COMMISSIE
COGEM
GENETISCHE
MODIFICATIE

‘The relationship between humans and animals is back on the agenda’

REPORT ON THE SYMPOSIUM ‘GENE EDITING IN ANIMALS’

19 AND 20 OCTOBER 2017 IN AMSTERDAM

Why this symposium?

New gene-editing tools such as CRISPR/Cas9 make it easier to modify the genomes of animals. Since the first transgenic mouse was created in 1980, however, there has been an ongoing debate about the genetic modification of animals. During the symposium 'Gene editing in animals' on 19 and 20 October in Amsterdam, 160 animals scientists, regulators and other professionals gathered to discuss the current developments and the ethical and societal aspects linked to gene-edited animals. One of the main questions was: Should these animals still be considered GMOs?

Biotechnologists are working on animals such as cows without horns, virus resistant chickens, lambs with more wool and pigs for xenotransplantation. To obtain these animals they have been using gene editing technologies including CRISPR/Cas, that make it possible to precisely 'edit' one or a few DNA base pairs. CRISPR/Cas is seen as easier, cheaper and more precise than older techniques.

But gene-editing also raises questions. Important questions that came up during the meeting were to what extent do gene-edited animals need the same kind of regulation as genetic modified animals required 25 years ago? Does gene editing (always) result in genetic modification as defined in the law? And should gene editing in animals be regulated differently from gene editing in plants? 'In the Netherlands, genetic modification of animals is seen as a violation of their integrity,' said Sybe Schaap, chair of COGEM, at the opening of the symposium. Genetically modified animals are therefore only allowed for specific purposes where no alternatives exist. They may be used for biomedical research purposes, but are prohibited for recreation and sport.

Schaap emphasized that the new gene-editing technologies bring these premises into question. The modifications made to the genome with gene editing can be extremely small compared with previously used modification techniques. Besides, changes made by using CRISPR/Cas are also

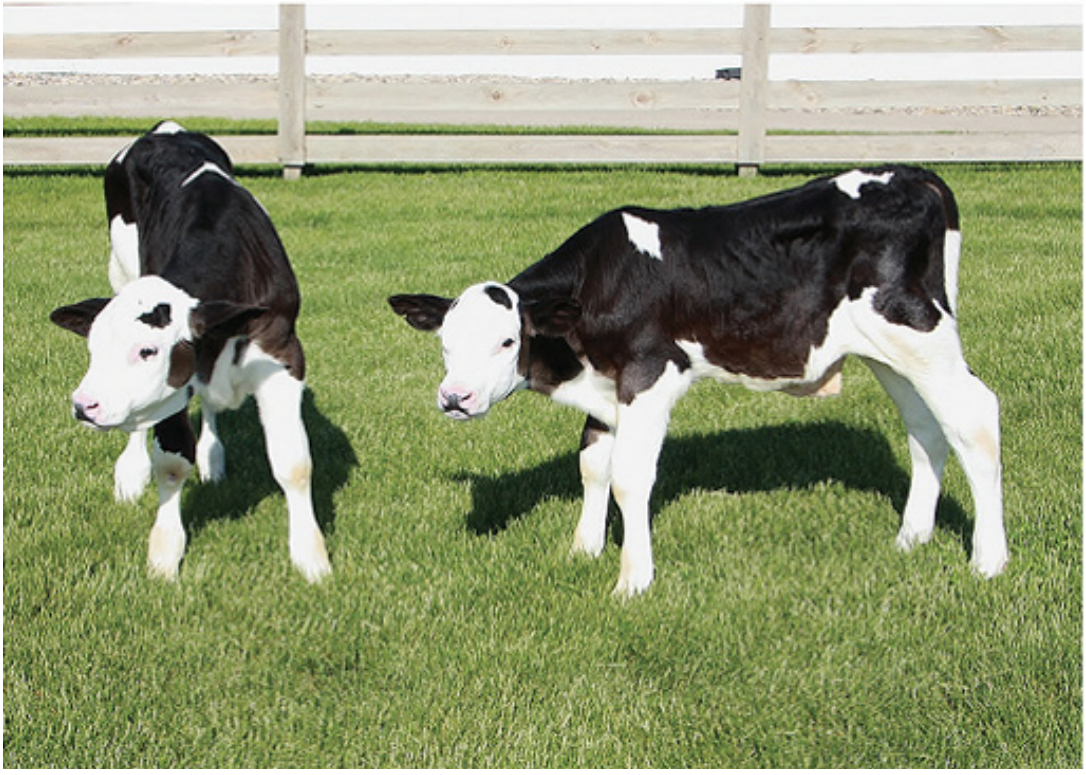
160 professionals gathered to discuss gene editing in animals: 'Changes made by using CRISPR/Cas are also ones that could arise spontaneously in nature.'

