Genetic Engineering Regulation

This article summarizes the current state of regulation in the field of genetic engineering.

Note – This was written in February 2020, and does not include developments after that.

Introduction

In the early 1970s, experiments demonstrated that DNA from different sources could be deliberately recombined into patterns distinct from those found in nature. The invention of "recombinant DNA" allowed cells and organisms to be genetically engineered. In turn, it fostered the creation of a new industry: biotechnology. Several years after the initial demonstration of genetic engineering, a human gene, somatostatin, was successfully spliced into E. coli.[1]

Within five years of the first deliberate recombination of DNA, ambition for the field had vaulted towards "the new era of 'synthetic biology' where not only existing genes are described and analysed but also new gene arrangements can be constructed and evaluated."[2] Synthetic biology has since moved well beyond this early conception of the field as one of rearranging genes. Now the field envisions not just the redesign of existing organisms, but even the *de novo* design and "programming" of genes and organisms. The current explosion of interest in synthetic biology is the culmination of a century of biological efforts to control, change, reengineer, and remake living systems at the molecular level.

As important as this is, the ethos of open science, and a concomitant distaste for intellectual property, represents what may be a significant influence in the development of synthetic biology.

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[1] Itakura, K., Hirose, T., Crea, R., Riggs, A., Heyneker, H., Bolivar, F. and Boyer, H., 1977. Expression in Escherichia coli of a chemically synthesized gene for the hormone somatostatin. *Science*, [online] 198(4321), pp.1056-1063. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/412251> [Accessed 22 April 2020].

[2] *Gene*, 1978. Nobel prizes and restriction enzymes. [online] 4(3), pp.181-182. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/744485> [Accessed 22 April 2020].

Current state of regulation in the field

The advent of regulation in bio-technology and gene-based patenting can generally be traced back to 1911 to the case of Parke Davis v. Mulford in the United States. The case was concerned with a patent on highly purified form of concentrated adrenaline, which is a naturally occurring hormone. Since then, there have been numerous developments in the field, but a historical review is beyond the scope of this article.

A recent major issue which had ramifications for the entire bio-technology industry was the CRISPR patent dispute in the United States, between the Broad Institute (MIT and Harvard University) and University of California, Berkeley.[3]

While CRISPR-Cas9 may revolutionize the way the scientific community approaches, and the medical community treats, genetic diseases, some critics fear that the technology will usher in a generation of designer babies and "a dystopia of super-people." OvaScience, a Cambridge, Massachusetts-based company in the US, argues that this technology will allow parents to choose not only "when and how they have children [but also] how healthy those children are going to be." David Sinclair, a geneticist at Harvard University and co-founder of OvaScience, stated at a commercial presentation in December 2016 that "there is no reason to expect" that the ability to remove defective genes, referring to those in genetic diseases, "won't be possible in coming years." [4]

On the one hand, it is relatively easy to understand society's unease about the extreme scenarios that could result from gene editing, scenarios that could catapult the world into an era that seems more appropriately confined to science fiction.[5]

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[3] Cross, R., 2018. Broad Prevails Over Berkeley In CRISPR Patent Dispute. *Chemical & Engineering News*, [online] Available at: <https://cen.acs.org/policy/litigation/Broad-prevails-over-Berkeley-CRISPR/96/web/2018/09> [Accessed 22 April 2020].

[4] Regalado, A., 2020. Engineering the Perfect Baby. *MIT Technology Review*, [online] Available at: <https://www.technologyreview.com/2015/03/05/249167/engineering-the-perfect-baby/> [Accessed 22 April 2020].

[5] Brownell, C., 2016. From curing diseases to making designer babies, human gene editing is coming. *Financial Post*, [online] Available at: <https://business.financialpost.com/executive/smart-shift/from-curing-diseases-to-making-designer-babies-human-gene-editing-is-coming> [Accessed 22 April 2020].

On the other hand, other members of the scientific community believe that the idea of genetically engineering a "perfect" society is nowhere close to being attainable. Dr. Stuart Kim, a genetics professor at Stanford University, argued that the notion of making an individual faster or more resilient is "still far enough off, [that it] might as well be the stuff of science-fiction." [6] Similarly, Rudolf Janeisch, a biologist at the Massachusetts Institute of Technology, stated that any "attempts to edit human embryos [are] 'totally premature.'

