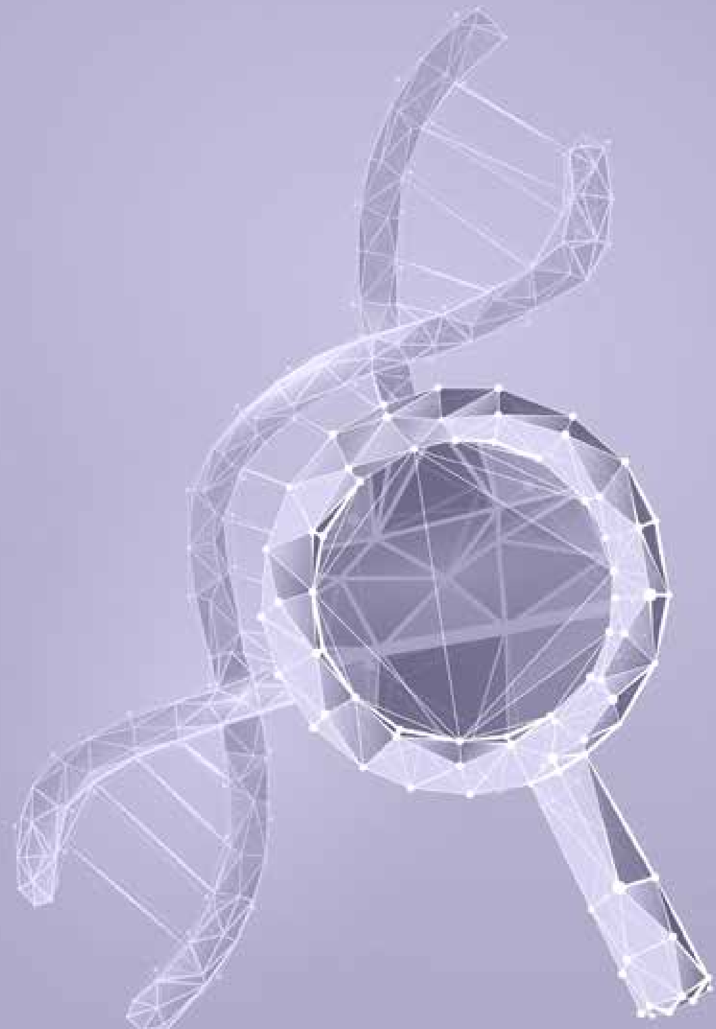


Points to Ponder on Gene Editing:

Can We Edit the Future of Food?

ISAAA Inc.

Can we achieve a food-secure future?

We pose this big question amidst a rapidly growing population, exponentially increasing demand for food, and a worsening climate crisis. The Food and Agriculture Organization of the United Nations (FAO) consistently calls for collective efforts to transform the agri-food system. Along with these transformations, all tools that can help achieve an increased food supply and improve nutrition must be harnessed.

With the contributions of gene editing to increasing yield, improving resistance to diseases and pest attacks, and biofortification of food crops, along with other enhancements, it is undeniable that this technology holds great promise in the future of food.

Like other emerging technologies, big questions are thrown towards gene editing, and these inquiries must be addressed to gain public understanding and confidence. Front-liners from the field were asked to tackle various facets of the technology and how each can contribute towards food security. The highlights of their answers are highlighted in this Biotech Communication Series to provide stakeholders with points to ponder and eventually have evidence-based decisions on the adoption of gene editing. The full discussions were published in ISAAA Brief 56 *Breaking Barriers with Breeding: A Primer on New Breeding Innovations for Food Security*.

Dr. Diana Horvath of the 2Blades Foundation tackles TALEN as one of the powerful molecular tools available to improve plant breeding. The contributions of gene editing to animal production are presented by Drs. Diane Wray-Cahen, and Justin Bredlau from the U.S. Department of Agriculture. Regulations must also be aligned with the research and development of gene-edited plant and animal products, and this is discussed by Martin Lema from the National University of Quilmes, Argentina. Current developments and future prospects in Asia and Africa were featured by Dr. Gabriel O. Romero of the Philippine Seed Industry Association and ISAAA AfriCenters' Dr. Margaret Karembu and Godfrey Ngure. Learnings in biotech communication are shared by ISAAA-BioTrust's Dr. Mahaletchumy Arujanan. Lastly, the big question on gene editing's impact on food security is answered by ISAAA Chair Dr. Paul Teng.

