MEETING SUMMARY

Proceedings of the International Summit on Human Gene Editing: a global discussion—Washington, D.C., December 1–3, 2015

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Abstract The US Academies of Sciences and Medicine, the Royal Society, and the Chinese Academy of Sciences convened a summit of experts in biology, medicine, law, ethics, sociology, and journalism, in December 2015 to review the state of the art in gene editing technology and discuss the medical and social ramifications of the technologies. The summit concluded with the following consensus recommendations: (1) intensive basic and preclinical research in animal and human models should proceed with appropriate legal and ethical oversight; (2) clinical applications in somatic cells must be rigorously evaluated within existing and evolving regulatory frameworks for gene therapy; (3) it would be irresponsible to proceed with any clinical use of germline editing until relevant safety and efficacy issues have been resolved and there is broad societal consensus about such a use; and (4) the international community should strive to establish generally acceptable uses of human germline editing.

Keywords Germline · DNA · Embryo · Stem cells · Reproductive rights · Inheritable disease

Capsule Biologists, medical and legal professionals, ethicists, social scientists, and journalists from around the world gathered in Washington, D.C., December 1st to 3rd, to debate the scientific and societal implications of human gene editing.

Based on presentations available at: <http://www.nationalacademies.org/gene-editing/Gene-Edit-Summit/Slide-Presentations/index.htm>

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The summit was chaired by Nobelist David Baltimore (California Institute of Technology) and hosted by the US National Academies of Sciences and Medicine, the Chinese Academy of Sciences, and the British Royal Society.

Klaus Rajewsky (Max Delbrück Center for Molecular Medicine) provided the scientific context with an overview of the molecular biology of the gene and advances in recombinant and gene-editing technology. Daniel J. Kevles (New York University) reminded the participants of past societal attempts to interfere with human reproductive rights and manipulate the genetic pool via eugenics. Alta Charo (University of Wisconsin) reviewed the current regulatory framework for national and international oversight of genetic technology.

The first panel discussion focused on the scientific progression of gene-editing technologies and was chaired by Jennifer Doudna (University of California Berkeley). Maria Jasin (Memorial Sloan Kettering Cancer Center) reminded the participants that the rationale for even considering modification of the human genome has been to ameliorate disease. The first widely used attempts relied on recombinant DNA technologies via either plasmids or site-specific double strand breaks to introduce specific DNA sequences into the genome. Emmanuelle Charpentier (Max Planck Institute for Infection Biology) summarized the CRISPR-Cas9 approach to altering DNA. The enzyme Cas9 is programmed with a guide RNA to target and cleave specifically DNA resulting in sequence-specific changes in DNA. Possible applications include agriculture, biosynthesis of useful molecules, and human medicine. There are numerous medical applications for this technology beyond editing the germline itself including discovery of pathways of gene expression, engineering of disease models, and

development, screening, and validation of novel therapies. Jin-Soo Kim (Seoul National University) cautioned about unresolved challenges in genome editing such as site-specific delivery and immunogenicity of nucleases, mosaicism, homology-directed repair versus nonhomologous DNA end joining, off-target mutations, and overcoming regulatory stumbling blocks. These all are issues requiring further investigation. Jonathan Weissman (University of California San Francisco) presented examples of how CRISPR can be “retooled” to turn genes on and off.