Researchers are only beginning to study the use of the technology as a treatment for single-gene disorders, but many traits, such as increasing resistance to muscular injury, involve multiple genes. Before being able to genetically modify an individual with the trait, scientists would need to determine how the genes interact. Nonetheless, this disagreement regarding the capabilities of CRISPR-Cas9 in gene editing illustrates the uncertainty as to what realms of genetic modification are possible currently and in the future. Without proper regulations and research, there are many technical and ethical issues that the international community should address to avoid exploitation - particularly given the problems seen in recent history, such as the forced sterilization laws of various countries and the eugenics practices of the past, it is worth trying to get a head start on the problem.

The capabilities of technology like CRISPR, enforce the belief that despite any uncertainty as to the full extent of the capabilities, there is a need for a global discussion on ethical limitations. Internationally, there are three countries that are at the forefront of gene editing: China, United States, and the United Kingdom. It is useful to analyse the current laws and regulations in place in these countries, since they are making the most leeway in research, it is likely that other countries will look to their actions in deciding how to regulate gene editing.

China

The People's Republic of China has, theoretically, an outright legislative ban on gene editing of

[6] Beresini, E., 2016. Could CRISPR Genetically Tailor Athletes? It's a Nice Idea. *Outside*, [online] Available at: <https://www.outsideonline.com/2045666/could-crispr-genetically-tailor-athletes-its-nice-idea> [Accessed 22 April 2020].

human embryos.[7] Yet despite this legislation, commentators have referred to China's stem cell treatment and research as "wild"[8] as China has "one of the most unrestrictive regulatory regimes"[9] Despite enacted regulations, there is a lack of enforcement mechanisms and loopholes in the guidelines are widespread. It is through one of these loopholes that, recently, Chinese researchers were able to become the first in the world to edit the genes of a human embryo.[10]

The ethical guidelines for regulating this type of research arise from a 2003 joint issuance from the Ministry of Science and Technology and the Ministry of Health, The Guidelines for Ethical Principles in Human Embryonic Stem Cell Research. These guidelines permit the use of embryonic stem cells in research from specified sources such as unwanted embryos from IVF, miscarriages, and voluntarily induced abortions, as well as donated germ cells. Still, the guidelines dictate a complete ban on "using human egg plasma and nuclear transfer technology for the purposes of reproduction, and the manipulation of the genes in human gametes, zygotes or embryos for the purposes of reproduction are prohibited."

Other agencies potentially involved include the National Health and Family Planning Commission (NHFPC) and the Chinese Food and Drug Administration (CFDA). The NHFPC is charged with the guidance and formation of scientific programs related to health and family planning. The CFDA regulates genetic testing and had previously banned prenatal DNA testing in 2014.[11]

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[7] Gould, S. and Loria, K., 2015. This map shows where researchers might design the first genetically engineered baby. *Business Insider*, [online] Available at: <https://www.businessinsider.com/what-countries-allow-researchers-to-edit-human-embryos-2015-10?IR=T> [Accessed 22 April 2020].

[8] Juan, S., 2015. Health authority announces step to rein in 'wild' stem cell treatment. *China Daily*, [online] Available at: <http://www.chinadaily.com.cn/china/2015-08/21/content_21662613.htm> [Accessed 22 April 2020].

[9] Zhang, L., 2012. Bioethics Legislation In Selected Countries. *Law Library of Congress*, [online]. Available at: <http://www.loc.gov/law/help/bioethics/bioethics.php> [Accessed 22 April 2020].

[10] Fox, M., 2018. Chinese researcher says he is 'proud' of gene-editing twins. *NBC News*, [online] Available at: <https://www.nbcnews.com/health/health-news/chinese-researcher-says-he-proud-gene-editing-twins-n941201> [Accessed 22 April 2020].

[11] International Rare Diseases Research Consortium, 2014. *China Imposes Restrictive Regulation Of Genetic Testing*, [online] China. Available at: <https://irdirc.org/china-imposes-restrictive-regulation-of-genetic-testing/> [Accessed 22 April 2020].

