STAGE 2 BIOLOGY

CRISPR

SCIENCE AS A HUMAN ENDEAVOUR INVESTIGATION

Kale Emmenopee

Kale has received an 'A' standard in each of the performance criteria for this task. Nice work Kale.

INTRODUCTION

CRISPR (Clustered Regularly Interspaced Palindromic Repeats) is a system of specialized molecules, including a Cas (CRISPR Associated) protein, capable of editing the genome of any organism. The system was first discovered in 1993 (Broad Institute, 2013) as a defense mechanism against repeated virus attacks in certain bacteria (Broad Institute, 2015). However, recent research has seen the modification of CRISPR for use as a human genome editing tool, thus causing complicated **ethical debates**. This investigation will focus on the CRISPR system, its development and potential applications as well as showing how this technology, and the accompanied debates, illustrate **the use of scientific knowledge can be influenced by social and ethical considerations.**

EXPLANATION OF SCIENTIFIC CONCEPTS

CRSIPR is a length of DNA naturally occurring in the genome of bacteria in a region called the CRSIPR array. CRISPR DNA is composed of a short repeating sequence of DNA nucleotides. These sequences consist of spacers, short lengths of viral DNA or DNA synthesized by scientists, and palindromes (Mahmoudian-sani.M, et. al, 2017). The palindromic nature of CRISPR facilitates the folding of the DNA into a hairpin structure, as the end of the strands are complementary. This process is shown in figure 1.

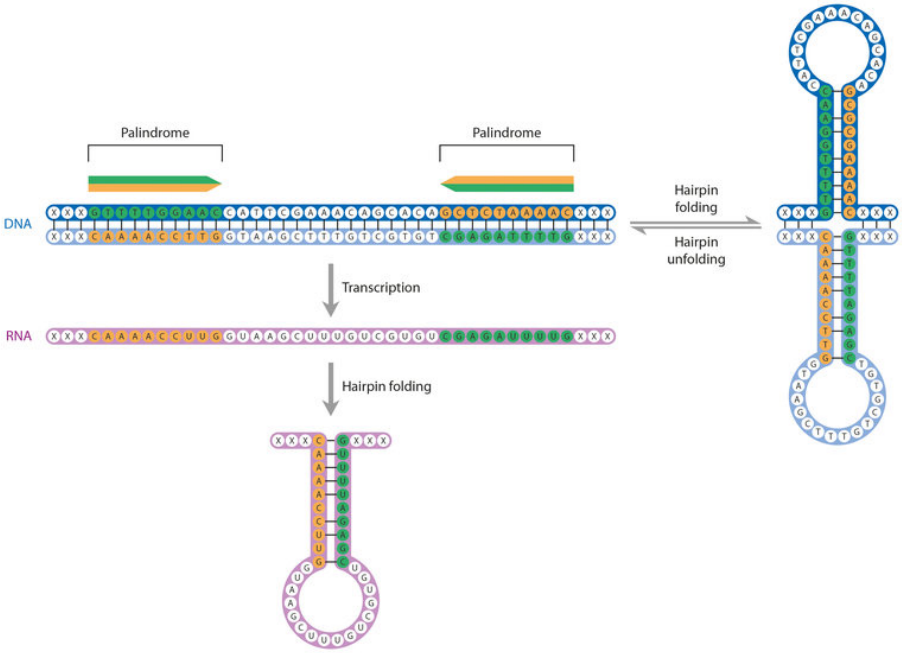

Figure 1: The Hairpin Folding of CRISPR (Max-Planck-Gesellschaft, 2018)

The CRISPR Array is transcribed to form an RNA strand (Mahmoudian-sani.M, et. al, 2017), this is also palindromic and will hence form a hairpin structure. (Rodriguez, 2016) (figure 1). The RNA strand is known as guideRNA (gRNA) as it is synthesized to have a complementary base sequence to the target DNA sequence in the genome. The gRNA strand may then be paired with a Cas protein, such as Cas9 (Baliou. S, et. al, 2018), to form a CRISPR-Cas complex which is able to modify the genome of an organism.

During the process of gene editing, the gRNA molecule guides the CRISPR-Cas complex to a desired site within the genome (Mahmoudian-sani.M, et. al, 2017) and bonds with the target DNA sequence through complementary base pairing. The Cas protein cuts the sugar-phosphate backbone of the DNA (Heidi Ledford, 2016) at specific locations. This is shown below in figure 2. Scientists may alter the nucleotide base sequence of the gRNA to allow any gene within the genome of an organism to be targeted (Heidenreich. H, Zhang. F, 2016).