ones that could arise spontaneously in nature. Schaap: ‘So should these animals still be considered GMOs?’ No answers were provided during this symposium, but the discussion has clearly started. Schaap: ‘Gene editing puts questions about the relationship between humans and animals back on the agenda.’

Breeding farm animals

Cows without horns

Genome-editing technologies have the potential to become the next ‘game changer’ in cow breeding, said animal scientist Han Mulder from Wageningen University & Research. His study, which he carried out together with animal breeding companies, found that genome editing can accelerate the introduction of the monogenic trait of ‘hornlessness’ in a population of dairy cows. Companies are eager to introduce this trait, which is rare in dairy breeds. At present farmers have to remove the horns to protect themselves and other cattle from injury. But this practice, which is painful for the cows, has come under increasing scrutiny from animal rights activists. To solve this problem, several laboratories have now edited the genomes of dairy cows to make them hornless. Mulder and his group calculated the breeding time and cost of using genetic selection only with



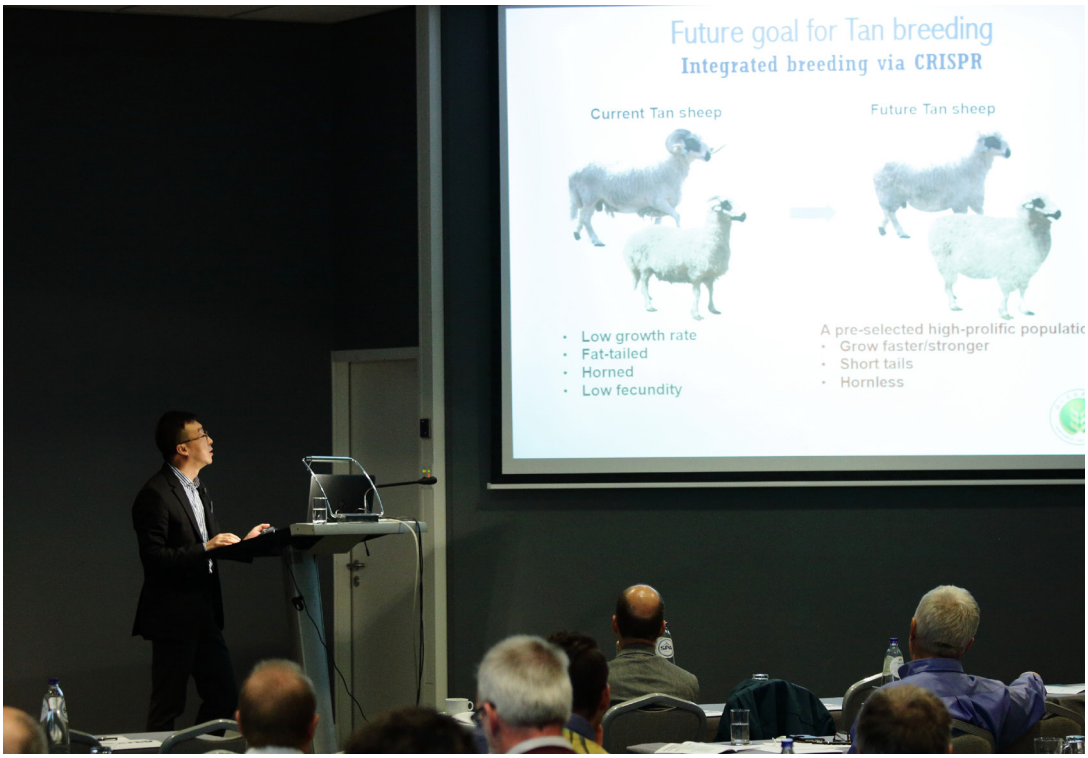
The university of Minnesota and Recombinetics have edited the genomes of dairy cows to make them hornless for the first time. Published in Nature Biotechnology May 2016

