A CRISPR *Way to* Splice DNA

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Humans have been selectively breeding plants and animals since before the dawn of civilization, resulting in extensive changes from their natural state. While science has made selective breeding more efficient in modern times, actual genetic engineering was not possible until the discovery of DNA. Scientists began applying this knowledge in the 1970's through recombinant DNA technology. Genetically modified (GM) plants and bacteria created with recombinant DNA have been on the market for decades (although not without controversy); one example is genetically modified foods, often referred to as genetically modified organisms or GMOs. While the first GM animal, a mouse, was produced in 1973, techniques applicable to animals were crude, limited, difficult, and expensive to use. They remained so until 2012, in spite of significant refinements.

The year 2012 marked a revolutionary change with the discovery that a bacterium, streptococcus pyogenes, has the natural ability to change the genetic makeup of viruses as an immune system mechanism. This mechanism was quickly isolated and used in genetic editing, with a successful demonstration of its accuracy in humans in 2013. It is known as CRISPR (clustered regularly interspaced short palindromic repeat). CRISPR makes it possible to target and excise any gene as desired, insert a new gene in an organism, or even to edit out a single base pair within a gene, thereby changing its effects.

Thus, CRISPR allows easy, extensive, and accurate editing of the genome, marking a quantum leap in the ease and affordability of the development of practical genetic engineering of animals and humans, while making the already established genetic engineering processes in plants and bacteria much more versatile and efficient. For example, it used to take approximately one million tries to get a mouse cell to accurately include a desired new characteristic; CRISPR can attain the same result in about 10 tries. CRISPR both makes established genetic engineering processes orders of magnitude more efficient and opens up many new areas that were not feasible with prior techniques. Due to its accuracy, CRISPR enables the prospect of routine genetic engineering of animals other than mice; before CRISPR, genetic engineering of other animals was so difficult that mice were virtually the only animals used in genetic modeling of human disease.

In every area of agriculture, livestock farming, and biotech applications, CRISPR speeds progress and reduces development costs, and thereby consumer prices. Scientists are developing new varieties of crops, incorporating added nutritional value and desirable characteristics such as pest resistance or ability to prosper under a wider range of conditions. All these developments have been ongoing, but they will be quicker and cheaper with CRISPR.

Genetic engineering of animals has both livestock industry and medical implications. It will greatly speed up the development of breeds of animals that have desirable characteristics such as leaner meat or greater milk production and, because of its accuracy in targeting genetic characteristics, it may avoid incorporating as many undesirable side-effects as standard selective breeding often does.

In drug development, CRISPR will enable the use of animals genetically engineered to develop various human genetically-related diseases that are much closer to the human genome than the mice currently used. This will lead to great improvement in the speed and accuracy of animal testing of experimental drugs and other therapies. Consequently, improved testing could result in quicker and better development of new drugs at lower costs, which could mitigate the current spiral of drug price increases.

Some scientists are hoping to use CRISPR to create gene-altered pests, such as mosquitoes, that no longer carry dangerous diseases, including malaria and dengue fever. The designer genes inserted into such mosquitoes could also be tweaked to have a natural characteristic known as "gene drive" which gives them a selective advantage; thus, seeding a relatively small percentage of the insect population could spread the characteristic throughout the population. Theoretically the U.S. Department of Agriculture (USDA), would regulate such releases of selectively viable GM insects, and researchers and companies would not undertake such activities without prior permission. Conversely, regulation on the release of GMOs that are selectively disadvantaged would be less strict, because these insects will presumably die out. In the United States, regulation of GMOs is relatively light and focuses on the safety of their uses, not on the

process of genetic modification. The U.S. Food and Drug Administration (FDA) and the USDA regulate GM crops. The FDA considers them "generally recognized as safe" and permits their sale without specific regulatory approval, unless the inserted genes result in the expression of foreign proteins that are different from the natural plant, in which case the FDA requires pre-approval under its regulations for food additives. GM crops that incorporate pesticide-producing genes are regulated by the U.S. Environmental Protection Agency, as are those that incorporate pesticide-resistant genes.

GM animals are regulated by the FDA on the theory that the recombinant DNA used to make the genetic modifications is a drug under applicable law. The production of animals that are not intended for introduction into the food chain is generally permitted without detailed pre-approval procedures, while those expected to get into the food chain will be regulated similarly to other new food additives or components.

The most controversial application of genetic engineering is its direct application to humans. It is current international consensus that human germ cell modification (where the change is transmitted to offspring) is prohibited. Any such application would clearly require prior medical licensing. It is likely that what are known as "negative eugenic" interventions to eliminate debilitating or developmental genetic defects at the germ cell level, such as Down syndrome, Huntington's disease, or cystic fibrosis, most likely in utero, may be more favorably considered in the future because of their ability to prevent these genetically inherited diseases. However, the concern about "playing God" with human heredity, even in such attractive applications, is likely to result in careful and prolonged review before any germ cell treatments are approved.

Gene therapy on patients to make a non-heritable correction of a congenital defect is far less controversial, but it is difficult to accomplish and has been of limited practicality, because it requires a change to be incorporated in millions of cells. Both because it operates so easily and because it can actually "repair broken genes," CRISPR increases the ability to target a specific gene in millions of cells and change enough of these cells to deliver meaningful therapeutic benefits without unacceptable side effects and with some prospect of developing effective treatment gene therapy for congenital diseases.

One biotech startup, Editas Medicine, received $120 million in August 2015 from a group of major investors led by Bill Gates; it plans to conduct a clinical trial in 2017 of CRISPR gene therapy on a variant of a rare congenital eye disease known as Leber congenital amaurosis. Other startups, such as Intellia Therapeutics and CRISPR Therapeutics, also plan to develop similar therapeutic applications for other congenital diseases. Like any other new medical technique, gene therapy is subject to extensive and detailed U.S. medical regulation before any therapeutic use is permitted. ◂