Gene editing is one of a suite of modern biotechnologies designed to change the genomes of living organisms for health or economic benefits. For agricultural applications, gene editing can be used to more rapidly achieve the same goals as traditional crossbreeding.

Gene editing creates small, subtle and precise changes to the DNA of plants, animals and humans bringing about changes to a gene or group of genes. Gene editing could mimic changes that may occur in the natural processes of genetic variation.

For plants, gene editing is usually performed on cultured plant cells, which are then regenerated into whole plants. For animals, gene editing is usually performed on the single cell (zygote) that develops into an embryo, which grows into an animal. In humans, gene editing may be a form of cell therapy where particular cells, such as the T-cells of the immune system, are taken from a patient, edited and returned as treatment.

With mapping of the genomes of many organisms and access to versatile gene-editing tools, scientists can find a specific gene on a genome, cut the DNA within that gene at a precise point, and ‘edit’ the components of the DNA to achieve a desired change in the expression of the target gene.

Most gene-editing procedures can be distinguished from ‘traditional’ genetic engineering because they do not incorporate foreign DNA into the genome of the edited individual. Gene editing uses new types of protein and RNA that guide and cut the target gene in the cell. These tools are quickly turned over and removed from the edited cell, as would be similar material made by immune cells when combatting an invading virus.
Agricultural applications

 Currently, gene editing is used primarily in research and development. Potential application is greatest for the improvement of plant and animal genetics, as well as for the management and improvement of human health.

The global gene editing market is expected to almost double in coming years, growing to a value of US$3.5 billion in 2019, through increased R&D expenditure, advances in technology, and investment in biotechnology and pharmaceuticals.

Speeding up plant and animal breeding
Conventional crossbreeding methods may take 10 to 20 years to select, breed and develop a stable line of plants or animals with a targeted trait. Biotechnologies have significantly sped up the breeding process but several years of selection are still required to ensure, depending on the technology, that the new trait is stable within the genome. Gene editing allows scientists to change the basic building blocks of the individual, i.e. the DNA that makes up the genes, such that the edited cell will grow into a plant or animal with the desired characteristics.

A biotechnology company in the US has used gene editing to produce a canola line tolerant of sulphonylurea herbicides. It is also working on a range of new traits in rice, potatoes and flax and anticipates that new and stable lines of several plants can be created within five years.

Gene editing enables specific traits of plants and animals to be targeted and changed whereas, other biotechnologies and crossbreeding are less specific. Other technologies may achieve the desired improvement in one trait but other traits may change to the detriment of health or productivity.

A US gene technology company has developed a line of polled cattle using gene editing. While crossbreeding has achieved the same result in dairy breeds, production traits were negatively affected and it took 25 years of backcrossing and selection to recover the production traits. Gene editing achieved the desired result within one generation, while maintaining all of the other high value genetics in the line. The same company also provides gene-edited embryos to increase particular characteristics within herds, such as greater tolerance of warm conditions, congenital corrections, foot and mouth disease resistance and improved muscle growth.

Improving animals for the health industry
In addition to producing food and fibre, agricultural animals are used for medical products and research, such as raising egg-laying chickens to source the egg white used for the production of vaccines. Researchers from CSIRO and Deakin University are investigating gene editing as a means of removing the allergenic properties of four key proteins in egg whites. The proteins cause most of the allergies that prevent some people, especially children, from receiving vaccines that use eggs, like the annual influenza vaccination. Edited allergen-free eggs might one day be an option for people who currently have to avoid this food.

Gene editing enables changes to the genomes of laboratory animals, such as mice, so their body systems more closely resemble those of humans, enabling more reliable testing of new drugs and medical devices destined for human use. For animals that provide organs, tissues and cells for transplants, gene editing can help reduce the likelihood of adverse immune responses in humans. A group of US scientists has edited more than 60 genes in pig embryos to remove viruses embedded in the pig genome that might be associated with transplant rejection responses.

