten Änderungen des Heilmittelgesetzes, Schlussbericht zu den Advanced Therapy Medicinal Products (ATMP). Basel/Luzern. https://perma.cc/4TG7-NTFU. (21. 11. 2024).

Kuhn, Thomas. 1962. *The Structure of Scientific Revolutions*. Chicago: University of Chicago Press.

Lanphier, Edward, Urnov, Fyodor, Haecker, Sarah Ehlen, Werner, Michael and Smolenski, Joanna. 2015. 'Don't edit the human germ line.' *Nature*. 519: 410–411.

Locatelli, Franco, Lang, Peter, Wall, Donna Meisel, Roland, Corbacioglu, Selim, Li, Amanda M, De la Fuente, Josu, Shah, Ami J, Carpenter, Ben, Kwiatkowski, Janet L, Mapara, Markus et al. 2024. Exagamglogene Autotemcel for Transfusion-Dependent β-Thalassemia. *The New England Journal of Medicine* Vol. 390(18): 1663–1676. http://doi.org/10.1056/NEJMoa2309673 (08. 08. 2024).

Long, Norman, and Long, Ann. 1992. *The Battlefields of Knowledge: The Interlocking of Theory and Practice in Social Research and Development*. London: Routledge.

Masson, Gabrielle. 2023. After long-running patent battle, Vertex pays $100M to license Editas' gene-editing tech. *FIERCE Biotech*, https://www.fiercebiotech.com/biotech/after-long-standing-patent-battle-vertex-pays-100m-license-editas-gene-editing-tech#:~:text=After%20long-running%20patent%20battle,license%20Editas%27%20gene-editing%20tech (08. 08. 2024).

Matthews, Duncan, Brown, Abbe, Gambini, Emanuela, Minssen, Timo, Nordberg, Ana; Sherkow, Jacob S., Wested, Jakob, van Zimmeren, Esther and McMahon, Aisling. 2021. 'The Role of Patents and Licensing in the Governance of Human Genome Editing: A White Paper, Response to the WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing.' *Queen Mary, University of London, School of Law Legal Studies Research Paper Series*. https://lucris.lub.lu.se/ws/portalfiles/portal/100796208/The_Role_of_Patents_and_Licensing_in_the_Governance_of_Human_Genome_Editing_A_White_Paper1.pdf (08. 08. 2024).

Matthews, Duncan, Minssen, Timo and Nordberg, Ana. 2022. 'Balancing Innovation, 'Ordre Public' and Morality in Human Germline Editing: A call for More Nuanced Approaches in Patent Law.' *Queen Mary Law Research Paper* No. 379/2022. https://papers.ssrn.com/sol3/papers.cfm?abstract_id=4036406 (08. 08. 2024)

Merelli, Annalisa. 21. 03. 2024. Getting CRISPR treatments to patients remains a major challenge. Could lab-developed tests help? *U.S.: STAT*, https://www.statnews.com/2024/03/21/crispr-gene-editing-personalized-medicine-batten-disease/ (08. 08. 2024).

Nordberg, Ana. 2020. Patents, Morality and Biomedical Innovation in Europe: Historical Overview, Current Debates on Stem Cells, Gene Editing and AI, and de Lege Ferenda Reflections. In *Fairness, Morality and Ordre Public*, edited by Daniel Gervais. Cheltenham: Edward Elgar, p. 243–267.

Normile, Denise. 30. 12. 2019. Chinese scientist who produced genetically altered babies sentenced to 3 years in jail. *Science*, https://www.science.org/content/article/chinese-scientist-who-produced-genetically-altered-babies-sentenced-3-years-jail (08. 08. 2024).

Regalado, Antonio. 2023. The first CRISPR cure might kick-start the next big patent battle. *MIT Technology Review*, https://www.technologyreview.com/2023/12/01/1084152/the-first-crispr-cure-might-kickstart-the-next-big-patent-battle/ (10. 10. 2024).

Scheufele, Dietram, Krause, Nicole, Freiling, Isabelle, Brossard, Dominique. 2021. 'What we know about effective public engagement on CRISPR and beyond.' *PNAS 118*(2): e2004835117.

Shakespeare, Tom. 2015. 'Gene Editing: Heed Disability Views.' *Nature 527*(446). https://doi.org/10.1038/527446a.

Standsfield, Noah. 27. 09. 2024. Canada Approves Vertex and CRISPR Therapeutics' Gene Therapy Casgevy for Sickle Cell Disease and TDT. *CGTlive*, https://www.cgtlive.com/view/canada-approves-vertex-crispr-therapeutics-gene-therapy-casgevy-sickle-cell-disease-tdt (05. 12. 2024).

Sterckx, Sigrid and Cockbain, Julian. 2012. *Exclusions from Patentability: How Far Has the European Patent Office Eroded Boundaries*. Cambridge University Press.

Storz, Ulrich. 2023. 'The CRISPR Cas patent files, part 1: Cas9 – Where do we stand at the 10 year halftime.' *Journal of Biotechnology 10*(379): 46–52.

Tang, Natacha. 2023. *Governance of Heritable Human Genome Editing. URPP Human Reproduction Reloaded | H2R* (University of Zurich), Working Paper Series, 01/2023. Zurich and Geneva: Seismo, https://doi.org/10.33058/wpuzh.2023.7227.

Vertex. 09. 01. 2024. Press Release: Vertex Announces Approval of First CRISPR/Cas9 Gene-Edited Therapy, CASGEVY™, for the Treatment of Sickle Cell Disease (SCD) and Transfusion-Dependent Beta

Thalassemia (TDT) in Kingdom of Saudi Arabia. *U.S.:Vertex,* https://news.vrtx.com/news-releases/news-release-details/vertex-announces-approval-first-crisprcas9-gene-edited-therapy (08. 08. 2024).

Wagners, Amy. 2024. Modeling and treating disease by in vivo gene editing with AAA-CRISPR. Talk delivered at Latsis Symposium on Genome and Transcriptome Engineering. ETH Zurich, Schweiz, June 14; 2024.

WHO Expert Advisory Committee. 2021. Developing Global Standards for Governance and Oversight of Human Genome Editing, Human Genome Editing: Recommendations, https://iris.who.int/bitstream/handle/10665/342486/9789240030381-eng.pdf?sequence=1 (08. 08. 2024).

WHQ. 02. 12. 2023. CASGEVY receives Bahrain approval for treatment, marking it the second country in the world. *Bahrain News Agency,* https://www.bna.bh/en/CASGEVYreceivesBahrainapprovalfortreatmentmarkingitthesecondcountryintheworld.aspx?cms=q8FmFJgiscL2fwIzON1%2BDkp9fN81LKKv1fvWGRd1HDU%3D (08. 08. 2024).

H2R Working Paper 01/2024