OneBeacon
TECHNOLOGY INSURANCE

A Member of OneBeacon Insurance Group®

Gene Editing: CRISPR/Cas-9 and Beyond

Author: Michael Campbell, Medical Technology Risk Control

Published: January 2019

Executive Summary

In 2003, the National Institute of Health's (NIH) "Human Genome Project"[1] (HGP) announced that it had completed its research involving the mapping of the entirety of the human genome. It revealed that there are over 20,000 [2] [3] individual genes in the human body, providing scientists and others with detailed information about the structure, organization and function of the human genome, along with a basic set of genetic patterns for the development and function of a human being.[4] It also allowed researchers to explore the association between genetic information and the development of human disorders,[5] by providing researchers with a range of tools.

These tools have since been used to explore the genomes of other organisms, comparing and contrasting their genetic information, finding analogues of their genetic makeup in human beings,[6] and enabling researchers to change an organism's DNA.[7] The project, considered to be biology's equivalent of the "moon shot,"[8] has since produced substantial economic and scientific benefits. As of early 2011, an initial investment of $3.8B has returned $796B in economic impact and has created 310,000 new jobs.[9] It is advancing medicine by targeting the genomic causes of a wide range of diseases such as cancer, cardiovascular and neuromuscular disorders, and identifying genetic mutations linked to undiagnosed diseases for which therapeutic applications are being developed.[10]

The outcomes of the HGP along with the emergence of CRISPR/Cas9 as a primary genome editing tool, has raised ethical concerns over the potential end uses of these tools.[11] As such, researchers have begun to identify ethical boundaries and limitations to ensure that the benefits of genomic editing outweigh the potential risks.[12]

At the end of November 2018, a researcher in China claimed that he has successfully used the CRISPR/Cas-9 gene editing technology to produce twin girls[13] whose genetic materials were edited to greatly improve the girls' resistance to HIV. This claim has not yet been corroborated,[14] but it has generated significant controversy.[15] Scientists have come down of both sides regarding whether this pushes boundaries of ethics too far.[16] Chinese authorities are also investigating the researcher for violation of Chinese law.[17]

What is Gene Editing?

The process involved in making changes to an organism's DNA is called genome editing.[18] This process has helped researchers develop and use a group of technologies to change an organism's DNA by adding, removing or altering genetic material at particular locations in the genome. The NIH maintains a database of various informatics technologies that have been developed in the years since the 2003 announcement and these were instrumental in the development of gene editing tools.[19] Several avenues of research have been pursued using these tools resulting in an improved understanding of an organism's genome.

Snipping Genes for Progress

Amongst these tools and their subsequent use, the best received has been the CRISPR/Cas-9 platform.[20] [21] [22] Announced in late 2015, CRISPR/Cas-9 (Clustered Regularly Interspaced Short Palindromic Repeats, or more commonly, CRISPR), relies on the use of sections of DNA from viruses that have attacked prokaryotes.[23] Prokaryotes are single celled structures such as bacteria, which are present in humans and other organisms. These viruses contain the DNA of the specific person they are in, and are known to trigger a defense mechanism in prokaryotes to detect and destroy DNA from similar viruses. The platform also takes advantage of this defense mechanism, using a specific gene editing capability of a group of proteins called Cas9.[24]

Cas9 is a bacterial enzyme produced by viruses for the purpose of cutting and replacing normal DNA with a mutation. By replacing the virus' mutation with an analogue viral DNA, researchers can alter the expression of the gene (what the gene does) and study the effects on the organism, and use this effect to potentially modify the human genome towards the prevention and rapid diagnosis of genetic disorders.[25] [26]

Since its introduction, the early use of CRISPR was to understand how genomes work.[27] Several companies have since developed uses for the CRISPR platform, which have promising applications in the prevention and cure of genetic disorders.[28] [29]

Concerns with CRISPR

During this time, there has also been skepticism expressed about the CRISPR platform citing issues such as:

- safety concerns
- limitations of the platform
- the effectiveness of current gene modification therapies[30]

The technology has also been scrutinized on medical, ethical, social, religious and legal grounds as well as the potential for malicious use.[31] In a 2017 study, patients treated with gene replacement therapy were identified as having "off target" genetic mutations such as additions and deletions, which may have potentially unknown and unexplored consequences. There is concern that gene editing may cause unrelated or unexpected genetic disorders.[32]

