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Genome Editing – Challenges for the Future

Programme and Abstracts of the Contributions of the Annual Meeting 22 and 23 September 2017 in Halle (Saale)

Edited by Jörg Hacker, President of the Academy

Deutsche Akademie der Naturforscher Leopoldina –
Nationale Akademie der Wissenschaften, Halle (Saale) 2017

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Abhandlungen der Deutschen Akademie der Naturforscher Leopoldina

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Thanks

We would like to thank the Alfried Krupp von Bohlen and Halbach-Stiftung for the generous support of the annual meeting.

Alfried Krupp von Bohlen
und Halbach-Stiftung

We would like to thank the Wilhelm and Else Heraeus-Stiftung for their generous support for a programme which enables – in collaboration with Gesellschaft Deutscher Naturforscher und Ärzte (GDNÄ) – the participation of secondary school pupils in the Leopoldina Annual Meeting.

Friday, 22 September 2017

9:00 am – 1:00 pm | Opening Ceremony*

Musical Intermezzi
Hallensia Quartett

Welcome Address
Gunnar Berg ML, Halle (Saale)
Vice-President of the Academy

Speech
Jörg Hacker ML, Halle (Saale)
President of the Academy

Awards
Jörg Hacker ML, Halle (Saale)
President of the Academy

- Cothenius-Medal
- Carus-Medal
- Schleiden-Medal
- Mendel-Medal
- Leopoldina Prize for Junior Scientists
- Georg-Uschmann-Award for the History of Science

10:20 – 10:50 am | Coffee Break

Welcome Address
Jörg Hacker ML, Halle (Saale)
President of the Academy

Short Welcoming Speech
Armin Willingmann
Minister for Economy, Science and Digitalisation of the state of Saxony-Anhalt

Short Welcoming Speech
Georg Schütte
State Secretary at the Federal Ministry of Education and Research

Speech
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Rolf-Dieter Heuer ML, Bad Honnef

11:50 – 12:00 am | Break

*** The Opening Ceremony as well as the scientific presentations given in German will be translated simultaneously.**

Introduction
Jörg Hacker ML, Halle (Saale)
President of the Academy

Keynote Lecture
Evolution – natural or man-made
Ernst-Ludwig Winnacker ML, München

1:00 – 2:00 pm | Lunch

Scientific Session I | Basics of Programmable Gene Scissors

Chair:
Franz Hofmann ML, München

2:00 – 2:45 pm **TALENs – Programmable gene scissors for plants***
Jens Boch, Hannover

2:45 – 3:30 pm **CRISPR/Cas9 – A game changer in genome engineering: Origins and overview**
Emmanuelle Charpentier ML, Berlin

3:30 – 4:15 pm **Stem cell technology, gene editing and disease research**
Rudolf Jaenisch ML, Cambridge, MA (USA)

4:15 – 4:45 pm | Coffee Break

Scientific Session II | Genome Editing in Clinical Context

Chair:
Claus R. Bartram ML, Heidelberg

4:45 – 5:30 pm **Correction of Duchenne Muscular Dystrophy by genomic editing**
Eric Olson, Dallas (USA)

5:30 – 6:15 pm **Genome editing for the treatment of HIV infections***
Boris Fehse, Hamburg

8:15 pm | Leopoldina Lecture

Chair:
Jörg Hacker ML, Halle (Saale)

How the genes determine our lives, and why women and men are different*
Axel Meyer ML, Konstanz

Saturday, 23 September 2017

Scientific Session III | Application Prospects

Chair:
Martin J. Lohse ML, Berlin

8:30 – 9:15 am
The implications of CRISPR-based gene-drive systems
Ethan Bier, San Diego (USA)

9:15 – 10:00 am
Targeting the Mutanome for cancer immunotherapy: Towards genomics-tailored drugs for each and every cancer patient
Ugur Sahin, Mainz

10:00 – 10:45 am
Precision surgery in plant genomes: methods, applications and regulatory consequences*
Ralph Bock ML, Potsdam-Golm

10:45 – 11:15 am | Coffee Break

Scientific Session IV | Societal Prospects

Chair:
Frank Rösler ML, Hamburg

11:15 – 12:00 am
Would there be a market for genetically modified food in Germany? – A social psychological analysis*
Wolfgang Stroebe ML, Groningen (NL)

