Gene Editing Enters the Food Supply**

Daniel F. Voytas, Ph.D., Professor, Genetics, Development and Cell Biology, and Director,
Center for Precision Plant Genomics, University of Minnesota, St. Paul, Minnesota
Chief Science Officer, Calyxt, Inc., Roseville, Minnesota

Summary: Plant agriculture is poised at a technological inflection point. Recent advances in gene editing make it possible to precisely alter DNA sequences in living cells, providing unprecedented control over a plant's genetic material. Crops derived through gene editing are already beginning to enter the food supply. Because gene editing technologies are advancing at such a rapid pace, traditional crops will soon serve as genetic chassis that are precisely engineered to produce an array of novel food products—fruit with enhanced nutritional value, flour with increased fiber, protein with a balanced amino acid composition, to name a few. Such crops will also be designed to withstand the many stresses created by a changing environment and to grow with fewer inputs, such as water and fertilizer. Appropriate regulatory structures need to be put in place to ensure that the food products developed through gene editing are safe for use as food and feed and for the environment. Public perception will also impact the extent to which gene editing enters the food supply and whether this powerful technology will contribute toward food security.

Current realities: Over the past 100 years, technological advances have resulted in remarkable increases in agricultural productivity. Such advances include the production of hybrid plants and the use of the genes of the Green Revolution (i.e., genes that alter plant stature and thereby increase productivity). More recently, transgenesis, or the introduction of foreign DNA into plant genomes, has been a focus of crop improvement efforts. In the U.S., more than 90% of cultivated soybeans and corn contain one or more transgenes that provide traits such as resistance to insects or herbicides.

Transgenesis, however, is limited since it is fundamentally a process of gene addition and does not harness a plant's native genetic repertoire to produce traits of value. Furthermore, public concerns over the cultivation of crops with foreign DNA, particularly those generated by the introduction of genes from distantly related organisms, have impeded their widespread use. The regulatory frameworks created to protect the environment and to address public safety concerns have added considerably to the cost and timelines for transgenic crop production. These costs have limited the use of transgenesis to a few high-profit crops (e.g., cotton, soybean, corn) and to traits that benefit the farmer (e.g., herbicide tolerance, pest resistance).

The advent of gene editing allows DNA in living cells to be precisely altered. Although gene editing can be used to add transgenes to specific locations in genomes, thereby offering an improvement over existing methods of transgenesis, modifying a plant's native genetic information offers many additional opportunities to produce traits of value. Traditionally, new traits are introduced into cultivated varieties through breeding regimes that take advantage of natural genetic variation. Alternatively, new genetic variation is produced through mutagenesis, which includes the use of chemical mutagens as well as ionizing radiation. With gene editing, it is possible to first determine the DNA sequence modifications that are desired in the cultivated variety and then introduce this genetic variation precisely and rapidly. The ability to control the type of genetic variation introduced into crop plants is a transformative advance in breeding technologies and is rapidly being adopted by the agricultural biotechnology industry.

This year, the first gene-edited crop entered the food supply. Calyxt, Inc., a company that uses gene editing to produce healthier food ingredients, developed a soybean variety that produces oil with an improved fatty acid profile. Specifically, oil from this soybean variety is higher in monounsaturated fats (i.e., oleic acid) and lower in polyunsaturated fats when compared to conventional soybean oil. The editing approach involved inactivating two genes in the fatty acid biosynthetic pathway by removing a few nucleotides in the genes' coding sequences. These genes normally produce polyunsaturated fats, and consequently, oil from this soybean variety is higher in monounsaturated fats and therefore healthier for consumers (monounsaturated fats have been linked to reducing low-density lipoproteins, cholesterol, and triglycerides and raising HDL cholesterol). Further, the high levels of monounsaturated fats increase the oil's shelf-life and fry-life. Because the oil does not need to be hydrogenated to lower the polyunsaturated fat content, the oil also has no trans fatty acids (zero grams trans fat per serving).

The USDA concluded that the soybean variety is not a regulated article under the Plant Protection Act. The soybean variety was also evaluated by the Food and Drug Administration (FDA) through the voluntary consultation process, and it meets all applicable FDA requirements. In February 2019, Calyxt sold its first improved soybean oil to the foodservice industry for frying and salad dressing as well as sauce applications. This sale marks the first time a gene-edited ingredient has entered the food supply.