the time and cost of using a smart combination of genetic selection and gene editing. ‘Gene editing results in an enormous increase in speed,’ Mulder said. Scientists who use gene-editing, are able to fix the allele for hornless in an elite population of Holstein cows in 2-5 generations, which is four times faster than it would take using only selection and results in less loss of useful

polygenic traits. But there are challenges. The break even costs depend on the value of the desired phenotype and the target population size. Furthermore, detecting off-target edits is still quite time-consuming. Mulder also stressed that public dialogue is 'very much needed'. Companies will probably be unwilling to use CRISPR-Cas9 as long as the cows are seen to be genetically modified cows.

Chickens producing eggs with more influenza vaccine

Tim Doran, a molecular biologist at CSIRO in Geelong, Australia, also concluded that gene-editing technologies can speed up the introduction of mutations that already exist in a species: the technology is precise and does not introduce deleterious or unwanted traits that can arise when traditional selective breeding is used. His group is working on chickens that produce eggs for enhanced influenza vaccine production. Since 1970, pharmaceutical companies are using chicken eggs to produce influenza vaccine. The yield of the vaccine, however, is still very low. To achieve eggs with higher vaccine yields, the group deleted a small part of a specific chicken gene to remove inhibitors of vaccine growth.



Xiaolong Wang: 'The future Tan sheep will grow faster, have a short tail and be hornless.'

But, before being able to do this editing, the group had to solve a problem that is specific to birds. Because egg cells are difficult to access while still inside the hen, CRISPR elements cannot be injected directly into the egg cells itself. To get around this, the researchers now use Primordial Germ Cells (PGCs) – immature cells that eventually turn into sperm or egg cells. They remove these cells from the blood, edit the genome and then put them back into the developing chicken in an early stage. They can also edit cells by injecting the CRISPR elements directly into the blood. Doran is also using these germ cells to create chickens that produce eggs without the proteins that cause egg-allergies (2.5 % of Australians have this allergy) and chickens that are resistant to a virus.

Tan sheep with higher body weight

'The future Tan sheep will grow faster, have a short tail and be hornless', animal scientist Xiaolong Wang predicted. His group, of Northwest A&F University Yangling in Chi, has created sheep and goats with higher body weight, higher meat quality and increased hair length to help improve the growing livestock husbandry sector in China. The group has edited genes from the indigenous Tan sheep by injecting one-cell-stage embryos with Cas9 mRNA and sgRNAs. These CRISPR elements, called nucleases, disrupted one or several genes with known functions: e.g. MSTN for muscle growth, FGF5 for fibre growth and BMPR1B and GDF9 for fecundity.

However, public debate is important in China too, Wang said. Despite the fact that hundreds of Chinese laboratories are working on GM animals and plants, there are still only two GM crops on the market: a cotton cultivar (1997) and a papaya cultivar (2006). 'It will take a long time before the public will accept these new GM sheep,' Xiaolong said. Public attitude can be influenced by ethical issues or by uncertainties about safety. One of the safety concerns is off-target mutations. So to provide a foundation to this safety question, his group studied the off-target mutations from 50 CRISPR sheep and goats including single nucleotide polymorphisms (SNPs) and deletions in the whole genomes. They found no detectable off-target modifications that could be attributable to the injected CRISPR elements.