12:00 – 12:45 pm
Pros and cons of genome editing in human embryos
Robin Lovell-Badge, London (UK)

12:45 – 2:30 pm | Lunch

2:30 – 4:30 pm | Panel Discussion

Chair:
Kathrin Zinkant, Süddeutsche Zeitung Berlin

Pros and cons of germline editing and non-heritable somatic gene therapy
Claus R. Bartram ML, Heidelberg
Silja Vöneky, Freiburg
Bettina Schöne-Seifert ML, Münster
Volker Gerhardt, Berlin
Bettina Keller, Junge Akademie, Berlin

4:30 – 5:00 pm | **Coffee Break**

Scientific Session V | **International Legal Perspectives**

Chair:
Ursula M. Staudinger ML, New York (USA)

5:00 – 5:45 pm
Human embryo genome editing: Regulation in Israel and ethical perspectives
Ephrat Levy-Lahad, Jerusalem (Israel)

5:45 – 6:30 pm
Human embryo genome editing: Regulation in the UK and ethical perspectives
Andy Greenfield, Harwell (UK)

6:30 – 7:15 pm
Human genome editing in the context of the German Embryo-Protection-Act*
Jochen Taupitz ML, Mannheim

7:15 pm | **Summary**

Ulla Bonas ML, Halle (Saale)
Vice-President of the Academy

8:30 – 10:00 pm | **Conference Dinner** (by invitation only)

Venue:
DORMERO Kongress- & Kulturzentrum Halle (Saale)
Leipziger Straße 76
Franckestraße 1
06110 Halle (Saale)

Abstracts of the Presentations

Keynote Lecture

Ernst-Ludwig Winnacker ML, München

Evolution – natural or man-made

Evolution is a stochastic process. According to Charles Darwin, it acts on populations of living organisms. Populations occasionally produce individuals, which can adapt better to changes in environmental conditions than other individuals. These changes can be natural disasters of all kind, like floods, volcano eruptions, or earthquakes but they can also be of a more subtle nature, like allergies or disease resistances.

Differences between individuals of a given population arise during the fusion of an egg and a sperm cell. This process of meiosis produces a random exchange between homologous chromosomes of father and mother. Thus, individuals of a certain species are always somewhat different. These differences are reflected in subtle changes of their respective genomes. Conversely, this means that targeted changes in a genome could lead to variations in the physical appearance of the corresponding organism.

This is easier said than actually done. Genome editing has been an old dream of molecular biologists. But it only came true recently with the discovery of the CRISPR/Cas system. Its application in our species and its germ line though is hampered by the complexity of the human genome, at least when it comes to the manipulation of higher cognitive activities of the human brain. This paper will discuss progress in this exciting field including the legal, scientific and ethical limits when trying to put the power of evolution into human hands.

Presentations

Jens Boch, Hannover

TALENs – Programmable gene scissors for plants

TALEs (transcription activator-like effectors) have revolutionized genome editing by being the first molecular tool with an easy to reprogram and highly specific DNA-binding capacity. They originate in plant-pathogenic *Xanthomonas* bacteria which use these proteins as weapons to reprogram host cells for a successful infection. Here, TALEs function as molecular switches to control the expression of plant genes. The power of TALEs resides in their modular DNA-binding domain which is composed of 34 amino acid repeats. Each repeat recognizes one base in the DNA via one amino acid. The nature of this amino acid determines which base is bound. Assembling the order of repeats thus results in any designer DNA-binding specificity. Fusions of TALEs to nucleases – termed TALEN – have turned them into molecular scissors which cut the DNA at precise locations within complex genomes enabling a simple way to perform targeted genome editing for scientists worldwide. Since then, TALEN have been applied for breeding of many major crop plants and animal livestock, with great prospects to help fulfill the urgent needs in agriculture. In 2015, TALEN-modified designer immune cells have cured humans from cancer, demonstrating the breathtaking power and potential of this most flexible of all genome editing tools.

Emmanuelle Charpentier ML, Berlin, Umeå (Sweden)

CRISPR/Cas9 – A game changer in genome engineering: Origins and overview

The CRISPR/Cas9 system has recently emerged as a transformative technology in biological sciences, allowing rapid and efficient targeted genome editing, chromosomal marking and gene regulation in a large variety of cells and organisms. The system consists of Cas9, an enzyme that can be programmed with RNA guides to target site-specifically any DNA sequence of interest. The system is efficient, versatile and easily programmable.