How will we produce enough food for the expected 2 billion additional people who will join us by 2050?

Diana Horvath, PhD
2Blades Foundation

Scientists are continuously developing better tools to improve plant breeding. New precision breeding innovations include both new digital tools—devices like sensors, detectors, and robotics—that have been combined with management technologies for precise and more efficient production system control, and genetic tools like new molecular breeding techniques for gene editing, such as CRISPR or TALENs.

TALENs were developed after researchers at Martin Luther University in Germany made a remarkable discovery in 2007 while studying bacterial spot disease, which attacks pepper and tomato. Plant pathogenic bacteria insert bacterial proteins—TALEs (Transcription Activator-Like Effectors)— into their plant hosts where they alter the expression of plant genes. By doing so, the bacteria essentially trick their plant host into making conditions more favorable for the bacteria to establish themselves and spread throughout the plant. In studying the TALEs, the scientists found that these bacterial proteins have a novel repeating structure that binds to specific DNA sequences with exquisite precision, and, most amazingly, the repeats use a simple cipher or "code" to interact with each DNA base. Not only could researchers identify the genes the bacteria were targeting for manipulation in pepper, rice, citrus, or other crops, but now scientists could create designer TALEs to target any DNA sequence of their choice. This new ease of design and ability to contact any DNA sequence was a huge step forward for precise manipulation of genomes.

Precision in gene editing is key to achieving desired crop characteristics. To mitigate biotic threats, TALENs can be used to edit genes to make plants less susceptible to pathogens, confer new specificity to existing resistance genes to match evolving pathogens, and to directly target and alter pathogen DNA. Additionally, researchers can use TALENs to introduce novel resistance genes and to create "multi-gene stacks" that combine multiple genes at a single location in the genome, ensuring that they don't get separated and lost during further breeding for other traits. This is a critical feature needed for creating long-lasting resistance to disease.