The second panel addressed the application of gene-editing technology to human germline modification. Robin Lovell-Badge (The Francis Crick Institute) outlined potential reasons for genome editing in human embryos in addition to advancing the understanding of human biology. These include the creation of models of human genetic disease for in vitro study, treatment of disease in somatic cells, and altering the germline for the prevention of genetic disease or for genetic enhancement. Theoretically, the genome of the human germline could be edited at different stages but with different efficiencies and disadvantages; first, at fertilization coincident with intracytoplasmic sperm injection; second, in one-cell zygotes by injection into the cytoplasm; third, in early embryos from the two-cell to blastocyst stages, though this approach would be likely to result in mosaicism; fourth, in post-implantation embryos, which could require a viral vector and also result in mosaicism; and fifth, gametes or gamete stem cells. Peter Braude (Kings College London) discussed the reproductive options for those at risk of inheritable diseases. Either they can gamble and hope they do not produce an affected offspring or they can choose among remaining childless, adopting children, or doing prenatal diagnosis and terminating a pregnancy. The use of preimplantation testing of embryos has been increasing steadily since 1997, primarily for aneuploidy testing but also for the detection of monogenic disease and chromosomal abnormalities; preimplantation testing for social sexing and sexing for X-linked disorders remain relatively infrequent. Since cleavage-stage embryos exhibit considerable chromosomal instability, the use of aneuploidy testing requires further research regarding its efficacy. Kyle Orwig (University of Pittsburgh) reviewed progress towards the development of germ cell stem cells in vitro, particularly spermatogonial stem cells. The ability to generate spermatogonial stem cells could provide an opportunity to edit genes and modify the germline in male germ cells. Ex vivo gene therapy and transplantation of spermatogonial stem cells is technically feasible in rodents at the present time. However, precision gene therapy in human spermatogonial stem cells requires the development of long-term cell

culture systems for the selection of accurate clones. George Daley (Boston Children’s Hospital) then presented the possible uses of gene editing in the germline and asked whether they are permissible under certain or all circumstances: prevention of disease, reduction in the risk of disease, or enhancement of individual characteristics. For example, is it appropriate to modify the germline when both intended parents of a couple are affected by a disease gene and there is no alternative to preventing disease in the offspring? Would it be appropriate to modify genes to eliminate the risk of contracting a disease? Would it then be appropriate to modify genes for such characteristics as learning and memory or physical stature? George Church (Harvard Medical School) added that treating and screening single germ cells is safer than treating millions of somatic cells, e.g., cancer, since each cell adds to the collective risk of cancer.

The third panel discussion, which was moderated by Annelien L. Bredenoord (University Medical Center Utrecht) dealt with the societal implications of emerging technologies. Hille Haker (Loyola University Chicago) raised the alarm about ethical issues around human germline gene editing. She proposed that research on *somatic* gene editing continues with appropriate oversight and ethical, social, and legal studies but that *germline* gene editing for reproductive purposes be banned. Her recommendation was based mainly on the postulates that reproductive germline editing exposes women and future children to non-justifiable health risks and violates the freedom rights of future children; disregards the moral status of a human embryo; and disregards the second patient, the future child. She further postulated that having genetically connected offspring is not a human right and, thus, intended parents could avoid having affected offspring through adoption or use of gamete donors. Sharon Terry (Genetic Alliance), on the other hand, stated that while the technical and ethical issues must be resolved satisfactorily, the need for gene editing in the germline is urgent.

Eric Lander (Broad Institute of Harvard and MIT) summarized the current state of knowledge of inheritable diseases. He reminded the participants that the vast majority of Mendelian diseases could be treated by preimplantation genetic diagnosis combined with in vitro fertilization. The most important intervention to avoiding devastating genetic disease is to ensure intended parents have access to genetic testing to know they are at risk. With the underlying genetic causes of polygenic diseases being identified rapidly, it is becoming apparent that genetic basis of human disease is more complex than previously thought and there are but a few plausible variants for editing. Great caution is

required before making permanent changes to the germline.

The fourth panel discussion addressed basic research into applications of gene-editing technology and was moderated by Duanqing Pei (Guangzhou Institutes of Biomedicine and Health). Rudolph Jaenisch (Massachusetts Institute of Technology) outlined limitations of current gene-editing techniques that could limit their human therapeutic application. For example, gene targeting by homologous recombination is inefficient in human embryonic stem cells. At present, CRISPR/Cas-mediated gene editing is inefficient and somewhat unpredictable in animal models with high rates of off-target cleavage. Nonetheless, the technique could be straightforward and efficient for inactivation of disease-susceptibility genes. Correction of disease-causing mutations would be more problematic since one would have to be able to distinguish mutant from wild-type embryos and the majority of manipulated embryos probably would be mosaic. Janet Rossant (The Hospital for Sick Children) further emphasized the usefulness of gene editing in elucidating the molecular programming of human development. Jinsong Li (Shanghai Institute of Biochemistry and Cell Biology) described how his laboratory has been able to use the CRISPR-Cas9 technology to edit genes in androgenetic haploid embryonic stem cells, which then are injected into oocytes to produce cloned mice.