CRISPR/Cas9 research has developed into one of the most dynamic and fastest-moving fields in life sciences and holds great promise for future biotechnical

and biomedical applications. The CRISPR/Cas9 system is remarkably simple in its design, close to a plug-and-play method, which can therefore be easily leveraged for a large variety of gene targeting. Application of the system has been extraordinarily broad, including among many others the generation of transgenic animals, genetic modification of various eukaryotic cell types, and genetic modification of plants and crops. Tool and kit service companies offer CRISPR/Cas9-related products, and at least three biotechnology companies have been founded during the past years to develop the technology for the treatment of serious human genetic disorders, with probably many more to come. The technology has likewise sparked interest in the pharmaceutical industry and in biotech – not only to leverage its potential for greatly simplified biomanufacturing and screenings, but also to apply the technology to the potential treatment of serious human diseases. Already, the CRISPR/Cas9 system is an integral and critical part of the toolbox for any researcher who intends to manipulate genetic information by means of targeted introduction or correction of mutations, replacement of genes, modification of DNA or modulation of transcription in any cell or organism – and the applications of this breakthrough technology are continuing to increase at a rapid pace.

Rudolf Jaenisch ML, Cambridge (MA, USA)

Stem cell technology, gene editing and disease research

The embryonic stem (ES) cell and induced pluripotent stem (iPS) cell technology in combination with gene editing approaches have revolutionized our ability to study development and diseases in defined *in vitro* cell culture systems. I will summarize the use of CRISPR/Cas-mediated gene editing to generate mice carrying specific mutations and human ES cells with disease relevant genetic alterations. My laboratory studies autism conditions (such as Rett syndrome and Fragile X) and neurodegenerative diseases (such as Parkinson and Alzheimer disease). The talk will illustrate the power of these new technologies to get insights into the pathogenesis of diseases and to devise new therapeutic strategies.

Eric N. Olson, Dallas (TX, USA)

Correction of Duchenne Muscular Dystrophy by genomic editing

Duchenne muscular dystrophy (DMD) is a severe, progressive muscle disease caused by mutations in the Dystrophin gene, which encodes a large intracellular protein that maintains integrity of muscle cell membranes. More than 4,000 DMD mutations have been identified in humans. The majority of mutations are deletions that cluster in hot spots, such that skipping of out-of-frame exons can potentially restore the reading frame of the Dystrophin protein. We have used CRISPR/Cas9 to generate new mouse models of DMD lacking the most prominently deleted Dystrophin exons in humans. To permanently correct DMD by skipping mutant dystrophin exons in postnatal muscle tissue *in vivo*, we have used adeno-associated virus-9 (AAV9) to deliver CRISPR/Cas9 gene editing components to dystrophic mice, a method we refer to as Myoediting. We have also optimized Myoediting of many types of DMD mutations in muscle cells derived from induced pluripotent stem (iPS) cells generated from blood samples of DMD patients. Opportunities and challenges in the path toward permanent correction of disease-causing mutations responsible for DMD and other monogenic disorders by genomic editing will be discussed.

Boris Fehse, Hamburg-Eppendorf

Genome editing for the treatment of HIV infections

Despite great progress in antiretroviral therapy, human immunodeficiency virus (HIV) infections remain incurable causing more than 1 million *Acquired Immune Deficiency Syndrome* (AIDS)-related deaths each year. Interestingly, HIV infections offer several potential targets for genome editing (GE). These include receptors used as entry points by the virus, particularly the chemokine receptor CCR5 that serves as co-receptor for R5-tropic strains mediating initial HIV infection. Homozygous carriers of the naturally occurring deletion variant CCR5Δ32 are almost completely protected from HIV. This protection is transferable to patients with an already existing HIV infection as documented by the only case of cure from HIV after stem cell transplantation from a CCR5Δ32-homozygous donor ("Berlin patient"). Based thereon, concepts have been developed for the genetic disruption (*"knockout"*) of CCR5 in HIV patients using so-called designer nucleases. A CCR5-specific Zinc-finger nuclease is already in clinical studies, whereas clinical testing of next-generation CCR5-TALENs (as developed by us) or CRISPR/Cas systems remains to be initiated. HIV itself is an-

other interesting point of attack for GE. Indeed, a high-activity recombinase (Brec1) has been developed that “cures” infected cells by cutting out integrated proviruses from their genome. Altogether, given the well-defined target points and easy accessibility of blood cells, HIV infection represents an ideal target for GE-based therapeutic approaches.