Crops and traits modified using TALENs

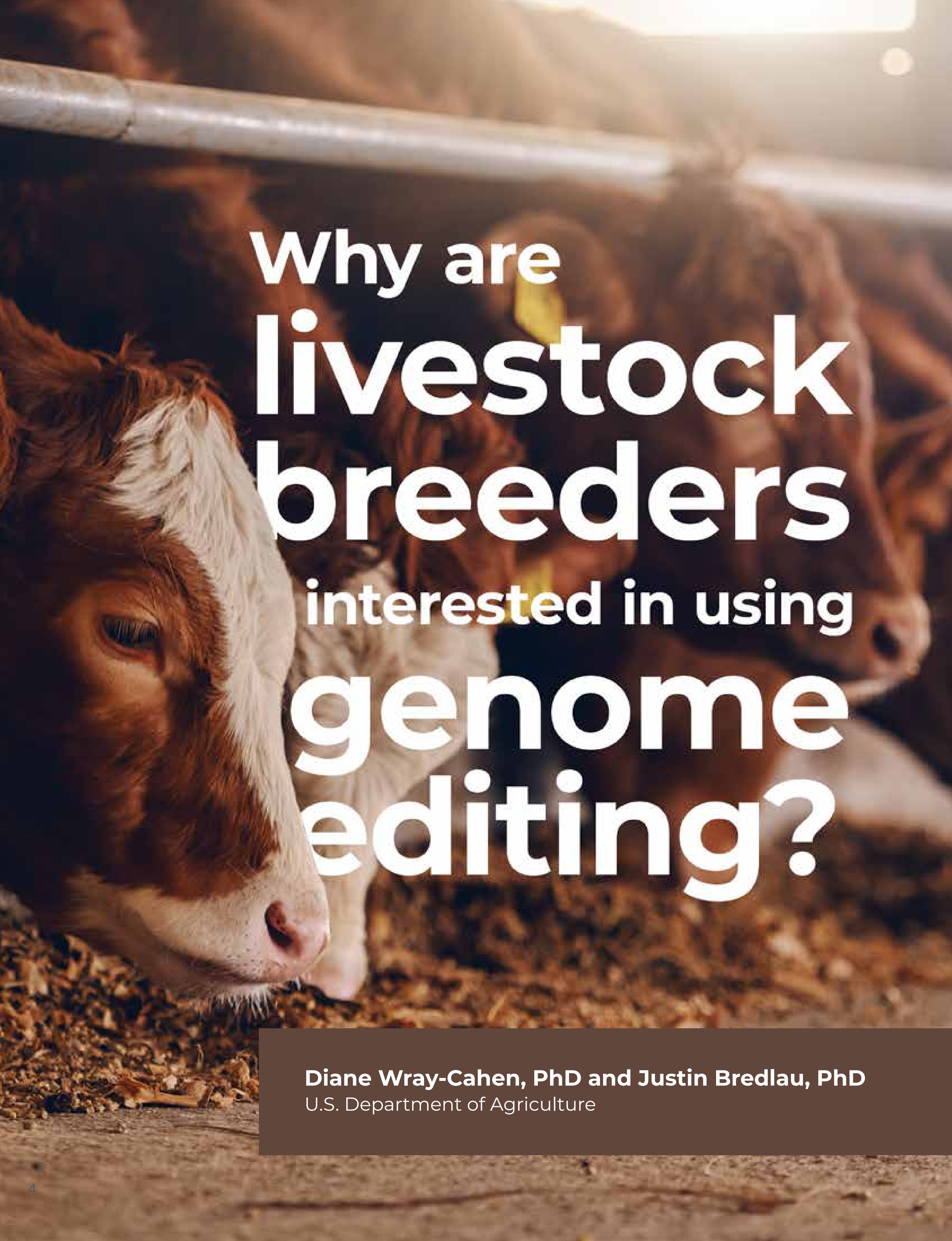
Oil quality; reduced polyunsaturated fats

Bacterial blight resistance, aroma

Reduced acrylamide, cholesterols

Visible gene marker

Powdery mildew resistance



Why are livestock breeders interested in using genome editing?

Diane Wray-Cahen, PhD and Justin Bredlau, PhD
U.S. Department of Agriculture

The discovery of genome editors, especially CRISPR, with its ease of use, has opened many new options for livestock breeding. The promises and opportunities for food and agricultural applications of genome editing are many. Traits have been created to control diseases and pests, improve animal welfare, create healthier or safer food, enhance animal production or yields, reduce the impact on the environment, boost animal's tolerance to changing climate conditions. Animal biotechnologies are also being used for biomedical uses targeting human health.

Protection from disease

The focus of much genome editing research in livestock has been on reducing the impact of disease and controlling its spread, including the control of insects that serve as disease vectors. Diseases result in financial losses to farmers, potential loss of genetic diversity, reduced food security, and also contribute to animal suffering. The goal is not only to reduce the impact and spread of disease, but also to reduce the need for antibiotics and insecticides.

Environmental resiliency and adapting to climate change

Researchers and livestock breeders are also working on introducing traits that reduce the environmental footprint of animal agriculture and on creating animals that are more resilient and tolerant to hotter temperatures.

