CRISPR-Cas Gene Editing to Cure Serious Diseases: Treat the Patient, Not the Germ Line

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CRISPR-Cas9 is a powerful new technique that allows for precise editing of DNA, the genetic code in all the cells of our body. It is also broadly available and easy to use, which has raised the fear of improper intervention into human biology and led to calls for a moratorium on some types of gene editing research (Lander 2015; Lanphier et al. 2015). As physicians experienced in the discovery and development of new treatments for disease (currently we are both senior executives of CRISPR Therapeutics), we do not believe that a blanket moratorium is the right approach. While we welcome considerations regarding the ethical uses of gene-editing technologies, it is at least as important—and ethically relevant—to also consider the powerful potential of gene editing in general, and CRISPR-Cas9 in particular, to treat the millions of patients who are impacted by a number of very serious diseases. For the vast majority of diseases, a gene editing approach need not employ the heritable germ line cells that transmit genetic information to subsequent generations. Instead, genetic diseases typically manifest in, and gene editing can be applied in, somatic cells, for which the older gene therapy methods are widely accepted and where a well-established and tested regulatory framework already exists in both the United States and Europe.

CRISPR-Cas9 itself and as a tool for gene editing was elucidated just a few years ago by a cofounder of CRISPR Therapeutics, Emmanuelle Charpentier, and her colleagues (Deltcheva et al. 2011), and in collaboration with Jennifer Doudna and colleagues (Jinek et al. 2012). The importance of this discovery—to be able to more easily and selectively edit the underlying DNA code of cells—cannot be overstated. CRISPR has already revolutionized basic research by allowing scientists to readily modify the genome of cells and model organisms, enabling the development of an expanding set of tools to understand fundamental biological questions. “CRISPR” derives from the “clustered regularly interspersed short palindromic repeats” in the bacterial genome where the gene editing machinery was found, and Cas9 is an endonuclease protein that breaks up and thus deactivates the DNA of invading viruses. This system has been characterized in a wide range of bacteria (reviewed in Makarova et al. 2013). The adoption of CRISPR gene editing for use in research, and for developing novel medicines, has been remarkably rapid, in part because it is so easy to apply these fundamental discoveries to higher organisms including, in principle, humans (reviewed in Doudna and Charpentier 2014). These easy and accessible methods are making DNA programmable in a way that is already having a profound impact on human, animal, and crop plant biology. The scientists and developers of treatments based on this new technology are becoming the ultimate coders (Keller 2015).

The rapid advance of CRISPR gene editing has evoked a predictable debate regarding “reprogramming DNA,” similar to the concerns regarding genetic manipulation that have been raised since the earliest days of gene cloning (reviewed in Comfort 2015). In particular, modifying DNA of germline cells, which is passed down to subsequent generations, may have lasting effects on the human gene pool. While the effects of modifying the genome with gene editing in a somatic, non-germline cell of a patient are increasingly being understood, the longer term effects of modifying the germ line, including in the patient’s descendants, are less well known. The concern is more than theoretical: A research group in China recently employed CRISPR-Cas9 technology to make changes in human germline cells, changes that could in principle both be expressed in a human being and then later be passed on via sperm or egg cells to subsequent generations. We should emphasize that these particular experiments were performed in nonviable human embryos and the results were never going to be able to be expressed in a human being. Nonetheless, the experimental approach of germline gene editing employed by this research group, if applied to viable human embryos, could potentially be expressed in a human and passed on to descendants.
Our company is not undertaking any editing of human germline cells and we have no plans to do so in the future. Virtually all serious genetic defects manifest in the nonheritable somatic cells, where we find the greatest and most immediate need, for therapeutic purposes, in editing or correcting the DNA. It is also more appropriate to apply a new technology like CRISPR-Cas9 in the setting in which the consequences of the therapy are directed only to the patient and are not passed on to or altering the gene pool for future generations. Ethical support for providing gene editing therapies in a somatic cell is much like any other therapy directed at and for the patient, grounded in the principles of autonomy (the patient’s right to decide), beneficence (providing benefit), and nonmaleficence (not doing harm). These issues are represented by the need for patient informed consent and a favorable risk–benefit profile for a treatment.

Yet even if parents and their physicians agree that avoiding heritable genetic disease in the current and future generations is desirable, there are already several ways to achieve this outcome. Couples can undertake genetic testing prior to pregnancy, or employ in vitro fertilization and preimplantation genetic diagnosis to implant only those embryos known to be not at risk for a specific disease. Some have argued for germline genome editing “in the extremely rare case when one parent is homozygous for a dominant disorder [so all offspring inherit one of the dominant disease-associated genes] or both parents are homozygous for a recessive disorder” (such that all offspring inherit two copies of the recessive disease-associated genes, one from each parent) (Lander 2015). Even in these rare cases, however, most diseases will occur, and in principle can be corrected, in specific somatic cells. Given the existence of alternative non-germline approaches to treat most Mendelian disorders and the uncertainty of the impact of the technology on the germline, no modern regulatory system would authorize clinical use of germline gene editing at the present time.