The fifth discussion centered around the application of gene editing to somatic cell therapy and was moderated by Adrian Thrasher (University College London). Fyodor Urnov (Sangamo BioSciences) emphasized that genome editing has expanded the meaning of “druggable target” because now, the genome is a “druggable target.” One seemingly successful approach has been to use zinc finger nucleases to disrupt the gene for CCR5, the HIV co-receptor, in T cells of HIV-positive individuals resulting in sustained increase in some subjects’ T cells and reduction in the viral load in the absence of anti-retroviral therapy. Marco Weinberg (Scripps Research Institute) cautioned that the applicability of ex vivo stem cell manipulation is limited. Matthew Porteus (Stanford University) noted that while advances in genome editing of somatic stem cells could eliminate or reduce the demand for germline genome editing, there remain serious issues with doing in vivo genome editing using nucleases. Problems yet to be addressed relate to immunogenicity of the nucleases, modes of delivery, and the risk of ongoing DNA damage due to sustained expression of the nuclease.

The focus of the discussion then shifted to issues of governance. Pilar Ossorio (University of Wisconsin Madison) moderated the session dealing with governance at the institutional and national level. Jonathan Kimmelman (McGill University) reminded participants of the difficulty in predicting the harms and benefits of translational trials, and thus, the necessity to weigh both ethical positions and scientific evidence to reduce the level of uncertainty. Barbara Evans (University of

Houston) posed the question of whether current ethical and legal standards for human subject research adequately address the generally accepted need for precaution in developing a new therapy such as human gene editing. She suggested that characterizing gene-editing technologies as devices rather than drugs might allow better regulation of research involving gene editing. Zhihong Xu (Peking University) reviewed the status of deliberations and regulations around human embryo research and gene editing in China. Jennifer Merchant (Université de Paris II) compared the approaches to governmental oversight of new technologies pertaining to human embryos in France and the UK, which both utilize top-down regulatory mechanisms. In France, the government organized three panel discussions of small groups of citizens that produced recommendations that mostly upheld previously accepted principles without addressing society’s broader concerns pertaining to gametes and embryos. In the UK, the Human Fertility and Embryology Authority conducted public consultations regarding mitochondrial transfer. These consultations were criticized for being more rule-guided and strategic than deliberative with unclear links between the consultation and any legislative outcome, but the outcome was a focused set of recommendations dealing with a single issue. Indira Nath of the All India Institute of Medical Sciences chaired the discussion of governance at the international level. First, Gary Marchant (Arizona State University) presented the evidence in support of the advantages and disadvantages of international regulations. On the pro side, (1) international standards would assure equal protection for citizens of all nations; (2) uniform national requirements would discourage medical tourism; (3) international standards would provide consistent requirements for companies and scientists in the field; (4) harmonized national standards would prevent trade disputes and would prevent “race to the bottom” or “risk havens;” and (5) regulators would benefit from economies of scale and sharing resources and workload. Arguments against international regulations include (1) each country has its own social, political, and ethical norms; (2) different national approaches allow for comparison among nations to determine the best approach; (3) the resources required for developing international standards and regulations could be better spent in developing national oversight mechanisms; and (4) it would be unlikely that all nations would agree and comply with universal regulations. Thomas Reiss (Fraunhofer Institute for Systems and Innovation Research) emphasized the urgent need for governance approaches to human gene editing based on a framework for responsible research and innovation. Governance of human gene editing needs to be anticipatory, adaptive, and broadly grounded on societal acceptability considering all relevant stakeholders. Philip Campbell (*Nature*) stated that the Nature group’s publications would be guided by safety considerations, compliance with applicable regulations, and the status of the societal debate on

the implications of germline modifications for future generations.