Improving animal welfare

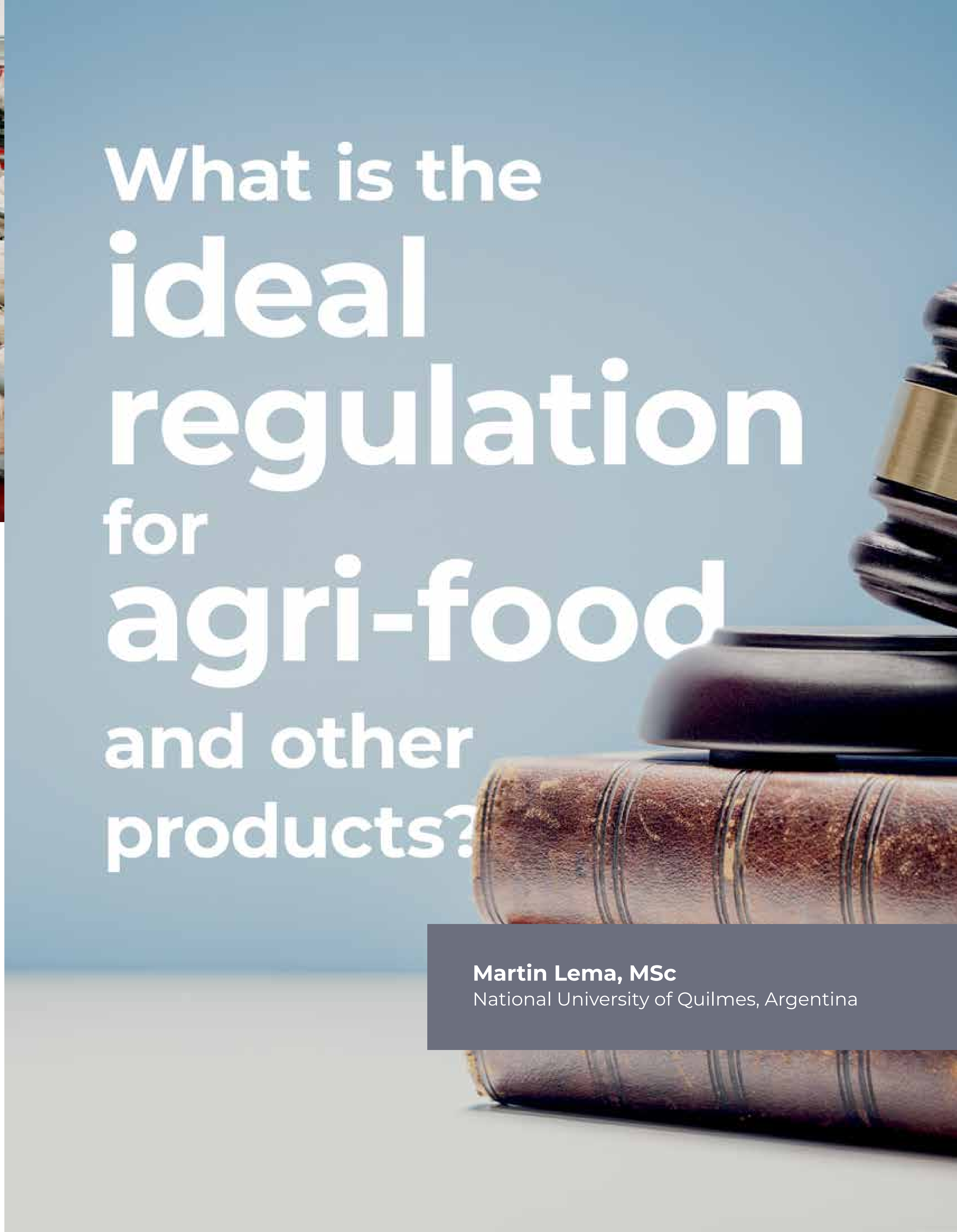
Genome editing can be used to introduce traits that are focused on addressing farm animal welfare issues. These include traits that eliminate the need for certain farm management practices such as castration and dehorning, as well as allowing sex selection in eggs prior to hatching in laying hen production.

New animal products for the consumer

Other traits are focused on creating healthier and safer food products for the consumer. Genome editing can be used to introduce genetic alterations to improve food quality, create foods with different nutrient profiles, or even reduce the allergenicity of food animal products.

Enhancing animal performance and agricultural productivity

Genome editing can also be used to improve animal productivity and traits such as meat production and milk yield or improved fiber production.



What is the ideal regulation for agri-food and other products?

Martin Lema, MSc
National University of Quilmes, Argentina

Should the products of gene editing be regulated as any other new mutant variety? Or should it also be under the regulatory framework for the so-called “modern biotechnology” enacted in the nineties?