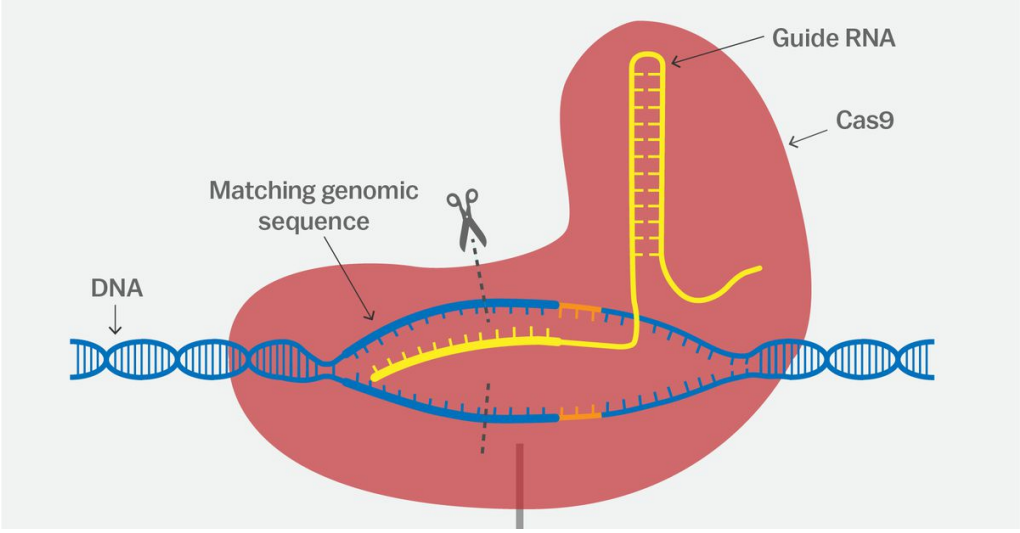

Figure 2:CRISPR-Cas9 Gene Editing Process (Plumer. B, et. al, 2018)

Once cut, the genome is repaired by inserting the desired gene or modifications. This repair process is primarily conducted through Homology Directed Repair (HDR) (Mahmoudian-sani. M, et. al, 2017). The HDR repair mechanism involves inserting a template DNA molecule, with sticky ends, for the desired gene. When the genome is being repaired, the DNA template strand will be copied resulting in the insertion of a desired gene (Baliou. S, et. al, 2018)

CONNECTION TO SHE

Since its beginning in the 1970s (Carroll. D, 2017), gene editing technology has been progressively developed, with the rate of development drastically increasing since the discovery of CRISPR. This has renewed intense **ethical debates** concerning gene editing and the **use of CRISPR** (National Human Genome Research Institute, 2017), particularly for human genome editing.

The primary **ethical debate** concerning the **use of CRISPR** surrounds its use for human germ-line editing (Shinwari. Z.K, Tanveer. F, Khalil. A.T, 2018). Germ-line editing involves making heritable edits to the genome of a human (Centre for Genetics and Society, 2015). This has generated intense **ethical debates** between members of **society**, such as researchers, scientists and the general public, as informed consent cannot be gained from an embryo concerning the editing of their genome, a major issue as it will impact their life and future generations. The **ethical debate concerning the acceptance and use of CRISPR** is furthered by the view that parents or guardians of children will already make complicated decisions with lifelong repercussions before their child is born. This debate is seen as Feng Zhang, a leader in the development of CRISPR, has been granted permission to use CRISPR on human embryos for research (Aparna Vidyasagar, 2018). However, other researchers such as Mike

Otieno, from Hekima University College, oppose his actions due to ethical issues with germ line editing (Otieno. M.O, 2015). Additionally, certain religious groups also oppose the editing of human embryos (National Human Genome Research Institute, 2017). This ethical debate is persisting and has clearly delayed the use of CRISPR within a clinical setting (Shinwari. Z.K, Tanveer. F, Khalil. A.T, 2018), thereby demonstrating that the use of scientific knowledge is influenced by ethical considerations.