The eighth discussion, which was moderated by Ernst-Ludwig Winnacker (Ludwig-Maximilians University of Munich), consisted of individual descriptions of different countries' research, ethics, and public policies pertaining to human gene editing. Presenters included Fola Esan (Nigerian Academy of Science); Bärbel Friedrich (Leopoldina—the German National Academy of Sciences); Pierre Jouannet (Université Paris Descartes); Ephrat Levy-Lahad (Hebrew University Medical Center); Keymanthri Moodley (Stellenbosch University); Staffan Normark (Karolinska Institute); and K. Vijay Raghavan (Government of India Department of Biotechnology). The level of interaction among scientists, clinicians, and policy makers varies considerably among countries, with about 70 % of countries legally prohibiting germline gene editing.

Françoise Baylis (Dalhousie University) next moderated a session dealing with “interrogating equity.” First, Tetsuya Ishii (Hokkaido University) proposed that germline genome editing using homology-directed repair with a single guide RNA might be justified when the benefits for the parents and/or child exceed any risks to the child. Gene disruption and gene addition would not be advisable but rather germline editing might be considered for preventing the rare cases of definitive inheritance of genetic disease where preimplantation genetic diagnosis is not appropriate. Second, Catherine Bliss (University of California, San Francisco) reminded participants that the social politics of race have highlighted the need to consider the ethical, legal, and social implications of human genome editing. Third, Ruha Benjamin (Princeton University) reviewed the history of humans making judgments about other humans based on physical characteristics different than their own. She emphasized the importance of avoiding a distortion of societal scientific goals by the well-intentioned charitable efforts of a few wealthy people seeking to remedy personal tragedy.

The final session dealt with governance, regulation, and control and was moderated by Hank Greely (Stanford University). David Relman (Stanford University) discussed biosecurity in the context of human gene editing. He pointed out that gene-editing technology could very easily be misused to create disease in humans, produce disease susceptibility, express detrimental factors, or induce harmful drug expression. These risks might be mitigated by regulating access to reagents and information, promoting awareness, sensitizing relevant communities, establishing norms, and preemptively anticipating threats to human safety. Richard Gold (McGill University) reviewed the principles guiding sharing of research data at his institution: (1) all

data and scientific resources must be made available by the time of publication; (2) all data and scientific resources generated through research partnerships also must be released by the time of publication; (3) the dignity, privacy, and rights of patient participants in research studies must be safeguarded; (4) researchers will not obtain patent protection or assert data protection rights in respect to their research; and (5) the institution supports the autonomy of researchers, staff, trainees, patients, and other stakeholders. Finally Charis Thompson (University of California, Berkeley) summarized the consensus points of the summit. She noted that several controversies and constituencies were absent from the discussion. These included health disparities, disability, race, gender, commercialization, medical tourism, and what actually constitutes a medical condition.

Summary

After hearing all of the presentations and discussion, the Organizing Committee developed the following consensus recommendations, presented by David Baltimore:

1. Basic and preclinical research. Intensive basic and preclinical research is clearly needed and should proceed, subject to appropriate legal and ethical rules and 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. 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.
2. Clinical use: somatic. Many promising and valuable clinical applications of gene editing are directed at altering genetic sequences only in somatic cells—that is, cells whose genomes are not transmitted to the next generation. Examples that have been proposed include editing genes for sickle-cell anemia in blood cells or for improving the ability of immune cells to target cancer. There is a need to understand the risks, such as inaccurate editing, and the potential benefits of each proposed genetic modification. 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.
3. Clinical use: germline. 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.

4. Need for an ongoing forum. While each nation ultimately has the authority to regulate activities under its jurisdiction,

the human genome is shared among all nations. The international community should strive to establish norms concerning acceptable uses of human germline editing and to harmonize regulations, in order to discourage unacceptable activities while advancing human health and welfare.

The Summit concluded with a call for the US National Academy of Sciences and US National Academy of Medicine, the Royal Society, and the Chinese Academy of Sciences “to take the lead in creating an ongoing international forum to discuss potential clinical uses of gene editing; help inform decisions by national policymakers and others; formulate recommendations and guidelines; and promote coordination among nations.”