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ALLEA Statement on

Patent-Related Aspects of CRISPR-Cas Technology

Statement prepared by the
**ALLEA Permanent Working Group on Intellectual Property Rights
and endorsed by ALLEA**

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Executive Summary

The principles enshrined in the EU Biotech Directive and the Implementing Regulations to the EPC, as applied in the patent granting practice of the European Patent Office to inventions related to the CRISPR-Cas technology, in the opinion of the ALLEA Permanent Working Group on Intellectual Property Rights, reflect that the patent law in force in the EU and set forth in the EPC provides, on the one hand, the necessary incentives for a successful development and use of CRISPR-Cas technology across all fields of life sciences, but at the same time also provides all the necessary safeguards that in particular no patents can be granted for inventions, also those using CRISPR-Cas technology, which could in any way offend human dignity and/or integrity. Those rules are flexible enough as to take into account also future regulatory developments which may provide new rules as regards the use of CRISPR-Cas technology in humans, but also in animals and plants. The ALLEA Permanent Working Group on Intellectual Property Rights is, therefore, of the opinion that the CRISPR-Cas technology at the present stage does not require any reforms in the patent law field.

Statement on Patent-Related Aspects of CRISPR-Cas Technology

1. The advent of recombinant DNA technology in the 1970s of the last century has revolutionised molecular biology and genetics in general. In combination with parallel developments of the necessary supportive techniques, modern biotechnology has led to useful genetic modifications of micro-organisms, plants and animals and generated, *inter alia*, a number of new therapeutics and diagnostics. From the very beginning of these developments, it had to be clarified whether and if, under which conditions and to what extent inventions related to living matter should be eligible for patent protection. In the European Union these questions were resolved by the EU Directive on the Legal Protection of Biotechnological Inventions 98/44 of 6 July 1998,¹ which contains detailed provisions on patent eligibility and some specifically aimed at preventing that patents could be granted for inventions affecting, for instance, human dignity.

2. Since scientists have discovered that bacteria and archaea have evolved a RNA mediated adaptive defence system called **C**lustered **R**egularly **I**nterspaced **S**hort **P**alindromic **R**epeats, CRISPR-associated Cas² that protects organisms

from invading viruses and plasmids,³ they also realised that the CRISPR-Cas mechanism could offer considerable potential for gene-targeting and genome editing applications.⁴ Since then CRISPR-Cas technology has been at the centre of scientific discussion. This is because the new technology permits the „direct manipulation of virtually any gene of a living organism more easily, cheaply, and accurately than has ever been possible before“.⁵

3. In response to the realistic prospect that the CRISPR-Cas technology could

L. A. Marraffini, E.J. Sontheimer, CRISPR Interference: RNA-directed Adaptive Immunity in Bacteria and Archaea, *Nature Reviews Genetics* 2010 Mar. 11 (3) 181-190 (accessible under <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2928866/> - accessed May 19, 2016); H. Deavau, J. E. Garneau, S. Moineau, CRISPR/Cas System and its Role in Phage-Bacteria Interactions, *64 Annual Review of Microbiology* 475-493 (7 June 2010) (accessible under <http://www.annualreviews.org/doi/full/10.1146/annurev.micro.112408.134123> - accessed May, 19, 2016); D. Bhaya, M. Davison, R. Barrangou, CRISPR-Cas Systems in Bacteria and Archaea: Versatile Small RNAs Adaptive Defence and Regulation, *45 Annual Review of Genetics* 273-297 (2011) (accessible under <http://www.annualreviews.org/doi/abs/10.1146/annurev-genet-110410-132430> - accessed May 19, 2016).

3 Because these repeats can store snippets of an invader's genome as „spacers“, which then constitute a heritable memory that can instruct an immune response against future encounters with foreign DNAs carrying those same sequences (E.J. Sontheimer and L.A. Marraffini, CRISPR Goes Retro, RNA Contributes Directly to the Immunological Memory Recorded in CRISPR Sequences, *351 Science*, 920-921 (26 February 2016).

4 M. Jinek, K. Chylinski, J. Fontana, M. Hauer, J.A. Doudna and E. Charpentier, A Programmable Dual-RNA-Guided DNA Endonuclease in Adaptive Bacterial Immunity, *337 Science* 816-821 (17 August 2012).