Leopoldina Lecture

Axel Meyer ML, Constance

How the genes determine our lives, and why women and men are different

From birth on, none of us is the same. With the exception of identical twins, each human is a little different from a genetic point of view. Neither better, nor worse, but different. What impact do our genes have? What is characteristic of men, what is characteristic of women? Gender is the most fundamental difference between all humans, certainly between most beings. This difference goes back to the basics of biology. This difference also represents the question of all questions which will accompany us all our lives: Who are we? How did we become what we are? Why do we conduct ourselves as we do? Many diseases have, at least to some extent, genetic causes, and we are given healthy or mutant versions of genes from our ancestors. In this process, even good luck and bad luck determine which genes we receive from our parents and grandparents. Obviously we cannot choose our parents. Thus, our genes are also our destiny. How does this genetic lottery of life work? And where does the power of genes end, and what can be changed through nutrition, education and culture? A unique genetic fate is granted to every one of us, we can only try to make the best of it!

The talk will discuss what is known about hotly debated issues such as sex versus gender, intelligence and homosexuality.

Presentations

Ethan Bier, San Diego (CA, USA)

The implications of CRISPR-based gene-drive systems

Classic rules of Mendelian inheritance impose several significant constraints on genetic manipulation of organisms (e.g., random segregation of distant loci and coinheritance of closely linked loci). In this talk, I will discuss how these "passive" rules of inheritance can be superseded by a new form of "active genetics" based on a self-propagating configuration of CRISPR/Cas9 components. In fruit flies, active genetic elements can act on the opposing chromosome in both somatic and germline cells resulting in their inheritance by nearly all progeny, a phenomenon often referred to as gene-drive. Similar results seen also in mosquitoes and yeast open the door to a new era of genetics wherein the laws of traditional Mendelian inheritance can be bypassed for a broad variety of purposes. I consider the implications of this fundamentally new form of "active genetics", its applications for gene-drives, various auxiliary genetic elements that can be used to update gene-drive systems, neutralizing elements that can freeze the spread of gene-drives in a population, split-drive strategies that could accelerate genetic manipulations in new and existing model systems, and ethical or biosafety considerations associated with such active genetic elements.

Ugur Sahin, Mainz

Targeting the Mutanome for cancer immunotherapy: Towards genomics-tailored drugs for each and every cancer patient

The establishment of immunotherapy as a standard of care is one of the key medical breakthroughs in oncology. Exploring the mode of action of successful cancer immunotherapies brought cancer mutations as T cell antigens into the spotlight. Somatic cancer mutations are ideal targets for cancer immunotherapy as they lack expression in healthy tissues and can potentially be recognized as neo-antigens by the mature T cell repertoire. Their systematic therapeutic targeting, however, had been hampered by the fact that every patient's tumor possesses a unique set of mutations ('the mutanome') that must first be identified.

We recently introduced the concept of cancer mutanome immunotherapies and implemented an mRNA-based approach to mobilize immunity against the full spectrum of individual cancer mutations. The approach comprises comprehensive identification of mutations from clinical cancer samples by next-generation sequencing, computational prediction of neo-antigens, and design and manufacturing of a vaccine encoding multiple targets unique for each patient. By solving key scientific and technological challenges we moved the approach from a mere preclinical vision into the first clinical example of genome tailored individual drug development. The concept holds the promise to solve key challenges in cancer treatment. The mutanome immunotherapy concept is a blueprint-approach that is universally applicable for treatment of essentially all types of cancers. Rather than restricting to the small common denominator of targets shared by many patients as pursued by current pharmaceutical concepts, the approach taps the large unique antigenic target repertoire of each individual patient and provides a universally applicable regimen from which each and every patient can profit. The availability of multiple vaccine targets for each patient allows addressing inter-individual variability and intra-tumor clonal heterogeneity, which are key to largely disappointing effects of currently used targeted therapeutics. Accordingly, how to transform cancer genomics data to actionable knowledge for tailoring individualized immunotherapies 'on demand' has become a novel research field with paradigm-shifting potential. The clinical implementation of the concept will foster paradigm shifts along the entire drug development process, including logistics, diagnostics, drug production, regulatory aspects and patient management. Thus, mutanome immunotherapies are expected to prototypically open up the territory of patient centric drug development and may provide best-practice blueprints for personalized genomics driven health care.