The challenge of developing CRISPR-Cas-based drugs for patients, therefore, is not to enable modification of DNA in germline cells, but rather to apply the current regulatory framework of somatic cell gene modification to CRISPR-Cas-based medicines. The U.S. Food and Drug Administration (FDA) guidelines and European Medicines Agency (EMA) guidelines already provide recommendations for manufacturing, preclinical assessment, clinical evaluation, and product approval for advanced therapy medicinal products (ATMP) and cellular and gene therapy products (e.g., see EMA 2010, 2015; FDA 2008, 2013, 2015). Yet the FDA and EMA procedures differ in important ways. In the United States the FDA Center for Biologics Evaluation and Research regulates cellular and gene therapy products on the basis of Section 351 of the Public Health Service Act (PHS Act 42 U.S.C. 262) on Cellular, Tissue and Gene Therapies. In the European Union (EU), a regulation and a set of directives specify the development of ATMP, regulated through a centralized procedure. A directive in the EU, but not the United States, also specifies that “no gene therapy clinical trials may be carried out which result in modifications to the subject’s germ line genetic identity” (European Parliament 2001). The regulatory oversight of clinical trials, and the release of genetically modified organisms (GMOs), are both governed by directives implemented into national law in each of the EU member states. Finally each member state can legislate additional national or regional regulations regarding clinical trials or GMO. For example, in the case of the recently approved mitochondrial donation therapy for parents of children conceived by in vitro fertilization, so-called “three-parent babies,” only the UK Human Fertility & Embryology Authority undertook a 4-year process of extensive ethical review, public consultation, reports on safety and efficacy, review of draft regulations, and recommendations for further research prior to legislative approval (UK Department of Health 2014). Considerable work remains to harmonize the processes in developing ATMPs across the EU member states.

Despite the complex landscape of regulations and regulatory processes across the United States and Europe, these are well established and tested in the context of somatic cell gene therapy, and issues requiring harmonization are being addressed. We strongly recommend their appropriate, flexible application to the clinical evaluation and marketing authorization of CRISPR-Cas gene editing, and oppose calls for a blanket moratorium. The vast majority of Mendelian diseases manifest in the somatic cells of a patient, and it is here, not in the germline, that we must focus our therapeutic efforts. Given the ease and facility with which CRISPR gene editing has been able to correct many different disease causing gene defects in the laboratory, we need to now move forward with developing new CRISPR gene editing therapies to treat, or even cure, the many patients currently suffering from a wide range of devastating diseases.

CONFLICTS OF INTEREST
Ante Lundberg is an employee and shareholder of CRISPR Therapeutics. Rodger Novak is an employee, shareholder and director of CRISPR Therapeutics.

REFERENCES


Deltcheva et al., 2011. CRISPR RNA maturation by trans-encoded small RNA and host factor RNase III. Nature 471:602–9


Concerns over the prospect of germline modification of the human genome have recently been rekindled by critical advances in genome editing paradigms and by a highly publicized effort to edit the genome of nontransferrable aneuploid (tripronuclear) human zygotes (Liang, Xu, and Zhang 2015). As such, these developments have reenergized the debate on the possibility of editing the genome of the human germline (as Charo and Greely [2015] note in this issue, animals raise some additional issues). The articles and commentaries that form this symposium cover many topics (including the use of metaphor, the role of social responsibility in science as an evaluative framework, model regulatory frameworks, and the sense of déjà vu to old debates), but they do not attempt to map the rapid development of policy in this area. In this commentary we trace the evolving reactions to the prospect of germline modification and examine where they are converging.

Early to recognize the profound implications of the new genome editing technology, some parties have called for an all-out voluntary moratorium on editing the genome of the human germline in both the research and clinical arenas (Lanphier et al. 2015; Wadhwa 2015). A comparable position statement issued by the Society for Developmental Biology proposed a “voluntary moratorium by members of the scientific community on all manipulations of pre-implantation human embryos by gene editing” (Society for Developmental Biology 2015). The American Society for Gene and Cell Therapy, for its part, advanced a “strong ban on human germ-line gene editing or other germ-line genetic modification” until such time that a “societal consensus [has been] reached” (Friedmann, Jonlin, and King 2015). Finally, the National Institutes of Health (NIH) announced that it “will not fund any use of gene-editing technologies in human embryos” (Collins...