Virus resistant sheep and sheep as a model for human diseases

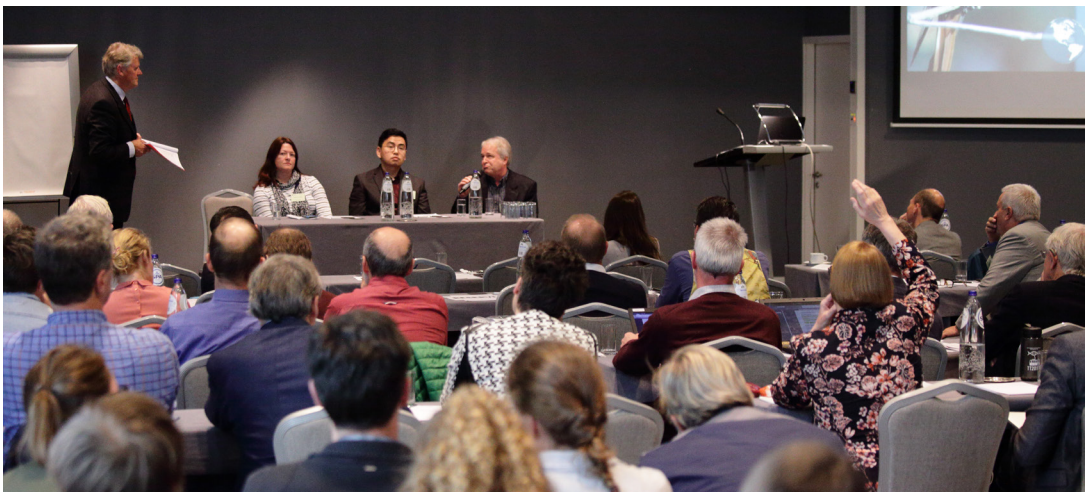
Alejo Menchaca, a biotechnologist at the Institute of Animal Reproduction Uruguay, also works on sheep. His laboratory has created sheep that combine traits from the Australian Merino sheep (superfine wool) and the Dutch Texel sheep (good meat quality). Menchaca confirmed that the CRISPR/Cas system has become a relevant tool for sheep breeding. His laboratory is also breeding sheep that are resistant to Jaagsiekte sheep retrovirus, a virus that causes lung cancer in sheep. The disease have been called Jaagsiekte, after the Afrikaans words for "chase" (*jaag*) and "sickness" (*siekte*), to describe the respiratory distress observed in an animal out of breath from being chased, indicating the breathing difficulty experienced by infected sheep. To make them resistant, elements from the CRISPR-Cas system were injected into zygotes to obtain a mutation in the gene that is responsible for the receptor protein that recognizes the Jaagsiekte sheep retrovirus. Without this receptor, virus infection is not possible. Fifteen lambs with this mutation were born this summer, the group is now testing their resistance.

'If you say that the CRISPR technology is more precise, then you have to be specific about what exactly is more precise.'

Menchaca is also working on another application: sheep as models for human diseases. In October 2017, 35 deaf GM lambs were born with a mutation that causes a specific genetic type of deafness that also occurs in humans. These sheep may be used to test therapies. 'Our models will have practical implications in the field of livestock production, animal health and medicine,' Menchaca concluded. But technical challenges still lie ahead. The success rate of the transformation and pregnancies (from the transferred embryos) is still quite low: the laboratory needed more than 300 embryos and 86 recipient sheep to produce the 35 deaf GE CRISPR lambs.