5 J. Benz-Schwarzburg and A. Ferrari, Super-Muscle Pigs, Trading Ethics for Efficiency, *Issues in Science and Technology* (Spring 2016), pp. 29-32.

be used for germline gene therapy in humans, the US National Academy of Science (NAS) and the US National Academy of Medicine (NAM) decided to host a large meeting at their Headquarters in Washington, D.C.. The Royal Society and the Chinese Academy of Sciences agreed to co-sponsor that event. The Advisory Committee for the meeting subsequently appointed a Planning Group to organise what would become the Summit on Human Gene Editing. Professor David Baltimore – Nobel Laureate, who was instrumental for the Asilomar 1975 Conference which paved the way for successful continuation of genetic engineering,⁶ was appointed to chair the Planning Committee. Despite the fact that the CRISPR-Cas technology is a platform technology applicable across the life sciences,⁷ the Advisory Committee

6 Cf. P. Berg, Meetings That Changed the World: Asilomar 1975: DNA Modification Secured, *455 Nature* 290-291 (2008).

7 Indeed, the use of CRISPR-Cas technology in plants and animals has already generated remarkable practical results. Using CRISPR-Cas techniques licensed from the Vilnius University in Lithuania and Berkeley, California-based Caribou Biosciences, Inc., DuPont Pioneer from Johnston, Iowa, by knocking out the endogenous waxy gene Wx1 in corn generated a waxy corn to contain starch composed exclusively of branched polysaccharide amylopectin - a commodity in processed foods, adhesives and high-gloss paper. The company expects to commercialise this plant within five years. Promising R&D work using CRISPR Cas technology is also reported for the gene edited mushrooms, fruit and vegetables, to knock out genes that encode polyphenol oxidase (PPO), an enzyme that causes browning in many fruit and vegetables (cf. E. Waltz, CRISPR Edited Crops Free to Enter the Market, *Skip Regulation*, *34 Nature Biotechnology* 582 (June 2016)). Successful use of CRISPR techniques for editing the genome of animals has also already been reported (cf., e.g., D.F. Carlson, et al., Production of Hornless Dairy Cattle From Genome-edited Cell Lines, *34 Nature Biotechnology* 479-481 (May 2016), and D. Carroll, et al., Regulate Genome-edited Products, Not Genome Editing Itself, *34*

decided to focus its attention on the use of the technology with human somatic and germline cells „because of the broad public interest in this aspect, and to keep the boundaries of discussion manageable.“⁸ The International Summit with 400 participants from all over the world took place in December 2015. Members of the Organising Committee, after three days of thoughtful discussions, have released a statement on „Human Gene Editing“.

4. The statement emphasises that „intensive basic and preclinical research is clearly needed and should proceed, subject to appropriate legal and ethical oversight, on (i) technologies for editing genetic sequences in human cells, (ii) the potential benefits and risks of proposed clinical uses, and (iii) understanding the biology of human embryos and germline cells.“ It adds, however, that, if, in the process of research, early human embryos or germline cells undergo gene editing, the modified cells should not be used to establish a pregnancy. As regards *somatic gene therapy* the view is expressed that „because proposed clinical uses are intended to affect only the individual who receives them, they can be appropriately and rigorously evaluated within existing and evolving regulatory frameworks for gene therapy, and regulators can weigh risks and potential benefits in approving clinical trials and therapies.“

Nature Biotechnology 477-479 (May 2016)).

8 Cf. K. Finneran, Responding to CRISPR-Cas9, *Issues in Science and Technology* (Spring 2016), pp. 33-34.

1 OJ EU No. L 213/13 of 30.7.98.

2 Cf. R. Barrangou, Ch. Fremaux, H. Devau, M. Richards, P. Boyaval, S. Moineau, D. A. Romero, CRISPR Provides Acquired Resistance Against Viruses in Prokaryotes, *315 Science* 1709-1712 (23 March 2007);