The regulatory system for modern biotechnology is expensive and time-consuming. Besides, it is highly politicized and thus uncertain, especially for newcomers and radical innovations. The burden of these regulations has hindered the use of many potentially useful transgenic organisms developed by public researchers and SMEs, which are left virtually out of the game. An ideal safety regulation for agri-food and other products should meet the following criteria:

Fit for purpose

Sanitary regulations are enacted to decide if a product can be safely allowed to enter the market. It is not about what politicians or other influential people feel or prefer about novel products. Therefore, all relevant considerations to assess safety must be included, but none other aimed at influencing trade or consumer choice.

Science-based

In connection with the fit-for-purpose element, regulations should rely only on the most updated scientific and technical analytic tools. Besides, the utility of such tools should be judged against a specific endpoint: deciding if there is enough evidence to conclude that a product can be safely allowed to enter the market.

Risk-proportionate

The objective of sanitary regulation should be avoiding concrete risks. Therefore, the risk level of a product should determine the number of safety studies warranted. Potential risks, in turn, result from the product’s characteristics or traits. Therefore, the same burden of proof (and regulatory burden) or, in other terms, the same “level of protection” should be required for products having the same or similar traits.

Separate products from process

In connection with the risk-proportionate principle, better (and more knowledgeable) regulations are triggered by and based on the characteristics of the final product, instead of the process used to obtain it.

International harmonization

The triggers and requirements of regulations for a specific type of product should be equivalent across countries. Whenever gross and unjustified differences in the regulatory burden or the information required arise between governments, a science-based dialogue (and subsequent regulatory updates) should take place to try equalizing those differences.

Do new breeding innovations hold promise in South & Southeast Asia's food and feed needs?

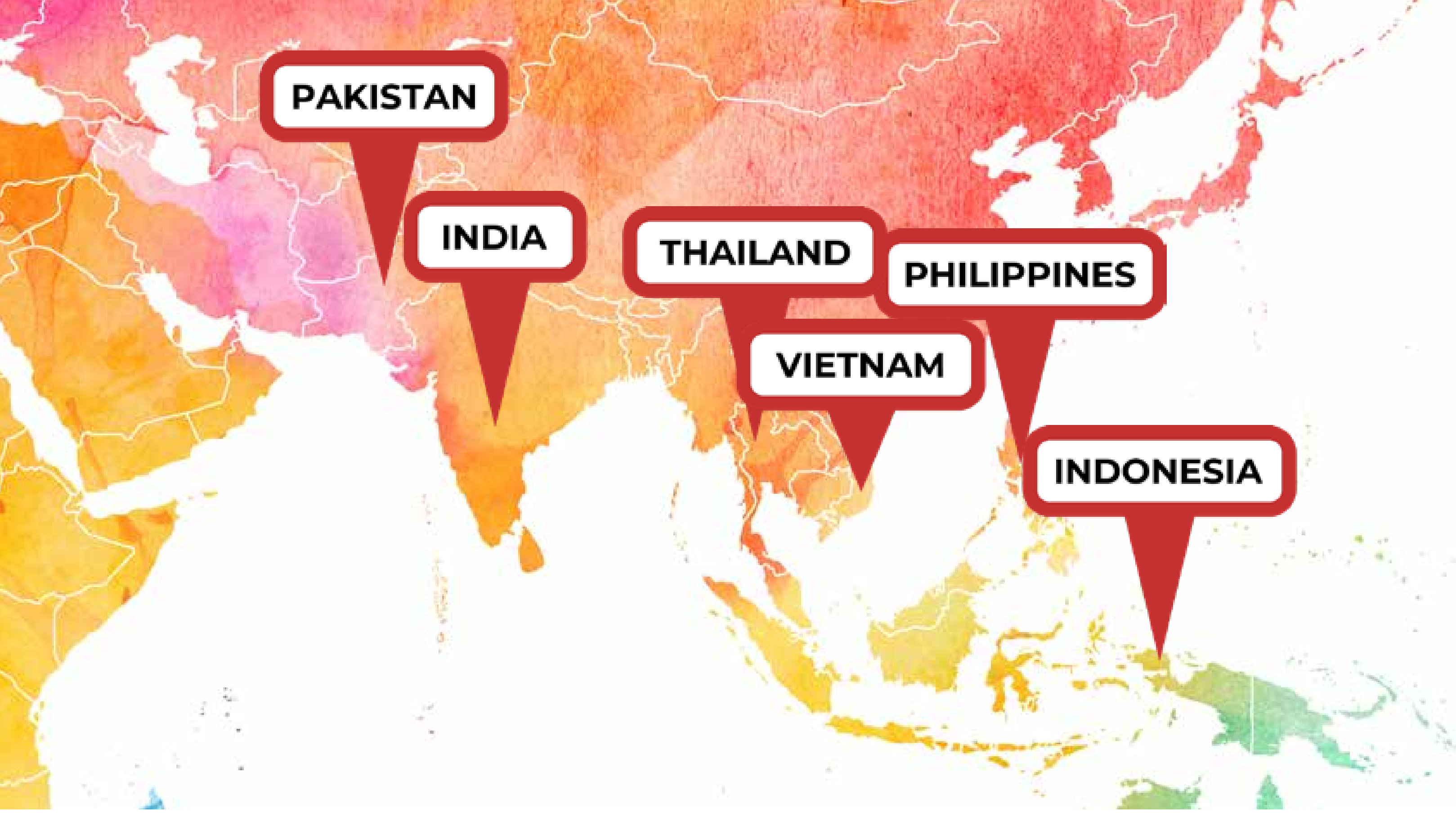
Gabriel O. Romero, PhD
Executive Director, Philippine Seed Industry Association