Targeting environmental and health pests
A new development that involves a component of gene editing is the so-called ‘gene drive’. It potentially controls pests by rapidly forcing genetic traits into wild populations through sexual reproduction. Driving traits such as susceptibility to a control agent or a single sex into a population could enable the control or local eradication of pests such as mosquitoes, ticks and cane toads, or a range of weeds. Though a powerful tool, there are regulatory and risk management issues to resolve. A national and international process has just begun for public engagement to ensure that there is ‘social licence to operate’.
Transforming agriculture

Gene editing provides scientists with a quick and accurate way to improve plants and animals to help agriculture remain sustainable and productive in a changing climate and under pressure from a growing global population.

The accessibility of gene editing took a significant leap in 2012, with the launch of the CRISPR/Cas9 tool, which is regarded by scientists as revolutionising not only gene editing but also biotechnology, including agricultural biotechnology. Gene-editing tools have been available for several decades and since 2000 and 2010 respectively, zinc finger nuclease (ZFN) and transcription activator-like effector nuclease (patented as TALEN®) have been successful but complex to use. The CRISPR/Cas9 tool makes gene editing easier, cheaper, more accurate and more flexible (as several genes can be edited at one time). It has resulted in rapid uptake of gene editing by researchers and biotech companies in recent years. The technique involves the clustered regularly interspaced short palindromic repeat (CRISPR) and the associated protein Cas9. The CRISPR matches a nucleotide sequence of the target DNA, enabling the Cas9 endonuclease to find, match and cut the DNA of a target gene in the plant or animal genome.

Gene editing, when combined with the knowledge gained from the mapping of genes for valuable traits on genomes, provides a precise method to develop lines of plants and animals that will thrive in new conditions, increase yields, produce higher quality food and provide products for new markets.

Targeted and responsive breeding programs
It has long been established that combinations of genes may affect a single trait, and that selective breeding for or against a gene can have unexpected results. The mapping of the genomes for many plants and animals has provided better understanding of the relationships between genes and characteristics within species and between species, including with wild relatives. Gene editing provides the opportunity to capitalise on this knowledge and target specific genes and their functions in order to develop lines and varieties that meet specific agronomic or husbandry requirements, product quality specifications or environmental challenges.

Since 2013, researchers at the University of Sydney have taken a step back from creating new lines to discovering and altering genes in canola to improve drought tolerance, photosynthetic capacity and seed oil content. Knowing which gene in the Arabodopsis plant imparts similar characteristics, has enabled the researchers to find the same gene in canola, and edit accordingly.

Faster commercialisation of R&D
Traditional breeding techniques in agriculture select and breed plants or animals with required characteristics across successive generations to create a new variety or line. Often the selection for or against a trait resulted in other characteristics changing inadvertently, such as the loss of productivity when selecting for dairy cows without horns.

Gene editing overcomes these drawbacks since it enables the required changes to be made to a single trait without changing any of the other high value genetics, such that the next generation retains the best genetics with the new trait added in.

Traditional genetic engineering, or modification (GM), introduced new genes to the DNA of plants or animals to impart new characteristics. The ability to transfer a gene from one species to another, or from one organism to another, was a significant development in biotechnology however its adoption was fraught with consumer aversion to plant or animal products that contained genetic material of another organism. Products of GM origin also require rigorous regulation, which can reduce the incentive for companies to commercialise such products.

By contrast, gene editing is a targeted technology that can produce improved crops and animals without the need to introduce foreign DNA into the genome of the individual, therefore overcoming the aversion of some groups in the community to products of genetically engineered plants and animals. As such, regulatory barriers to adoption of gene editing are likely to be much lower. However, gene editing may be used for more ‘traditional’ introduction of new genes but with much greater control and precision.
Checking your chickens before they hatch

Gene editing may provide the Australian egg industry with a solution for managing male chicks. A new marker gene will enable fertilised eggs to be sorted on the basis of sex, eliminating the need to incubate and then cull the males after they hatch.

The issue
Female chickens are the foundation of the Australian egg industry, while male chickens have no economic value and are culled soon after hatching. It is estimated that more than 12 million day-old male chicks are culled in Australia each year, either through maceration or gassing with CO₂. These practices are used across the entire egg industry, including organic, caged and free-range. While both practices are legal and endorsed by the RSPCA, there is mounting concern from consumers.