In regards to *germline gene therapy*, the statement observes that, in principle gene editing might also be used to make genetic alterations in gametes or embryos, which will be carried by all of the cells of a resulting child and will be passed on to subsequent generations as part of the human gene pool. Such modifications of human genomes might include the introduction of naturally occurring variants or totally novel genetic changes thought to be beneficial. The statement emphasises that „It would be irresponsible to proceed with any clinical use of germline editing unless and until (i) the relevant safety and efficacy issues have been resolved, based on appropriate understanding and balancing of risks, potential benefits, and alternatives, and (ii) there is broad societal consensus about the appropriateness of the proposed application. Moreover, any clinical use should proceed only under appropriate regulatory oversight. At present, these criteria have not been met for any proposed clinical use: the safety issues have not yet been adequately explored; the cases of most compelling benefit are limited; and many nations have legislative or regulatory bans on germline modification. However, as scientific knowledge advances and societal views evolve, the clinical use of germline editing should be revisited on a regular basis.“⁹ In a statement released already

in July 2015, the Berlin-Brandenburg Academy of Sciences and Humanities expressed similar views, i.e. pleaded for a temporary moratorium as regards germline therapy. It recommended that the period of moratorium should be used for further research on the opportunities and risks of the method and for social debate on the ethical and legal questions of germline therapy.¹⁰

5. In line with the International Summit statement, which emphasised the need of basic and preclinical research, in particular on understanding the biology of human embryos and germline cells, in February 2016 the UK Human Fertilisation and Embryology Authority permitted the Francis Crick Institute in London to use the CRISPR-Cas technology to switch genes on and off in a newly fertilised egg. The research of Dr K. Niakan at the Francis Crick Institute aims to find out which genetic processes are essential for the

on Science and Technology (Spring 2016), pp. 55-56. Cf. D. Baltimore, Why We Need a Summit on Human Gene Editing, Issues in Science and Technology (Spring 2016), pp. 35-38; contributions on the same issues by R.A. Charo, The Legal and Regulatory Context for Human Gene Editing, Issues in Science and Technology (Spring 2016), pp. 39-44; D.J. Kevles, The History of Eugenics, Issues in Science and Technology (Spring 2016), pp. 45-49; A.I. Miller, Germline Gene Therapy, Don't Let Good Intentions Spawn Bad Policy, The proposed moratorium on clinical applications of gene editing technology reveals ignorance about how innovation works, and callousness about human suffering, Issues in Science and Technology (Spring 2016), pp. 57-60.
¹⁰ J. Reich et al. (2015): Human Genome Surgery – Towards a Responsible Evaluation of a New Technology. Analysis by the Interdisciplinary Research Group Gene Technology Report“. Berlin-Brandenburg Academy of Sciences and Humanities, Berlin (<http://edoc.bbaw.de/frontdoor/index/index/docId/2486> . accessed 11 May 2016).

successful growth of an early human embryo and to understand how its cells begin to develop specialist roles before it implants itself into the womb. It is reported that the scientists at the London institute will let the embryos die after seven days.¹¹ This decision

of the UK authority has provoked worldwide critical reactions and comments, which also reached the daily press and in which a number of ethical concerns against the use of CRISPR-Cas technology in humans at this point in time were raised.

¹¹ Cf. the Reports by C. Cookson, UK Gives Green Light to Controversial Genetic Research on Human Embryos, Financial Times of 2 February 2016, p. 1; and C. Coombs, Muddied Waters: The CRISPR IP Landscape

in Europe, Life Sciences Intellectual Property Review of 18 February 2016 (<http://www.lifesciencesipreview.com/article/muddied-waters-the-crispr-ip-landscape-in-europe> - accessed 22 February 2016)

6. In view of the ethical concerns raised against the use of the CRISPR-Cas technology for interventions in humans and bearing in mind the exceptional potential for the use of this technology across all fields of life sciences, which has been referred to as „the biggest biotech discovery of the century“,¹² the ALLEA Permanent Working Group on Intellectual Property Rights observes as follows:

» Notwithstanding the ingenuity of the idea underlying the CRISPR-Cas technology, this technique does not fundamentally differ from the known techniques of rDNA technology, but rather enables its more precise, efficient and safe use. Its core sits in transfer vectors designed following the insights gained from the CRISPR-Cas mechanism. Consequently, patenting of CRISPR-Cas technology as such does not pose any specific problems. Problems, however, arise when the use of this technology in particular in humans is at stake.