However, the ban allowed clinical applications of gene sequencing to continue if they were approved by the NHFPC and were done according to regulations. Given the country's restrictive guidelines prohibiting gene editing for the purpose of reproduction, speculation arose as to how the Chinese research team was able to conduct this research experiment. The researchers might have used non-viable embryos-those unable to develop into humans because they were fertilized by two sperm. Secondly, China's regulatory bans actually "consist mostly of guidelines," which are considered "soft laws," leaving sanctions ambiguous and possibly unenforceable.[12]

United States

Shortly after the news spread of the Chinese researchers' gene editing experiments on twin human babies, the National Institutes of Health (NIH) in the United States issued a statement that it would "not fund any use of gene-editing technologies in human embryos."[13] The NIH proclaimed that not only is the use of this technology "a line that should not be crossed," but also that "there are multiple existing legislative and regulatory prohibitions" which prohibit such work.

One such regulatory barrier to gene editing of human embryos is the Dickey-Wicker amendment. The amendment prohibits the Department of Health and Human Services (HHS) from using any appropriated funds for both "the creation of a human embryo or embryos for research purposes" and "research in which human embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on foetuses in utero" according to applicable federal law.

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[12] Friedman, L., 2015. Tweaking the genes in human embryos is technically legal in many countries, and a new experiment could open up the floodgates. *Business Insider*, [online] Available at: <https://www.businessinsider.in/science/tweaking-the-genes-in-human-embryos-is-technically-legal-in-many-countries-and-a-new-experiment-could-open-up-the-floodgates/articleshow/47032030.cms> [Accessed 22 April 2020].

[13] National Institutes of Health, 2015. *Statement On NIH Funding Of Research Using Gene-Editing Technologies In Human Embryos*. Director, NIH. Available at: <https://www.nih.gov/about-nih/who-we-are/nih-director/statements/statement-nih-funding-research-using-gene-editing-technologies-human-embryos>

Still, there is some suggestion that the United States may be moving towards eliminating some of these restrictions. The organizational structure for regulating gene editing, which does not relate to the banned research on human embryos, is multi-faceted. The NIH's Recombinant DNA Advisory Committee (RAG) determines whether to approve gene-editing proposals that seek government funding.[14] Recently, the RAG approved "the first clinical protocol to use CRISPR/Cas9-mediated gene editing" in an effort to treat multiple kinds of cancer.[15]

David Magnus, the Director of the Stanford Centre for Biomedical Ethics, and Nicole Martinez, a lecturer and fellow at Stanford University, have criticized the United States regulatory control of gene editing "as a 'wild west' of reproductive technology."[16]Although HHS and the NIH limit what research may receive funding, there is no government agency or authority that regulates privately funded projects. Therefore, unlike the United Kingdom, it is not illegal in the United States to implant a genetically modified embryo to begin a pregnancy.

Moreover, due to separation of governing powers between the federal government and the states, some states are looking to their laws and guidelines to see if it is permissible to fund research on the gene editing of human embryos. The California Institute for Regenerative Medicine is considering whether to fund such an endeavour, and it would do so with the state of California's taxpayer dollars.

United Kingdom

Discussions of reproductive medicine have often focused on the United Kingdom, perhaps more so than any other region in the world. England was the first country to have a test-tube baby, to

[14] FDA Sketches Out Approach To Regulating Genome-Edited Products. *GenomeWeb*, [online] Available at: <https://www.genomeweb.com/gene-silencinggene-editing/fda-sketches-out-approach-regulating-genome-edited-products#.Xp-diZnhXIU> [Accessed 22 April 2020].

[15] Begley, S., 2016. Federal panel approves first use of CRISPR in humans. *STAT*, [online] Available at: <https://www.statnews.com/2016/06/21/crispr-human-trials/> [Accessed 22 April 2020].