Scientifically credible approaches and challenges: Gene inactivation, as carried out by Calyxt to produce its high oleic soybean variety, is one of the easiest types of gene edits to execute. In this particular case, loss of gene function disrupted a metabolic pathway (i.e., fatty acid biosynthesis) and changed the relative levels of fatty acids produced in the soybean seed. Other editing approaches allow for a greater diversity of changes to the genetic code (e.g., specific nucleotide substitutions can be introduced that alter protein function or change levels of gene expression). This control over genetic circuitry makes it possible to dial up or down the activity of certain genes and more precisely control metabolic pathways to produce specific types and quantities of carbohydrates, proteins, or fatty acids. In the technology's current form, typically one to a few genes are edited in a genome to produce one or a few traits at a time. Rapid advances in the technology, however, will soon make it possible to introduce hundreds to thousands of edits simultaneously, allowing a redesign of the genetic code on a much larger scale and the introduction of many traits simultaneously.

While the ability to produce designer organisms may seem revolutionary, gene editing is only an extension of what has occurred in plant genomes for centuries. For example, compare modern maize to its wild ancestor, teosinte. The latter is a tall, highly branched grass that produces a handful of seeds, in stark contrast to its modern descendent, which produces a single stalk with ears full of carbohydrate-rich grains. The genetic blueprint of modern maize began as teosinte and was edited by humans over centuries through selection. Every year, seed for the next crop was selected from the plants that produced the most grain. Underlying these subtle increases in productivity were DNA sequence changes that occurred naturally. Year after year, by selecting increasingly more productive plants, the teosinte genome was rewritten, resulting in a new species, *Zea mays*. In the past century, new tools have made it possible to induce genetic variation through mutagenesis and more recently, through transgenesis. The advent of gene editing makes it feasible to decide in advance the exact types of genetic changes that one wants to produce in a crop plant.

The advent of gene editing also requires a new lexicon to describe applications of biotechnology to food. What does the term "genetically modified organism (GMO)" mean? Many consider a GMO to be a plant that has foreign DNA added to its genome, typically DNA from a distantly related, non-sexually compatible species. But is not *Zea mays* a GMO when compared to its ancestor, teosinte? Are plants that have been mutagenized using chemicals or ionizing radiation not GMOs? Gene editing can already produce diverse DNA sequence alterations, from DNA deletions to insertions to base substitutions. Currently, an easy path is to place new plant varieties into one of two classes: GMO or non-GMO. This approach, however, is an unfair depiction of the matter since it does not provide the consumer with the desired clarity about how the food they purchase was developed. It also invokes a sense of fear that might harm the overall use of a truly transformative technology—a technology that could help produce healthier, more abundant food to meet the demands of a burgeoning global population and a rapidly changing climate.

Evidence-based options and real-world opportunities:

- Foster collaboration between the agriculture and food industries to demonstrate that biotechnology can benefit consumers and improve sustainability. Initially, biotech products were focused on benefiting the farmer and therefore the consumer found little value in traits such as herbicide tolerance or pest and pathogen resistance. The initial gene-edited products need to focus on traits of value to the consumer (e.g., healthier food with increased nutrients, fibers, proteins and reduced saturated fats or allergens). If consumers see a benefit, they are less likely to dismiss the underlying technology outright.
- The USDA, FDA, and EPA need to create and enforce a vocabulary that clearly defines how biotechnology is applied to food. While the public wants to know how their food is produced, the scientific complexity and nuances of how biotechnology is used in food makes it difficult to provide clear, understandable explanations for the consumer (i.e., terms such as GMO, organic, or bioengineered).
- Develop the evidence-based regulatory frameworks the USDA, FDA, and EPA need to evaluate the products developed using new technologies and that are less concerned with the technology itself (i.e., the process used in food production need not trigger regulation).
- Governmental regulatory agencies need to exercise their regulatory authority to avoid confusion concerning the role of non-governmental groups (e.g., the Non-GMO Project) that attempt to usurp the role and credibility of regulators.
- Harmonize international regulatory frameworks to avoid confusion in global agricultural markets, especially with respect to the distinctions between GMO and gene-edited foods and ingredients.

*** A position paper prepared for presentation at the conference on Innovative Foods and Ingredients convened by the Institute on Science for Global Policy (ISGP), with support from the U.S. Food and Drug Administration, on June 23-27, 2019, in Minneapolis, Minnesota, United States.*