Ralph Bock ML, Potsdam-Golm

Precision surgery in plant genomes: methods, applications and regulatory consequences

Plant cells possess three genomes: a big one in the nucleus and two smaller ones in the chloroplasts and the mitochondria. Two of these genomes, the nuclear genome and the chloroplast genome, are currently amenable to genetic engineering. Whereas chloroplast genome engineering has always been possible with absolute precision, targeted alterations in the nuclear genome have not been routinely feasible until very recently. However, the development of genome editing tools, such as the CRISPR/Cas technology, has facilitated the efficient site-directed engineering of nuclear genomes in plants with unprecedented accuracy.

In my talk, I will explain how plant genomes can be modified through genetic engineering. I will highlight the exciting new possibilities in plant breeding and biotechnology that are opened up by the application of genome editing tools and similar high-precision genetic engineering methods. Using selected examples, I will also describe how the development of new technolgies, but also the discovery of natural gene transfer processes that move genetic information between species (referred to as horizontal gene transfer), have blurred the boundery between naturally occurring genetic changes in plant genomes and man-made genetic engineering. Finally, I will illustrate the irresolvable dilemma these new findings have caused for the politically motivated, largely technology-based regulation of genetically modified plants in the European Union.

Wolfgang Stroebe ML, Groningen (The Netherlands)

Would there be a market for genetically modified food in Germany? – A social psychological analysis

Opinions of Germans – as well as of Europeans in general – about genetically modified food (GM food) are mostly negative, and the majority would not buy such food under any circumstances. This confirms results of social psychological studies that intentions to buy GM food depend mainly on the social attitudes of consumers towards GM food (i.e., their positive or negative evaluations of this food), which in turn are based on their opinions about benefits and risks of GM food. Research has further demonstrated that these attitudes are embedded in a system of general attitudes. Individuals, who perceive themselves as "green" consumers and/or are concerned about the environment, hold particularly negative attitudes. Attempts to reduce fears about risks of GM food with information campaigns are hampered by the fact that opponents of GM food have little faith in the credibility of government, food industry or science. Whereas it will hardly be possible to influence these opponents of GM food, there is a minority of approximately 40 % of Europeans who seem to be prepared to purchase GM food, if it had significant advantages over conventionally grown fruit and vegetables. Evidence from experimental studies conducted in several European cities by researchers of the University of Otago (New Zealand) will be presented which show that GM food can be competitive if it has clearly *recognizable* advantages over conventionally grown fruit and vegetables. Implications of these findings will be discussed.

Robin Lovell-Badge, London (UK)

Pros and cons of genome editing in human embryos

The possibility that we might be able to deliberately alter our own genes has been debated for decades with each new relevant method, from recombinant DNA, transgenics, *in vitro* fertilization (IVF), homologous recombination in embryonic stem cells or via cloning or induced pluripotent stem (iPS) cells. Because the methods have been too inefficient and/or inaccurate, it has been difficult to propose their use even for purposes of basic research, while clinical applications to make heritable changes would be unsafe and out of the question. But in the last few years with the development of genome editing methods, notably those involving the CRISPR/Cas9 system, these arguments may no longer hold. They are now ubiquitous in basic research and have proven to be immensely invaluable. They can be used to make precise genetically altered animals and human cells in culture with efficiencies approaching 100 %. I will discuss the use of the methods to address questions about the biology of human germ cells and of pre- and peri-implantation human embryo development. I will also discuss the use of the methods in germ cells and early embryos to explore whether clinical applications, to make heritable changes for the purposes of avoiding disease, would be feasible and practical. This will include what has been achieved to date as well as a consideration of the standards and checks that would have to be applied to make such uses safe and acceptable.