Such mutations are believed to increase risk of cell death or transformations, and further improvements are being recommended, particularly where gene editing is to be used for therapeutic purposes.[33] Earlier this year, a study suggested that organisms, including humans, might have immunity to the bacterial agents used in the CRISPR technology.[34] More recently, studies have suggested that a form of genetic immune response to the technology might cause an increase in tumors[35] because the editing process can alter the action of a gene known to play a role in tumor prevention. The release of this study promptly led to a sell-off in companies that are further developing this technology.[36]

The safety of CRISPR continues to be debated[37] with some expressing that concerns over CRISPR's safety are exaggerated.[38] There are also ethical concerns over the use of gene editing in non-therapeutic applications.[39] For example, the ability to preselect favorable physical, behavioral and aesthetic qualities in a human presents both ethical and social challenges. For example, individuals who have undergone such gene therapy may eventually receive preferential treatment given their superior genetic traits.[40]

Additionally, legal considerations have been raised over the possibility that human/animal chimeras[41] might be used for the purpose of growing and harvesting human organs; this is generating debate as to the legal and ethical rights of such organisms.[42]

Advancements beyond CRISPR

Meanwhile, researchers have begun to develop additional gene editing technologies. These are complementary to CRISPR, such as TALEN,[43] and also take advantage of advancements in alternative gene editing technologies that existed prior to CRISPR, such as gene targeting in yeast cells and in mouse embryos.[44] [45]

Others have identified additional bacteria that modify gene sequences in a manner similar to that of Cas9.[46] Organizations have already begun exploring these bacteria in the potential treatment of disorders beyond that of Cas9. Researchers have identified two new groups of proteins, CasX and CasY, which might be effective in the treatment of disorders such as herpes and hepatitis B.[47] More recently, researchers used a similar group of proteins called adeno-associated virus serotype 9 (AAV9) to demonstrate a positive therapeutic effect in dogs with Duchenne muscular dystrophy (DMD), potentially leading to similar treatment of DMD in humans.[48]

There are even discussions about how artificial intelligence (AI) might be used to help solve some of the problems and unknowns that have arisen with the emergence of CRISPR/Cas9. For example, using machine learning to better understand the relationship between genes targeted for editing and the unintended consequences such editing might produce.[49]

Conclusion

When the term CRISPR/Cas9 was first published in 2002[50] it was poised to have a transformative effect on gene editing in many areas of biological research. It has been widely embraced and its use has spread quickly due to the advantages it offers—it is easy to use, offers quick results and it efficiently edits DNA sequences. As the technology has developed, a number of concerns were expressed which questioned the safety, ethics and efficacy of gene editing. While these difficulties were being worked out, researchers have explored and expanded the effectiveness and the use of previously existing gene editing tools. They have begun to demonstrate uses for CRISPR that go well beyond its use in performing gene editing.[51] It remains one of researchers' most useful tools in the field of genomics, and it has the potential to be a multifunctional instrument that can work in any of a number of potential applications associated with the science of gene editing.[52] With the range of preventive and therapeutic possibilities emerging, CRISPR technology remains a powerful toolset for addressing genetically-based illness and disabilities.

Contact Us

To learn more about how OneBeacon Technology Insurance can help you manage online and other technology risks, please contact Dan Bauman, VP of Risk Control for OneBeacon Technology Insurance at dbauman@onebeacontech.com or 262.966.2739.

References

[1] "Human Genome Project." Wikipedia. Accessed August 2018. http://en.wikipedia.org/wiki/Human_Genome_Project

[2] Ibid 1

[3] (May 11, 2016). “An Overview of the Human Genome Project.” National Institutes of Health. Accessed August 2018. http://www.genome.gov/12011238/an-overview-of-the-human-genome-project/

[4] Ibid 3

[5] Ibid 1

[6] Ibid 3

[7] “What are genome editing and CRISPR-Cas9?” National Institutes of Health. Accessed August 2018. http://ghr.nlm.nih.gov/primer/genomicresearch/genomeediting

[8] (November 17,2011). “Human Genome Project produces many benefits.” National Institutes of Health. Accessed October 2018. https://www.genome.gov/27549135/nov-2011-human-genome-project-produces-many-benefits/