CRISPR/Cas: not so easy to communicate

'So if you say that the CRISPR technology is more precise,' a science journalist commented during the discussion, 'then you have to be specific about what exactly is more precise.' Menchaca



Tjeerd Kimman, Samantha O'Loughlin, Jianghong Min and John Godwin during a discussion: 'Carefully assessing the potential of gene drive technology is important.'

agreed, and said that he wished he could speak more often with science journalists. 'Help me to communicate better.' Another question from the audience was how long it is likely to take from the birth of a first gene edited animal to an animal reaching the market. According to the researchers, it would take 10 years to set up a population of hornless cows that would be big enough to produce for the market. For gene edited chickens this would only take two years. But a participant from a company voiced reservations: companies are not so eager to invest in this technology. This is not only because the authorization process can take years (gene edited animals are still regarded as GMOs), but also because the monogenetic mutation that Doran's first virus-resistant chicken had could be less sustainable. 'We have seen this also in plants: you do a massive amount of work and then the virus adapts itself to the mutation.' This is the reason another participant gave for preferring to focus on 'polygenetic robustness and tolerance' instead of virus resistance based on mutations in a receptor gene.

Eradicating pests

Further global trade and climate change will lead to more invasive species including pest species. So new methods to combat pest species are very welcome. During this symposium, it became clear that laboratories can use CRISPR/Cas not only to accelerate farm-animal breeding, but also for the eradication of pest species. Governments could use this method to eradicate a pest in a particular area, such as mice on a tropical island or malaria mosquitos in East Africa. The pest animals are given a 'gene drive': a construction based on CRISPR/Cas9 that accelerates the spread of a specific trait among a population, for instance disease resistance or male or female sterility.

Malaria mosquitos with a gene drive

The international 'Target Malaria' programme, financed by the Gates Foundation, is using this gene-drive technology to obtain sterile male mosquitos. 'The current methods won't enable us to eliminate the malaria mosquito' said Samantha O'Loughlin from Imperial College London. Gene drive might be a method to realize this goal. The teams are testing mosquitos with a gene drive in laboratories (England and Burkina Faso) and in large cages (Italy). And Mali and Uganda want to start with laboratory experiments.

Gene drives, however, are raising concerns that the technology is too powerful, as it would theoretically enable researchers to eradicate a species on a global level. Scientists, NGOs, regulatory authorities and the media have all been warning about this danger since the idea for this technology arose in 2013. As a result, Target Malaria is employing a step-wise, multi-disciplinary approach for the transition from lab to field. The interdisciplinary teams in the different countries are not only involved in technical and safety issues, but also in regulatory issues, science communication and community engagement on all levels – from international to national and local levels. 'We want to ensure that all concerns from stakeholders can be addressed in a transparent and systematic way,' O'Loughlin said.

Gene drives are raising concerns that the technology is too powerful, as it would theoretically enable researchers to eradicate a species on a global level.

Jianghong Min from MIT Media Lab (US) described how his lab has developed DNA technology to control spread of a gene drive on a global level. 'We are in need of technologies that can limit the geographical spread of gene-drive organisms, as deployment of global drive systems ought to be reserved for only the most extreme of circumstances,' he said. The team has therefore developed locally confined drive systems: by adapting the design of a specific CRISPR construct, a laboratory can 'build in' the number of generations for which the gene drive will spread the trait. The group is now testing their constructs in nematodes.

Eradicating house mice on islands

Some nature conservation organizations are against the use of CRISPR-based gene-drive constructions because of the perceived risks; others want to find out whether the technology can be used to eradicate exotic invasive animals. Now exotic animals are often poisoned, or shot off, but these methods have severe disadvantages.

