Further Applications of Genetic Engineering

Collaborate With a partner, discuss the benefits and risks of transgenic mosquitoes for humans and ecosystems.

New technologies can have unforeseen impacts on society and the environment. The positive effects of controlling mosquito populations with transgenic mosquitoes are clear: reduced illness and death due to infections from mosquito-borne viruses. There are also negative effects to this solution, though, that may be hard to believe. Mosquitoes may be pests for humans, but they are a food source for other animals.

Impacts on Conservation

In the future, ecosystems may undergo rapid change due to climate change, habitat destruction, and human influence. Populations may be forced to adapt or move to new habitats to survive. This is a problem because natural selection, the mechanism by which populations adapt, is not a rapid process and works over many generations. Scientists are looking for ways to help threatened species.

FIGURE 15: The ‘i’iwi.

Hawaii had no mosquitoes until the early 1800s when a whaling vessel carrying water from Mexico brought them to the islands. Today, avian malaria, carried by these invasive mosquitoes, has decimated the native bird population. The ‘i’iwi, or Hawaiian honeycreeper, and other birds native to Hawaii are going extinct. Many scientists think the only way to save these birds is to wipe out the mosquito population. Scientists are considering releasing GM mosquitoes that will die prematurely, reducing the mosquito population and hopefully saving Hawaii’s native birds.

For species threatened by climate change or low genetic diversity, scientists are investigating a process known as facilitated adaptation. Facilitated adaptation involves humans guiding adaptations in threatened populations by changing the species’ genome. Advantageous genes can be added to a genome through hybridization, selective breeding, or genetic engineering using recombinant DNA technology. For example, scientists are considering inserting genes from species that can tolerate higher temperatures into different species suffering from global warming.

One drawback of facilitated adaptation is the possibility of unintended effects related to changing genomes that have evolved over millions of years. Scientists may be able to identify the main function of a gene, but they cannot determine all the ways a gene interacts with the rest of the genome. Loss of function, or an unintended new function, may occur by changing an organism’s genome. Facilitated adaptation could also lead to an unintended loss of genetic diversity. If the genetically engineered individuals are much more successful than normal individuals, that single gene could become widespread in the population.

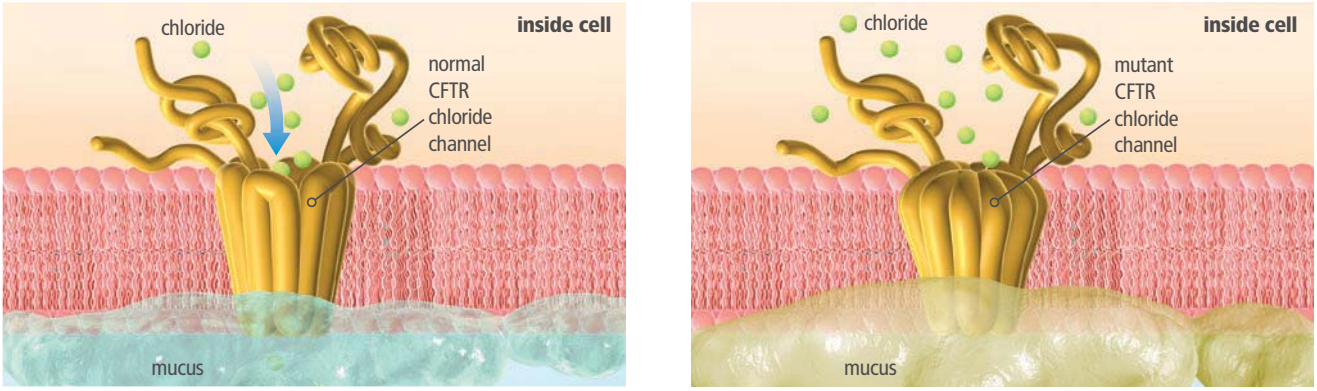
Engineering Define a problem facing conservation. Explain what role genetic engineering could play in solving that problem. Use evidence to support your claims.

Gene Therapy

Gene therapy uses genetic engineering to treat or prevent the genetic basis of disease. A common gene therapy technique uses a delivery mechanism, or vector, such as a bacterium or virus, to deliver a new gene to target cells. Once the gene enters the cells, the new DNA is transcribed and the new protein is expressed.