[9] Tripp, Simon; Grueber, Martin. (May 2011). “Economic impact of the Human Genome Project.” Battelle Memorial Institute. Accessed October 2018. https://www.battelle.org/docs/default-source/misc/battelle-2011-misc-economic-impact-human-genome-project.pdf

[10] Ibid 8

[11] (August 3, 2017). "Genome Editing." National Institutes of Health. Accessed October 2018. https://www.genome.gov/27569225/what-are-the-ethical-concerns-about-genome-editing/

[12] Rodriguez, E. (March 24, 2016). "Ethical Issues in Genome Editing using CRISPR/Cas9 System." Journal of Clinical Research & Bioethics. Accessed October 2018. http://www.omicsonline.org/open-access/ethical-issues-in-genome-editing-using-crisprcas9-system-2155-9627-1000266.php?aid=70914

[13] Marchione, Marilynn. (November 26, 2018). “Chinese researcher claims first gene-edited babies.” AP News. Accessed November 2018. https://www.apnews.com/4997bb7aa36c45449b488e19ac83e86d

[14] Ibid 13

[15] Ibid 13

[16] Regalado, Antonio. (November 26, 2018). “The Chinese scientist who claims he made CRISPR babies is under investigation.” MIT Technology Review. Accessed November 2018. https://www.technologyreview.com/s/612466/the-chinese-scientist-who-claims-he-made-crispr-babies-has-been-suspended-without-pay/

[17] Ibid 16

[18] "Genome editing." Wikipedia. Accessed August 2018. http://en.wikipedia.org/wiki/Genome_editing

[19] (June 9, 2016). Genome Sequencing Informatics Tools (GS-IT), National Institutes of Health. Accessed August 2018. http://www.genome.gov/27546195/genome-sequencing-informatics-tools-gsit/

[20] "CRISPR: A game-changing genetic engineering technique." Harvard University, Graduate School of Arts and Scientists. Accessed August 2018. http://sitn.hms.harvard.edu/flash/2014/crispr-a-game-changing-genetic-engineering-technique/

[21] Phelan, Meagan. (December 17, 2015). "Science Selects CRISPR Genome-Editing Tool as 2015 Breakthrough of the Year." American Advancement of Science. Accessed August 2018. http://www.aaas.org/news/science-selects-crispr-genome-editing-tool-2015-breakthrough-year

[22] "CRISPR." Wikipedia. Accessed August 2018. http://en.wikipedia.org/wiki/CRISPR

[23] "Prokaryotes." Wikipedia. Accessed August 2018. http://en.wikipedia.org/wiki/Prokaryote[24] “Cas9.” Wikipedia. Accessed August 2018. http://en.wikipedia.org/wiki/Cas9

[25] "CRISPR: A game-changing genetic engineering technique," embedded illustration. Harvard University, Graduate School of Arts and Scientists. Accessed August 2018. https://i1.wp.com/sitn.hms.harvard.edu/wp-content/uploads/2014/07/Pak-Fig-1.jpg

[26] "Questions and Answers about CRISPR." Broad Institute. Accessed August 2018. http://www.broadinstitute.org/what-broad/areas-focus/project-spotlight/questions-and-answers-about-crispr

[27] Ledford, Heidi. (March 7, 2016). "CRISPR: gene editing is just the beginning." Nature. Accessed August 2018. https://www.nature.com/news/crispr-gene-editing-is-just-the-beginning-1.19510

[28] Lakusta, Gabrielle. (March 22, 2018). "4 Gene Therapy Stocks to Watch." Investing News Network. Accessed August 2018. http://investingnews.com/daily/life-science-investing/genetics-investing/4-gene-therapy-stocks-to-watch/

[29] Gatlin, Allison. (February 2, 2018). "Can CRISPR And These 3 Small Biotechs Cure 10,000 Diseases?" Investor's Business Daily. Accessed August 2018. http://www.investors.com/news/technology/crispr-gene-editing-biotech-companies/

[30] Kaiser, Jocelyn. (May 3, 2016). "The gene editor CRISPR won't fully fix sick people anytime soon. Here's why." Science Magazine. Accessed August 2018. http://www.sciencemag.org/news/2016/05/gene-editor-crispr-won-t-fully-fix-sick-people-anytime-soon-here-s-why