[16] Magnus, D. and Martinez, N., 2016. In Embryo Research We Need Laws First, Then Science. *Time*, [online] Available at: <https://time.com/4204059/crispr-regulation/> [Accessed 22 April 2020].

use pre-implantation genetic diagnostics, and to clone a higher vertebrate. It has also been a leader "in human embryonic stem cell derivation and banking." [17]

The Human Fertilisation and Embryology Act governs the Human Fertilisation & Embryology Authority (HFEA), which regulates all research involving human embryos in the United Kingdom.[18] The Act imposes strict limitations, including an outright ban on the use of modified embryos for pregnancy, stating that it only permits implantation of an embryo if "no nuclear or mitochondrial DNA of any cell of the embryos has been altered and no cell has been added to it other than by division of the embryo's own cells."[19]

However, researchers did use the licensing system recently to gain permission to genetically edit human embryos. A couple donated the embryos, which doctors or researchers could never legally implant per regulations, from their surplus after IVF treatment. [20] The HFEA granted the license on February 1, 2016. The research license allows for the keeping, use, and storage of embryos for a period of three years, with the option of renewal. The license notes that these activities are for the purpose of "developing treatments for serious disease or other serious medical conditions," "increasing knowledge about the development of embryos," and "promoting advances in the treatment of infertility." [21]

Nonetheless, the HFEA committee reiterated the prohibition that the research project can never involve placing non- permitted embryos, eggs, or sperm in a woman, or keeping or using

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[17] Franklin, Sarah, and Celia Roberts. Born and Made: An Ethnography of Preimplantation Genetic Diagnosis. STU - Student edition ed., Princeton University Press, 2006. JSTOR. Available at: <https://jstor.org/stable/j.ctt4cgd33>. [Accessed 21 April 2020].

[18] Human Fertilisation & Embryology Authority (UK), *Embryo Research Project Summaries*. Department of Health. Available at: <https://www.hfea.gov.uk/donation/donors/donating-to-research/embryo-research-project-summaries/ > [Accessed 22 April 2020].

[19] *Human Fertilisation and Embryology Act*, 3(5)(4)(b-c). Available at: <https://www.legislation.gov.uk/ukpga/2008/22/contents> [Accessed 22 April 2020]

[20] Callaway, E., 2016. UK scientists gain licence to edit genes in human embryos. *Nature News*, [online] Available at: <https://www.nature.com/news/uk-scientists-gain-licence-to-edit-genes-in-human-embryos-1.19270> [Accessed 22 April 2020].

[21] 2015. License Committee Minutes. [online] Human Fertilization & Embryology Authority. Available at: <https://ifqlive.blob.core.windows.net/inspectiondocuments/5768.pdf> [Accessed 22 April 2020].

embryos after fourteen days from the date of creation or upon the appearance of a primitive streak, a structure that arises during embryologic development that is considered the beginning of the neural tube and nervous system. Additionally, no research using gene editing can take place until the research receives an ethics approval.

Although China was the first to use CRISPR-Cas9 for gene-editing purposes, this licensure approval represents the first endorsement worldwide of research of this kind by a national regulatory authority, and some believe that it has established a precedent for this type of research.

Conclusion

As gene editing implicates patent law, fertility treatments, and the development of medicine, one could make an argument that it implicates trade too. Few countries are willing to adopt binding measures, as was seen in the adoption of UNESCO's **Universal Declaration on Bioethics and Human Rights**; perhaps more so in the scientific realm where each country wants to be the first to make a breakthrough in the newest field of research, whether it be for financial opportunities or prestige.

The ambition of synthetic biology is to "make biology easier to engineer" through standardization and associated technical processes. Early successes indicate the promise of this field and help to explain why advocates of openness are concerned to see it develop in a publicly beneficial manner. However, what openness exactly might mean in the patent-dominated context of biotechnology remains unclear.

The **Universal Declaration on the Human Genome and Human Rights**, pioneered through UNESCO, provides an opportunity to establish such a consensus in an already existing instrument. The non-binding nature of declarations, and the ease in their adoption and revision, eliminates the hesitation many countries have in entering more formal instruments, such as binding treaties, and provides flexibility to modify the declaration. This ensures that ethical obligations will not unnecessarily hinder science, but also that the international research community will not take them lightly. Relying on soft law ensures that the international consensus on gene editing can adapt as researchers better understand the technology. This may

not only prevent a resurgence of the mistakes of our past, but may also allow for a future in which genetic engineering can eradicate detrimental problems that plague us.