Not all diseases are good candidates for gene therapy. For example, a disease caused by the interaction of multiple genes is not a good candidate because the necessary modification of genes would be too complex. Also, if the genetic basis for a disease is not understood, it is not a good candidate. Scientists need to know which gene to modify to combat the disease. If the biology of the disorder is not understood, the disease is also not a good gene therapy candidate. Finally, if there is no way to get new genetic information to affected cells, the disease is not a good candidate for gene therapy.

FIGURE 16: Cystic fibrosis is caused by a mutated CFTR protein.



a Normal CFTR protein

b Mutated CFTR protein

Cystic fibrosis (CF) is an inherited disease that affects the respiratory and digestive systems. Airways and some organs are naturally lined and protected by a layer of mucus. Cystic fibrosis causes abnormal, sticky mucus secretions in these areas. Symptoms include coughing and wheezing, digestive problems, and increased probability of infections. The most common cause of death in untreated CF patients is a fatal lung infection.

The protein that regulates mucus secretion in the respiratory, reproductive, and digestive systems is encoded by the Cystic Fibrosis Transmembrane Conductance Regulator (*CFTR*) gene. A normal version of the *CFTR* gene produces a protein that acts as a channel to move chloride ions across the cell membrane in mucus-producing cells. This helps regulate the water content of surrounding tissues, leading to normal, moist mucus. A mutated gene leads to disruption of the chloride channels, lowering the water content of nearby cells. This causes the thick, sticky mucus characteristic of cystic fibrosis.

Cellular functions are highly related to the structure of DNA. In the case of cystic fibrosis, the change in the DNA sequence of the mutated *CFTR* gene results in a different amino acid sequence in the CFTR protein. Typically, a phenylalanine amino acid is missing from the protein sequence. When this protein is expressed, the abnormal structure leads to a loss of protein function.

As shown in Figure 16a, with normal CFTR function, chloride ions move across the cell membrane and congregate on the outside of the cell, making an ionic gradient. The hypertonic solution outside of the cell attracts more water and maintains mucus of a normal consistency. A healthy, watery mucus layer traps particulates and bacteria before they can harm the cell. The cilia of the cell are free to move and sweep away the foreign matter.

Gather Evidence Does cystic fibrosis meet the criteria to be considered for gene therapy? Use evidence to support your claims.

In a person affected by cystic fibrosis, the irregular protein produced by the mutated *CFTR* gene cannot transport chloride ions across the cell membrane, as shown in Figure 16b. This loss of protein function results in a higher concentration of chloride and sodium ions inside the cell and a lower concentration of these ions outside of the cell. The hypotonic solution causes water to move into the cell, drying out the mucus layer. The thick, sticky mucus prevents the cilia from moving and clearing debris. The increased presence of debris and pathogens causes increased infections in individuals with cystic fibrosis.

Engineering

Developing Approaches to Gene Therapy

The problems gene therapy attempts to solve are broad and span many kinds of diseases, from genetic immune disorders to cancers. Many different approaches are required to solve these problems. To alleviate respiratory symptoms of cystic fibrosis (CF), for example, scientists need to deliver a functioning copy of the *CFTR* gene to lung cells. However, it is hard to access and modify every lung cell. A solution to this problem is to deliver the gene therapy through an aerosol that patients inhale. Affected cells that receive a functioning copy of the gene will begin to show normal gene expression, which alleviates the symptoms of cystic fibrosis.

Analyze A loss-of-function mutation results in a mutated protein that does not function correctly. How could gene therapy treat this type of genetic disorder?

Gene therapy is not always this straightforward. For example, some mutations produce a dominant-negative protein. This type of mutated protein does not do its job correctly and also blocks normal proteins from functioning. Simply delivering a working copy of the gene to affected cells won't work because the dominant-negative protein would still block the function of normal proteins. A solution to this problem is to "silence," or turn off, the mutated gene so that no protein is produced. Huntington's disease produces a dominant-negative protein and is a promising candidate for gene-silencing therapies.

Gene therapy relies on many different biotechnologies. Without genetic testing, it would be harder to determine which patients would benefit from gene therapy. The genes required for insertion into affected cells are produced through PCR. Without the rapid amplification of DNA through PCR, gene therapies would take much longer to produce. CRISPR is a relatively new tool, but it is already affecting gene therapy by making it easier to cut and edit DNA segments of a mutated gene.

Explain Think back to the fluorescent zebrafish from the beginning of this lesson. Using this example, explain some implications of being able to edit genes. Where do you think science will go from here?