[31] Ibid 12

[32] (May 29, 2017). "CRISPR gene editing can cause hundreds of unintended mutations." ScienceX Network. Accessed August 2018. http://phys.org/news/2017-05-crispr-gene-hundreds-unintended-mutations.html

[33] Ibid 12

[34] Zhang, Sarah. (January 9, 2018). "You May Already Be Immune to CRISPR." The Atlantic. Accessed August 2018. http://www.theatlantic.com/science/archive/2018/01/crispr-humans-immune-system/549974/

[35] Houser, Kristin. (June 12, 2018). "There Could Be a Dangerous Problem With Using CRISPR on Humans, New Research Shows." Science Alert. Accessed August 2018. http://www.sciencealert.com/new-studies-show-there-could-be-a-deadly-problem-with-using-crispr-on-humans

[36] Kilgore, Tomi. (June 12, 2018). "CRISPR-related stocks sink after report that gene-editing technology might cause cancer." MarketWatch, Inc. Accessed August 2018. http://www.marketwatch.com/story/crispr-related-stocks-sink-after-report-that-gene-editing-technology-might-cause-cancer-2018-06-11

[37] (July 19, 2018). "The safety of CRISPR-Cas9 gene editing is being debated." The Economist. Accessed August 2018. http://www.economist.com/science-and-technology/2018/07/19/the-safety-of-crispr-cas9-gene-editing-is-being-debated

[38] Speights, Keith. (April 3, 2018). "Oops! CRISPR Concerns Turn Out to be a Big Nothingburger." The Motley Fool. Accessed August 2018.http://www.fool.com/investing/2018/04/03/oops-crispr-concerns-turn-out-to-be-a-big-nothingb.aspx

[39] Ibid 12

[40] Ibid 12

[41] "Chimera." Merriam-Webster. Accessed October 2018. https://www.merriam-webster.com/dictionary/chimera

[42] Ibid 12

[43] Stanganelli, Joe. (February 22, 2017). "Beyond CRISPR Cuts: Five Complements To Cas9." Bio-IT World.Accessed August 2018. http://www.bio-itworld.com/2017/2/22/beyond-crispr-cuts-five-complements-to-cas9.aspx

[44] Ibid 43

[45] Ledford, Heidi. (August 8, 2016). "Beyond CRISPR: A guide to the many other ways to edit a genome." Nature. Accessed August 2018. http://www.nature.com/news/beyond-crispr-a-guide-to-the-many-other-ways-to-edit-a-genome-1.20388

[46] Leitch, Carmen. (February 14, 2018). "Beyond CRISPR: Finding More Bacterial Immune Systems." LabRoots, Inc. Accessed August 2018. https://www.labroots.com/trending/microbiology/8064/beyond-crispr-finding-bacterial-immune-systems

[47] Taylor, Nick Paul. (November 13, 2017). "Moving beyond Cas9, Excision licenses CRISPR gene editors." FierceBiotech/Questex, LLC. Accessed August 2018. http://www.fiercebiotech.com/biotech/moving-beyond-cas9-excision-licenses-crispr-gene-editors

[48] (September 12, 2018). "Dogs with muscular dystrophy receive CRISPR treatment: What does this mean for humans?" Harvard University. Accessed October 2018. http://sitn.hms.harvard.edu/flash/2018/dogs-muscular-dystrophy-receive-crispr-treatment-mean-humans/

[49] Saracco, Roberto. (January 17, 2018). "Beyond CRISPR, Leveraging on Artificial Intelligence." The Institute of Electrical and Electronics Engineers (IEEE). Accessed August 2018. http://sites.ieee.org/futuredirections/2018/01/17/beyond-crispr-leveraging-on-artificial-intelligence/

[50] "CRISPR-Cas9: Timeline of key events." What is biotechnology? Accessed October 2018. http://www.whatisbiotechnology.org/index.php/timeline/science/CRISPR-Cas9

[51] Brown, Kristen V. (February 16, 2018). "CRISPR Isn't Just for Gene Editing Anymore." Gizmodo. Accessed August 2018. http://gizmodo.com/crispr-isnt-just-for-gene-editing-anymore-1823074499

[52] Moulten, Megan. (December 26, 2017). “CRISPR isn’t enough anymore. Get ready for Gene Editing 2.0.” Wired. Accessed October 2018. https://www.wired.com/story/whats-next-for-crispr/