To be sure, most if not all countries in the region are GM crop users for direct use as food, feed, and processing. The main differentiation is on the issue of cultivating GM crops, with only a handful allowing it, such as India, Pakistan, Philippines, Vietnam, Myanmar, and Indonesia. The main issue facing these countries is how to regulate the genome-edited products as their current GM regulations seem to be too overbearing for these products that, except for the use of recombinant DNA, appear to be very much like conventional varieties. As such, the looming question is whether a biosafety assessment is necessary.

India has adopted biotechnology and is involved in R&D of emerging applications like genome editing. On May 20, 2022, the country released a suitable, science-based guideline for genome-edited products. According to the guidelines, genome-edited plants without foreign DNA are exempted from the rules applied to genetically modified plants.

Pakistan's regulatory environment around GM crops is unpredictable and still lacks genome editing policy. A local research agency, the National Institute for Biotechnology and Genetic Engineering (NIBGE), began applying the new editing tool to improve rice.

The Philippines has been known as a crop biotechnology leader in Asia in the cultivation and direct use of GM crops. Local research in genome editing is also gaining momentum. In May 2022, the country implemented the rules and procedures for the evaluation of products of plant breeding innovations (PBI), which states that PBI products without the presence of a novel combination of genetic material are considered as conventional products.



Vietnam's regulatory policy is still under development. The government and private sector have collaborated in exploring a suitable regulatory treatment for genome editing. The Agriculture Genetics Institute in Vietnam stresses the potential of genome editing to significantly improve the efficiency and timelines of breeding programs.

Indonesia is inclined to follow the global trend in genome editing. In the meantime, contained use and open release activities for genome editing are regulated by the existing regulatory framework. Gene edited crops will be regulated as LMOs/ GMOs if they fall under the definitions of the current policy. The policy is process-based with the use of modern biotechnology as the trigger.

Thailand needs to review and make appropriate adjustments to their biotechnology guidelines to keep pace with its neighbors and for its farmers and consumers to enjoy the benefits of plant breeding innovations.

Countries like most of the rest of the South and Southeast Asian region that never had experience with GMOs may find genome editing a direct extension of the current conventional breeding methods. If necessary, minimal adjustments can be made to their regulatory framework for conventional crops to accommodate genome editing.

What lies ahead for genome editing in Africa?

