ADVANCEMENTS IN TRANSGENIC TECHNOLOGY BRING AGRICULTURAL APPLICATIONS BACK INTO THE FOCUS

G. Laible
AgResearch, Ruakura Research Centre, Hamilton, New Zealand.

Humans have a long history in shaping the genetic makeup of livestock for improved production characteristics to meet crucial human demands for food and animal fibres. Until recently, this has been exclusively achieved through traditional breeding and selection schemes. Progress with this improvement strategy is however painstakingly slow. The modification of the genome is based on the generation of novel allelic combinations through recombination events during sexual reproduction that reshuffle the genome and the occurrence of spontaneous mutations. Due to the random nature of these changes, they can have both desirable and undesirable effects (that may also be linked) on the resulting phenotype. Strong selection for desirable trait characteristics can identify animals with the best phenotypes but overall, possible genetic improvements are restricted to only incremental gains. The true potency of the strategy only reveals itself over an extended period of time when large numbers of small gains have the ability to accumulate into substantial improvements.

Although this approach has been very successfully applied in the past, the achievements were realised on the back of relatively stable conditions that are compatible with such a slow but steady approach. Predictions of a rapidly growing human population combined with extensive changes of the world climate over a relative short time period herald a fast approaching departure from these stable conditions. In the face of these pressing global challenges, faster and more flexible strategies will be required to adapt current livestock for farming under more extreme climate conditions, shrinking land resources and the increased food demands of a larger population. Genetic modification (GM) technology offers the potential for a more targeted approach to enhance specific characteristics at unprecedented magnitudes and the ability to achieve the improvements within a single generation. Rather than having to rely on good fortune for the production of new, more favourable combinations of the entire gene pool within the genome, GM technology can introduce specific changes at the single gene level. Moreover, the technology is not restricted by the gene pool available in a given livestock population but can utilise genes from otherwise inaccessible populations and even other species to introduce entirely new and unique characteristics.

More than 25 years ago, the prospects of the technology for agriculture triggered a first wave of applications of the technology to improve agriculturally important livestock traits. Many of these initial GM livestock studies had to contend with low efficiencies, limitations in appropriately controlling the activity of the newly introduced gene and low acceptance of the technology by the general public. Further difficulties for the generation of specific and improved phenotypes arose because many important livestock traits are complex and often controlled by multiple genes and the underpinning scientific knowledge about their impact was still very limited. This saw the main research efforts shifting away from agricultural and towards biomedical applications which offered greater economic incentive and ethical justification with a much higher acceptance for this application of the technology by the public. Furthermore, some of the biomedical applications, such as biopharming, are technically less challenging and based on a simple overexpression strategy of a single gene for the production of a biopharmaceutical protein. Research efforts in this field have resulted in the commercialisation of the first animal produced drugs for the treatment of human health conditions. In both cases the expression of the introduced gene construct has been targeted to the mammary gland for production of the recombinant protein in milk from where the two pharmaceutically valuable proteins, recombinant human antithrombin and recombinant human C1 esterase inhibitor, can be readily accessed and isolated. Marketed under the brand names Atryn™ and Ruconest™ they are now in clinical use to prevent inappropriate blood clotting (e.g. during surgery) and reduce acute swelling of soft tissues, respectively.

Remarkable technological advances over the last few years now allow for a more efficient and more precise introduction of genetic changes. The latest technological improvements comprise the development of genome editing tools in the form of nucleases that can be custom designed to target essentially any site within the genome for specific modifications. In quick succession zinc finger nucleases (ZFNs), then transcription activator-like effector nucleases (TALENs) and the latest addition to the tool kit, clustered regularly interspaced short palindromic repeat (CRISPR) – Cas9 nucleases, were shown to be capable of introducing site-specific edits with unprecedented efficiencies, including changes that will be indistinguishable from naturally occurring mutations. This has been paralleled by the continuous increase in our understanding of the functional relationship between livestock genes and production traits. Together, these developments provide us with a greatly improved ability to precisely and efficiently redesign livestock with specific and purposeful genome alterations. At a time of mounting pressures on food security for a dramatically growing human population, these exiting new editing technologies are well placed to support global efforts in increasing food production by making significant contributions towards the improvement of livestock and associated food production. While the technological advances will also provide a boost for biomedical applications it should bring the long neglected agricultural applications of the technology back into focus.

The presentation will use important existing agricultural animal models to illustrate the range of benefits the technology can provide for animal production. Growth-enhanced salmon that reaches market size much faster and changes to the milk composition of sows that increases survival of piglet reared with this milk are applications that have a direct impact on production efficiency. The development of BSE- and mastitis-resistant cattle and avian influenza-resistant chicken demonstrate improved animal welfare and production. Probably more importantly, these resistance traits are simultaneously associated with increased food safety and reduced health risks for humans. Pigs that can better utilise phosphorus from their feed are a compelling example for reducing the environmental footprint of intensive farming. Several models exemplify the development of animals capable of producing novel food products with additional health benefits for the consumer such as pork meat containing omega-3 fatty acids associated with reduced risk for the development of coronary heart disease and cattle and goats producing milk enriched for antimicrobial proteins such as lactoferrin and lysozyme that when consumed improve gastro-intestinal health and reduce or prevent infections.

The ability to introduce precise changes at the single gene level will be first described with the help of a recent study that used RNA interference technology to prevent the production of an allergenic milk protein, beta-lactoglobulin (BLG) in cows' milk. Expression of a micro RNA that was designed to specifically interfere with the messenger RNA encoding BLG was targeted to the mammary gland. Analysis of milk produced by a cow expressing the BLG-specific micro RNA revealed that the milk no longer contained any detectable levels of BLG. The validation of RNA interference technology as an effective strategy to alter specific livestock traits will be complemented by an overview of the main characteristics of the new genome editing tools, including experimental results from livestock applications of the technology to illustrate the possibilities this powerful new technology has to offer.

Technical difficulties, socio-ethical concerns, regulatory uncertainties and political interference were the main causes for a strong decline in research activity directed towards the development of GM animals for agricultural and food applications. So far, no food products from GM animals have been approved for the human food chain. The development of ever more efficient and precise tools and pressing challenges to feed a rapidly growing human population provide strong arguments that we can no longer discount such a powerful technology and might be able to change the present situation. The new possibilities with the advanced technological capabilities have spurred great excitement in the science community. Whether the anticipated next wave of purposefully shaping livestock genomes for agricultural applications triggered by pressing global issues and much improved technical abilities will have the chance to deliver lasting impacts is far from predictable. This will ultimately depend on how successful the prospects of the technology can be translated into true benefits for agricultural productions systems, how strong the squeeze from global pressures will become and how these two factors can positively influence public perceptions and political attitudes towards GM and genome editing technologies.