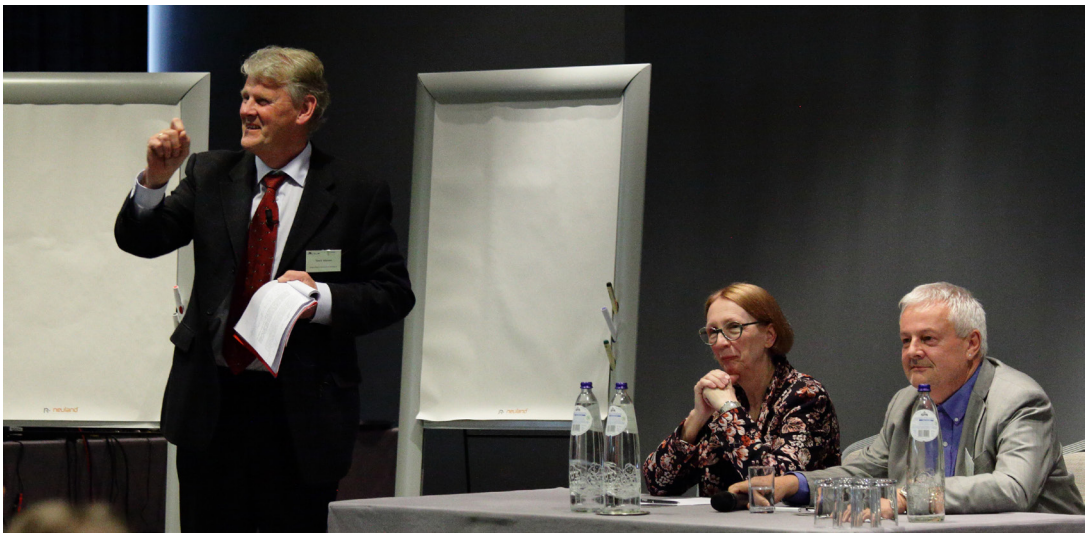
A huge problem for nature conservation are rodents on tropical islands. 'Mice on islands attack young birds such as albatrosses, and are therefore partly responsible for the extinction of birds,' explained John Godwin, a scientist at North Carolina State University in the US. His organization, Genetic Biocontrol of Invasive Rodents, is an international partnership made up of six research centres and a nature conservation organization, Island Conservation. The partnership is trying to solve the problem using CRISPR-based gene drive technology. The researchers are now producing house mice that spread the trait of sterility. The goal is to reduce reproduction and potentially eliminate invasive rodent populations on islands.

'Carefully assessing this potential, however, is important,' said Godwin. 'You can test the mice in small cages, but this doesn't provide a complete picture for the field situation.' In the field, there are many more variables that are of influence on a population. So the researchers first want to test the mice in simulated natural environments measuring 30 x 30 feet (9 x 9 metres). The partnership is committed to being overseen by an external ethics advisory committee and to early and sustained engagement with stakeholders, island communities and regulatory authorities.

Could local communities decide?

Philosopher Jeantine Lunshof, of the University of Groningen and Harvard Medical School, raised the question of who should make decisions about gene drives? On a global or even national level,

stakeholders are unlikely to agree about the (possible) advantages and the risks. So should local communities decide, and if so, how do you organize such a process? Lunshof is an advisor on an MIT-project that is trying to combat Lyme disease on two islands in the US: Martha's Vineyard and Nantucket. Lyme disease is spread by ticks that are carried by mice, and now the biotechnologists have bred mice that are immune to the ticks. Releasing these mice might help solve the problem of Lyme disease. The biotechnologists have made immune GM mice with and without a gene drive (the latter will spread the new trait quicker, so this intervention might be cheaper and easier). The island residents are now deciding whether they want these GM mice, and if so, do they want mice with or without a gene drive? The laboratory will design a mouse in accordance with their (ethical) preferences.



Tjeerd Kimman, Jeantine Lunshof and John Godwin during one of the discussions: 'There is a need for better interaction between scientists and citizens.'

'We have developed a model for Responsive Science,' Lunshof explained. 'This is a way of conducting research that invites community involvement from the earliest stages of each project.' The continuous interaction between scientists and citizens allows concerns to be identified before experiments are performed. In addition, it encourages new technologies to be redesigned in response to societal feedback. Developing DNA constructs that limit the geological spread of gene-drive organisms, as explained by Min, is also an example of adapting a technology in response to ethical concerns.