Margaret Karembu, PhD[1] and Godfrey Ngure[2]
[1]Director, ISAAA AfriCenter
[2]Program Officer, Open Forum on Agricultural Biotechnology in Africa - Kenya

African researchers are on the frontline of employing new breeding innovations to provide solutions to challenges in agricultural production. Research is primarily being focused on developing crops and animals resistant to economically important diseases and pests endemic in the continent. Here are some of the trailblazer genome editing projects in Africa:

Evaluation of Striga resistance in mutant sorghum

This project is evaluating LGS1 gene knock-out in conferring Striga resistance in sorghum. Preliminary results show that mutant alleles at the LGS1 locus drastically reduce Striga germination stimulant activity.

Project leader: Prof. Steven Runo, Kenyatta University, Kenya.

Controlling maize lethal necrosis in Africa

This project is working to introduce resistance against MLN disease directly into parent inbred lines of popular commercial maize varieties, which are currently susceptible to the disease, and reintroduce them into the farmers' fields in Kenya with possible scaling out to other countries in East Africa.

Project leader: Dr. James Karanja, Kenya Agricultural and Livestock Research Organization

CGIAR research program on roots, tubers and banana

The Consortium of International Agricultural Research Centers (CGIAR) research program on roots, tubers, and bananas is working to harness the untapped potential of crops in order to improve food security, nutrition, income, climate change resilience, and gender equity of smallholders. One aim of the project is to use genome editing to target disease susceptibility loci of popular roots, tubers, banana varieties, and promising breeding stocks.

Project leader: Dr. Leena Tripathi, International Institute of Tropical Agriculture

Transgenic goat for genetic control of animal diseases

Animal African Trypanosomiasis is one of the diseases that cause huge losses to livestock- dependent communities in sub-Saharan Africa. Scientists have discovered a gene (*Apolipoprotein L1* or *APOL1*) in primates that encodes proteins that cause lysis of trypanosomes in the body, making the primates resistant to trypanosomiasis. This project is investigating the feasibility of introducing a synthetic APOL1 gene into the genome of a group of goats and evaluating resistance to trypanosomiasis.

Project leader: Dr. Wilkister Nakami, International Livestock Research Institute

The Mzima cow project

This research is aimed at improving cattle production in Africa that are resistant to trypanosomes, the parasite responsible for African sleeping sickness in humans. The disease, prevalent in 36 countries of sub-Saharan Africa is caused by extracellular protozoan parasites – Trypanosoma that are transmitted between mammals by Tsetse flies (*Glossina* sp.).

Project by International Livestock Research Institute and Centre for Tropical Livestock Genetics and Health

Maize lines tolerant to drought, genotoxic, and oxidative stresses

This project focused on metabolic engineering of Poly-ADP-ribosylation pathway (a stress response pathway) to broaden stress tolerance in plants by maintaining energy homeostasis during stress conditions. Knock-down of the maize PARP gene expression using CRISPR-Cas9 genome editing was employed as a strategy for abiotic and genotoxic stress tolerance.

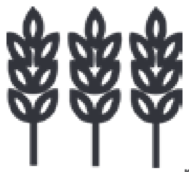
Project leader: Dr. Elizabeth Njuguna, Ghent University, Belgium

Improving oil qualities of Ethiopian mustard

This project is developing *Brassica carinata* genotypes with low erucic and glucosinolate for food and feed application using CRISPR-Cas9.

Project leader: Prof. Teklehaimanot Haileselassie Teklu, Addis Ababa University, Ethiopia.

Developing sal1-mutant drought-tolerant wheat using CRISPR-Cas genome editing



This project is employing CRISPR-Cas9 genome editing techniques to generate drought stress tolerant wheat by inactivating *sal1* gene, a negative regulator of drought tolerance.

Project leader: Prof. Naglaa Abdallah, Cairo University, Egypt

What are the bloopers in communicating biotechnology and how can we refrain from repeating them?

Mahaletchumy Arujanan, PhD
ISAAA-BioTrust, Global Coordinator
Executive Director, Malaysian Biotechnology Information Centre

Many grave and costly mistakes were made in communicating GM crops. These mistakes will serve as great lessons in developing effective communication strategies for gene-edited crops.

Blooper 1: Good science needs good communication and not propaganda rhetoric

It is time to move away from extreme and overpromising propaganda. Benefits of gene editing should be packaged in a way that does not oversell the technology, and risks are openly discussed to build trust.