The egg industry uses a different breed of chicken to the meat industry. The egg-laying breed is smaller and slighter in frame than the meat breed, so male chicks that hatch in the egg industry cannot be transferred to the meat industry to be grown out for meat consumption.

In addition to concerns about animal ethics, the egg industry also seeks to minimise the number of male chicks in order to use resources more efficiently, by reducing the costs of incubation, culling and disposal.

The Australian egg industry has been investing in new technologies for more than five years to address the issue of male chick culling.

The technology
In association with the Poultry CRC, researchers Dr Tim Doran and Dr Mark Tizard from the CSIRO Animal Health Laboratory in Victoria have discovered a way to identify male chicks before they hatch.

The researchers are using the new CRISPR/Cas9 gene-editing tool to introduce a biological marker to the male chicks, so that males and females can be determined and sorted before they hatch.

Dr Tizard explained that with recent advancements in gene editing, it is now possible for scientists to specifically place a biological marker on the sex-determining chromosome of the chicken.

“Sex is determined by chromosomes and there is a chromosome that tells you whether to be female or male.

“We’re working to place a biological marker on the chicken’s sex-determining chromosome, marking the chromosome that says ‘become male’. The marker gene, known as green fluorescent protein, therefore stays with the males and the females cannot have it (or they would turn out male).”

After the egg is marked with the new gene, a chick hatches which will be used to generate a transgenic breeding flock.

The females in that flock will lay eggs in which the male offspring contain the fluorescent marker. The marker will be visible when the eggs are screened using a laser light and the eggs containing male embryos can be removed before incubation, and an animal will never have to hatch.

Dr Tizard said that by placing the fluorescent marker gene on the chromosome, the male chick has been genetically modified but the female, naturally not having a male sex chromosome, is not genetically modified. So there is no opportunity for genetically modified product to reach the plates of consumers.

“That marked chromosome segregates. If the chick is male, it will carry the gene; if it’s female it won’t. It’s an on–off situation. You can’t partly carry the gene.”

New biotechnology may be an alternative and more favourable option for the egg industry rather than the culling of day-old male chicks.
The benefits
Being able to identify male chick embryos in the egg will ensure only female chicks are incubated and hatched, preventing the need for culling of male chicks. This technology provides obvious animal ethics benefits but also creates efficiencies in operating costs after hatching, by reducing the need to manage, sort and cull male chicks.

Dr Doran said the screening method would be easily automated and integrated into existing farming practices, potentially making it easy for hatcheries to adopt.

"Before incubation, all eggs are checked for viability (candling), so an additional check or scan to detect males could be done at the same time."

The new technology not only reduces the need to cull chicks, it also provides the hatcheries with a new opportunity to supply eggs for vaccine production.

"Vaccine production is a very high-value application. The industry requires fertilised eggs and the biggest global manufacturers of vaccines can use in excess of one million eggs per day."

"The technology has potential benefits in terms of animal ethics, use of farm resources and supporting other important industries."

The future
The US egg industry has committed to phasing out the culling of male chicks by 2020 and the German government is supporting research to make in-ovo chick sexing commercially viable, with a view to ending the culling of male chicks by 2017.

While Drs Tizard and Doran have the gene marking process worked out, commercialisation depends on the development and adoption of a screening process for operation at hatcheries. The adoption of the technology will most likely occur when local and overseas hatcheries are harder pressed to find an alternative solution to culling male chicks than they are currently, and that may occur overseas before it does in Australia.

While some groups in the community are concerned about products of gene editing, the application of the technology in this instance will not be imposed on consumers. It is the male sex chromosome that carries the modification, and that automatically quarantines the marker gene from the egg market.

Gene editing to insert a gene marker on the male chromosome will enable male eggs to be removed from the production systems before incubation and hatching.
Challenges for adoption

The excitement and optimism shared by many about gene editing, especially with the development and accessibility of the CRISPR/Cas9 gene-editing tool, does not translate to ready adoption by agriculture, as at 2016.

The adoption of gene editing is limited primarily by the uncertain regulatory environment for products of gene editing. The uncertainty reflects the diversity of views held by the general public, some of which arises from the complexity of the science underlying gene editing.