Another ethical debate concerning CRISPR that demonstrates the use of scientific knowledge can be influenced by ethical considerations surrounds the possibility of off-target effects and mosaicism. Off-target effects occur when edits to the genome occur in undesired locations. This stems from having similar DNA nucleotide sequences in multiple places within the genome and may cause undesired consequences. Mosaicism occurs when some cells carry the desired edit, but others do not and also causes undesired consequences (Rodriguez. E, 2016). At CRISPR's current stage of development, both off-target effects and mosaicism occur too often for the system to be considered appropriate for clinical use and ethical debate surrounds whether, even when properly developed, the risk of both off-target effects and mosaicism will be too great to guarantee the safety of all patients (The Royal Society, 2018). This ethical debate is seen in the discussion between Hong Ma, a scientist at the Oregon Health and Science University, and other scientists concerning the progression of CRISPR to the clinical trials stage. Hong Ma is confident that testing's have proven CRISPR safe enough to be progressed, however, others, such as Hannah Brown, a reproductive epigenetic researcher at Adelaide University, and Dr. Sarah Chan, from the University of Edinburgh, disagree (Brown. H, 2017; The Royal Society, 2018). Therefore, this ethical debate has delayed the application of CRISPR as bodies such as National Human Genome Research Institute (NHGRI) release policies tending to the more conservative side, delaying the progression of CRISPR to clinical trials. Thereby clearly demonstrating the use of scientific knowledge, such as CRISPR, can be influenced by ethical debate, such as that concerning patient safety.

The use of CRISPR is also influenced by social considerations. This is evident as both the informed general public and various researchers or scientists, such as Dr. Shinwari from the Department of Biotechnology at Quaid-i-Azam University, show concern over the impact the CRISPR may have on the structure of society (Shinwari. Z.K, Tanveer. F, Khalil. A.T, 2018). The CRISPR gene-editing tool has the capacity to create 'designer babies', babies in which desired traits have been selected (i.e. high intelligence). This may cause a level of injustice and inequity within society (National Human Genome Research Institute, 2017) due to discrimination between the genetically enhanced ('designer babies') and non-genetically enhanced. This may be seen in health care distribution, insurance policies, sporting leagues and many other situations, thereby creating potentially adverse impacts on how society operates. This debate was prominent during a recent conference concerning the ethics of CRISPR. Professor Lovell-Badge suggested that the general public were correct in their distress concerning the effect CRISPR may have on society, however, Baroness Helena Kennedy QC sparked debate by saying, "public discourse needs to move past slogans such as 'designer babies'…" in order to advance CRISPR (The Royal Society, 2018). The concerns of Professor Lovell-Badge have been adopted by the NHGRI, who have responded by releasing guidelines suggesting that the use of CRISPR for genetic enhancing be strictly regulated (National Human Genome Research Institute, 2017). Therefore, it is evident to see that CRISPR demonstrates the use of scientific knowledge can be influenced by social considerations.

APPLICATION & IMPACTS

The excitement behind CRISPR stems its inexpensive nature and easy use compared to other gene-editing technologies (McKinsey & Company, 2017), such as TALENS (Aparna Vidyasagar, 2018), but also the vast range of applications and huge impact that CRISPR may have (Das. R, 2017).

Perhaps the biggest impact CRISPR may have on society is the possibility of 'designer babies'. 'Designer babies' will massively impact society as the genetically enhanced may see themselves as superior. As a greater proportion of the population becomes genetically enhanced, society may begin to more openly discriminant between the genetically enhanced and the non-genetically enhanced (McKinsey & Company, 2017). Thus, demonstrating the drastic and adverse impact that CRISPR may have on **societal structures.**

CRISPR also has a wide range of applications that will be entirely beneficial to society. This includes the potential to cure genetic diseases such as Alzheimer's disease and HIV (Crawford. M, 2017). In the case of diseases such as Alzheimer's, CRISPR can be used to identify sections of the genome which control cellular processes that lead to neurodegeneration (Baliou. S, et. al, 2018), thereby allowing scientists to alter the nucleotide sequence of the particular segment of the genome, hopefully leading to a cure (Crawford. M, 2017). HIV may be cured in a similar although, instead of editing the nucleotide base sequence of the genome, CRISPR will allow the removal of any viral DNA from an individual's genome (Mahmoudian-sani. M, et. al, 2017).

Another application of CRISPR is within the agricultural industry. In many countries, food shortages due to population growth is a pressing crisis. CRISPR provides and inexpensive and 'easy to use' solution for this by enhancing crop yield and crop hardiness (Das. R, 2017). CRISPR may be used to edit the genome of plants and crops in order to induce desired traits such as increased yield, quick growth and resistance. Therefore, increasing the efficiency of crop growth and harvesting.

CONCLUSION

CRISPR is a gene-editing tool with huge potential due to its inexpensive cost, ease of use and high efficiency. CRISPR may be used for curing a vast amount of genetic diseases seen within the human population as well as increasing crop yield to aid food shortages. However, CRISPR is also capable of facilitating the introduction of 'designer babies'. This has renewed intense **ethical debates**, with further **ethical debates and social considerations** surrounding the safety of patients and germ-line editing. These **ethical and social considerations** have delayed the application of CRISPR< thereby demonstrating that CRISPR shows **the use of scientific knowledge can be influenced by social and ethical considerations.**

WORD COUNT: 1515

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