Blooper 2: Lack of shared values

Start the conversation with shared values and not the benefits of the technology which is the point of contention. Sharing examples that the public could immediately relate and see the impact of GM technology might open room for deeper conversation.

Blooper 3: Communication is not just about giving information

Experts are used to giving information instead of asking questions. Asking questions makes the audience evaluate their claims and accusations against GM technology.

Blooper 4: Data that lacks soul

Experts are used to crunching and sharing data. Science lacks storytelling. What is needed are anecdotes and real-life stories relating the benefits of the technology and not just numbers.

Blooper 5: Too much farmer-centric messaging

Knowledge shared must be relevant to the audience. Reframing the messages and making it relevant to the general public would make gene-editing part of everyone's life,

How can new breeding innovations contribute to a food-secure future?

Paul Teng, PhD
Chair, ISAAA Board of Directors
Dean and Managing Director, National Institute of Education International (NIEI)

One answer to food security challenge lies in giving the farmer the best seeds derived from the latest science and technology because seeds are the foundation on which high crop yields can be expected and these seeds should preferably possess one or more traits.

Higher potential yield

All seed genotypes have a potential yield which is embedded in the seed's DNA and represents the highest possible yield if there were no constraints during the crop growth period. However, farmers don't usually get the potential yield in their fields because of the many stresses in the environment. Biotechnological approaches such as those represented by new breeding innovations offer opportunities to use existing crop genomes to change the potential yield to approximate theoretical yields. Higher farmer's yields would have a profound effect on raising crop production overall and contribute to food security.

Tolerance to environmental stresses

Environmental stresses and limitations of water and nutrients in the environment are responsible for causing yield gaps between potential and actual yields. The environmental stresses are often described as abiotic, and represent traits to tolerate flooding (submergence) and drought, both of which are known to be multigenically-determined and have been difficult to breed using traditional phenotypic breeding and screening. There is much hope that the use of NBIs such as gene editing alone or in combination with other techniques may quicken development of genotypes with strong tolerance to both.

Resistance to insect pests and diseases

Annually, insect pests and diseases are estimated to cause between 30-50% crop losses in many crops, contributing to yield gaps in farmers' fields. NBIs such as genome editing with induced gene silencing (GeiGSTM), a RNAi technique, offers opportunities to build on earlier successes at pest management with biotechnology plants, and enable scientists to tackle some of the most serious diseases and confer resistance to severe diseases such as Panama Wilt on bananas or blast on rice.

Modified nutritive value or flavor

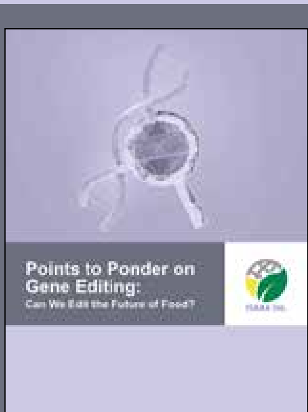
There are now efforts to use the NBI gene editing to change the nutritive value and flavor of food and beverages, for example, the nature of coffee beans to reduce caffeine content.

Delayed decay or senescence

Food loss and waste due to decay is responsible for as much as 30% of food not being consumed. There is anticipation that gene editing will enable the development of horticultural crops with fruits which have delayed ripening. Experimental protocols have been developed and in the near future the anticipation is that delayed ripening will become a common feature in fruits, together with delayed senescence in leafy vegetables. Both will help greatly reduce food waste.

To be better than current or older methods of plant breeding, NBIs need to demonstrate clearly that they can confer benefits to farmers and consumers by addressing the traits previously discussed. Although NBI products are only starting to emerge into the marketplace, early indications are positive.

Early indications from several countries (U.S.A., Australia, Japan, and others) are further, that the crop varieties and seeds produced using NBIs do not need to undergo the complicated regulatory approval processes such as with the older biotechnology crops, as long as no transgenes are incorporated. This would mean that yield gaps faced in many crops and losses caused by abiotic and biotic factors could be drastically reduced by the new NBI varieties, and all in a shorter time frame. This last aspect is critical to global efforts to ensure that food security is still possible by 2050.



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