Ethics of gene editing
Gene editing promises many benefits, particularly in areas of human medicine. In 2014, scientists were able to edit the genes of mice to prevent muscular dystrophy. In 2015, gene editing was used to cure a child of leukaemia. In 2017, it is hoped that gene editing can be used to cure a form of blindness in adults. While gene editing may improve health and cure disease, the very same technology has potential to change the genes of human embryos. The 2015 International Summit on Human Gene Editing called for a moratorium on using the latest gene-editing techniques on human egg and sperm cells until ethical questions arising from the technology were addressed.

The gene editing of animal genomes also raises ethical issues regarding animal welfare and the creation of animals with novel features ‘just because’, rather than for recognised benefit. Such concerns are more apparent overseas than in Australia, although there is acknowledgement of these issues in research institutions.

The use of gene editing to eradicate pests and disease-carrying insects raises environmental concerns. While the immediate goal is beneficial, the wider impact on the ecosystem and its food chains by removing a pest species must be clearly understood before consideration is given to the deployment of ‘gene drives’.

Consumer understanding of the science
The greatest challenge to adoption of gene editing may be educating the general public about this complex science, so that the benefits and the risks are understood. Gene editing employs several different methods using an evolving suite of tools and exploits the natural capacity of DNA to quickly repair itself after a break.

Depending on where along the genome the DNA is ‘cut’, the repair to the targeted gene may change the coding of DNA, resulting in loss of function or the repair may subtly reinspect the gene, giving it new properties. These techniques do not introduce DNA to the edited genome, and no trace of the gene-editing tools will remain in the edited cells. These approaches are being termed precision breeding.

Conversely, gene editing can be used in the ‘traditional GM’ way to introduce additional DNA to the target genome, and depending on the source of the introduced DNA, the process could be regarded as transgenic.

Uncertain regulation
For Australian agriculture, gene editing is used in research and has huge potential for practical application. However, at the present time there is little investment in the commercial development of plants and animals by gene editing. Current regulations do not adequately distinguish between ‘traditional GM’ and the new gene-editing techniques, leaving confusion as to whether regulators will interpret products of gene editing as genetically engineered. The Australian Gene Technology Act 2000 will undergo its statutory five-year review in 2016 and this will be a priority question to be resolved. Scientists and biotech companies in Europe share the same concerns in regards to the interpretation of products of gene-edited organisms by the community and regulators.
Policy and regulation

Gene editing is a rapidly evolving field of biotechnology that has already outpaced existing legislation. New policies and regulations are essential to ensure the benefits of the technology are realised.

In Australia, as at 2016, agricultural products derived from gene editing are subject to the same assessment that applies to all agricultural produce, and are primarily regulated by Food Standards Australia New Zealand (FSANZ) and the Australian Pesticides and Veterinary Medicines Authority (APVMA). However, if a regulatory organisation considers that a product is genetically modified, the product also will be referred to the Office of the Gene Technology Regulator (OGTR), which operates under the Gene Technology Act 2000.

The Act is reviewed and amended every five years, and scheduled for review in 2016. Given that gene editing is a relatively new technology and adoption has accelerated since 2012, there will be more specific focus on gene editing than previously. In the meantime, FSANZ has assessed a range of new plant breeding technologies, and concluded that the method of gene editing would determine if a food product was genetically modified or not. Therefore assessments and subsequent regulation would need to be on a case by case basis. The APVMA has adopted a similar approach.

Due to the complexity of the science behind gene editing and the rapid rate of change in methods, there is still public concern about the safety of the technology and whether or not the technology is the same as genetic engineering. Regulators in the US and Europe are faced with similar challenges; although several food products created by gene editing in the US, for example non-browning mushrooms, have not required regulation by the United States Department of Agriculture on the basis there is no foreign DNA in the new product. The US is however reviewing its rules for genetically modified organisms as regulations there also pre-date gene editing.

Across all industries, the use of gene editing will be considered in terms of human ethics, animal welfare and environmental responsibility. Currently, gene editing at a research level is guided by the National Framework of Ethical Principles in Gene Technology 2012 established through the OGTR.
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