Ephrat Levy-Lahad, Jerusalem (Israel)

Human embryo genome editing: Regulation in Israel and ethical perspectives

In Israel, human embryo genome editing is encompassed by the "Law forbidding genetic intervention (human cloning and genetic manipulation of germ cells)" (1999). This law has dual aims: (*1*) to ban cloning a human being; (*2*) to examine continuously policies regarding clinical germline interventions, accounting for their moral, legal, social and scientific implications. Ongoing examination is enabled through two mechanisms. The law expires every 5 years, and must be re-ratified by Parliament (currently enacted through 2020). In addition, the National Ethics Committee, which oversees all genetic and reproductive research, can recommend new interventions to the Minister of Health. Interventions deemed as compliant with human dignity, can be allowed by the Minister, contingent on prior license, monitoring and over-

sight. This legal and regulatory structure, which may be applicable in other countries, provides flexibility to accommodate medically significant advances, while maintaining centralized supervision. For research purposes, genome editing is subject to the same regulation as any human embryo research (e.g. human embryonic stem cells), through the National Ethics Committee. Finally, broad ethical discussion of embryo editing is still nascent, but will likely be informed by Jewish perspectives on the embryo, and on the social importance of specific applications, particularly those regarding fertility.

Andy Greenfield, Harwell (Oxfordshire, UK)

Human embryo genome editing: Regulation in the UK and ethical perspectives

By law, anyone in the UK wishing to provide assisted reproduction services or undertake research involving human embryos can only do so under a licence from the Human Fertilisation and Embryology Authority (HFEA). The UK has a tradition of innovation in the field of assisted reproduction and research involving human embryos. For example, in February 2016 the HFEA licensed the use of genome editing in human embryos in a research context, and in March 2017 it approved an application to perform mitochondrial donation (or mitochondrial replacement therapy) in a clinical setting.

Given this regulatory landscape in the UK, what are the prospects for the use of genome editing in a clinical (reproductive) context? The use of genome-edited human embryos (or gametes) to establish a pregnancy would currently be unlawful. So, in the UK, the question amounts to a discussion concerning whether the HFE Act *should* be amended, and whether such an amendment is *likely*. I will draw comparisons with two lawfully regulated procedures – preimplantation genetic diagnosis (PGD) and mitochondrial donation. PGD can be used only if particular criteria are satisfied: there must be a particular risk that the embryo to be tested may have a genetic, mitochondrial or chromosomal abnormality, and that a person with the abnormality will have or develop a serious disability, illness or medical condition. Similarly, mitochondrial donation can only be offered to a woman if there is a strong probability of her transmitting high levels of pathogenic mitochondrial DNA (mtDNA) to her offspring, such that PGD is unlikely to be successful in eliminating this risk. I will discuss the question whether these two procedures – both in terms of what they seek to effect clinically and the ethical issues that they raise – are reliable guides for exploring the acceptability of reproductive genome editing.

Jochen Taupitz ML, Mannheim

Human genome editing in the context of the German Embryo-Protection-Act

Sec. 5 of the Embryo-Protection-Act criminalizes changes in the human germ line unless the change is the involuntary side effect of, e.g., a somatic gene therapy. The prohibiton was introduced due to the uncertainties of the methods available when the statute was adopted in 1990; it was argued that the non-controllable risks for the individuals concerned by germ-line changes rendered the therapies irresponsible human experiments. Should the methods for genome editing eventually turn out to be safe enough, the legislature's underlying reason for the prohibition would become obsolete. Then at the latest the question of eliminating the prohibition will be raised, which in turn creates the need for a societal discussion already today. In doing so, different and conflicting constitutional rules have to be balanced and brought into equilibrium. The production of artificial germ cells prompts completely novel inquiries regarding the creation of humans. If somatic cells are reprogrammed into induced pluripotent stem cells and then differentiated into germ cells, children with only one genetic parent or with two same-sex parents are possible, even in the biological (and not merely legal) sense. Genetic interventions not covered by the Embryo-Protection-Act are possible on every step of the development of artificial germ cells. Moreover, the need for discussion transcends these fundamental questions. Thus, it is uncertain whether Chinese experiments with non-viable embryos are prohibited by German law; likewise, the legality of mitochondrial transfers is unclear.

Meeting Venue

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Jägerberg 1
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