» As already emphasised, the EU Biotech Directive of 1998 contains rules which were specifically designed to prevent patents which would offend the dignity and integrity of the person. Therefore the human body, at any stage in its formation or development, including germ cells, cannot be patented [Recital 16 and Article 5 (1)]. The same is true for processes, the use of which offends against human dignity, such as processes to produce chimeras from germ cells or totipotent cells of humans and animals [Recital 38].

¹² A. Regalado, Who Owns the Biggest Biotech Discovery of the Century, Technology Review of 4 December 2014 (<https://www.technologyreview.com/s/532796/who-owns-the-biggest-biotech-discovery-of-the-century> - accessed 29 April 2016).

⁹ On Human Gene Editing, International Summit Statement by the Organising Committee, Issues

» Of direct importance as regards the use of CRISPR-Cas technology in humans and animals are the rules of the Directive which explicitly declare the following inventions as *unpatentable*:

- The human body, at the various stages of its formation and development [Article 5 (1)];
- processes for modifying the germ line genetic identity of human beings [Article 6 (2)(b)];
- uses of human embryos for industrial or commercial purposes [Article 6 (2) (c)];
- processes for modifying the genetic identity of animals which are likely to cause them suffering without substantial medical benefit to man or animal, and also animals resulting from such processes [Article 6 (2)(d)].

» Moreover, Article 9 of the Directive sets forth, on the one hand, that the protection conferred by a patent on a product containing or consisting of genetic information shall extend to all materials in which the products is incorporated and in which the genetic information is contained and performs its function, but, on the other hand, clarifies that this protection does not extend to the human body at its various stages of its formation and development [“save as provided in Article 5 (1)”]. This clarification is of particular importance because CRISPR-Cas technology has opened new avenues for the somatic gene therapy, which is, in principle, eligible for patent protection, and whose application will result in introducing into the human body also patented products „containing or consisting“ of genetic information.

» The above explained legal situation is well reflected in the present patent granting practice of the European Patent Office, where patents with claims were granted for compositions based/using CRISPR-Cas technology, but where claims for the use of such compositions for genome engineering were limited by the clarifying addition: „Provided that such 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.“

» Considering that a patent for invention does not authorise the holder to implement that invention, but merely entitles him to prohibit third parties from exploiting it for industrial and commercial purposes, considering further, that substantive patent law cannot serve to replace or render superfluous national, European or international law which may impose restrictions or prohibitions or which concern the monitoring of research and of the use or commercialisation of its results, notably from the point of view of the requirements of public health, safety, environmental protection, animal welfare, the preservation of genetic diversity and compliance with certain ethical standards (Recital 14), it is up to the national, European or international legislator to decide if and how to regulate the use of advances which the CRISPR-Cas technology offers for intervention in humans, animals and plants. The existing specific EU patent rules, which were also incorporated into the Implementing Regulations to the European Patent Convention (EPC), offer an efficient fence against patents which would offend human dignity and human integrity, or which would cause animal suffering without substantial medical benefit to man or animal. Those specific non-exhaustive rules are complemented with the general clause, setting forth that inventions shall be considered unpatentable where their commercial exploitation would be contrary to *ordre public* or morality (Article 6 (1), Article 53 (a) EPC).

7. Taking into account the principles enshrined in the EU Biotech Directive and the Implementing Regulations to the EPC, further taking into account the patent granting practice of the European Patent Office, the ALLEA Permanent Working Group on Intellectual Property Rights is of the opinion that the patent law in force in the EU and set forth in the EPC provides, on the one hand the necessary incentives for successful development and use of CRISPR-Cas technology across all fields of life sciences, but at the same time also provides all the necessary safeguards that no patents can be granted for inventions, also those using CRISPR-Cas technology, which would in any way offend human dignity and/or integrity, or lead to animal suffering without sufficient justification. Those rules are flexible enough as to take into account also future regulatory developments which may provide new rules as regards the use of CRISPR-Cas technology in humans and animals, but if it proves necessary, also in plants. Legislative reforms in patent field are not required at the present stage.

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