Interaction with citizens full of pitfalls

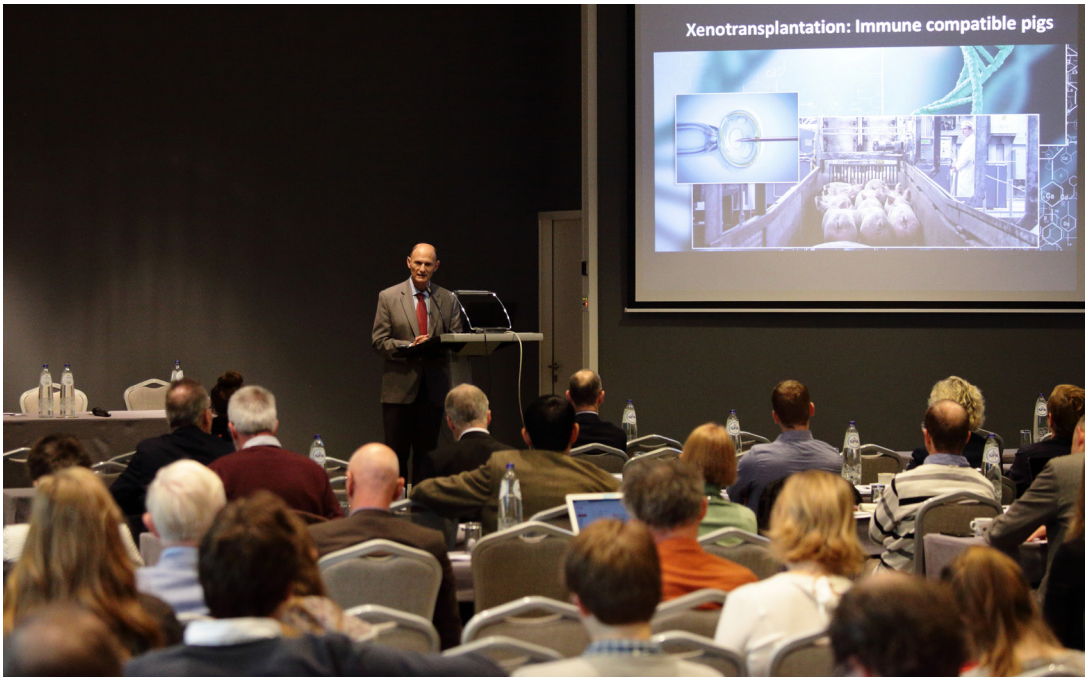
During the discussion, several participants stressed the need for better interaction between scientists and citizens. Philosopher John Dupré from the University of Exeter, however, foresaw problems concerning communication about CRISPR-based technologies. When explaining what the technologies could mean for society, scientists and science journalists tend to use metaphors for the genome such as 'blueprint', 'recipe' and 'book of life'. 'But these terms suggest a genetic programme for the different traits,' Dupré said. 'As if, in a magical thinking, you change a gene and the new trait appears. But that's quite misleading: a genome is not a static entity, but constantly changing in a dynamic interaction with the environment.' So we need a more sophisticated understanding, and communication, of what genome editing is.

Dupré also stressed the importance of discussing the bigger picture when talking about the

advantages and risks of the new CRISPR technology. For instance, when it comes to hornless cows, we can say that gene editing is good for animal welfare because the farmer doesn't need to remove the horns anymore, which is quite painful. But are hornless cows really needed for sustainable food production? We should also discuss the fact that the same intensive cattle rearing industry that is pushing for hornless cows has many disadvantages for the environment and animal welfare. So wouldn't it be better to search for alternative methods of food production?

Large animals for xenotransplantation and disease models

A solution for the current shortage of kidney and heart transplants in hospitals could be xenotransplantation, the transplantation of organs from animals. Decades of scientific setbacks has kept clinical trials of this approach on the horizon. Gene editing, however, increases the possibilities for xenotransplantation. This is because the animal in which the (human or pig) organ has to be grown, can easier be made immune compatible with humans. Improved technologies to modify pluripotent germ cells are also bringing xenotransplantation closer to clinical practice.



Juan Carlos Izpisua Belmonte succeeded in producing pig embryos that have incorporated a small number of human cells.

Pig-human chimeras

Scientists can use CRISPR/Cas, and other new technologies, to develop chimeras – animals that can produce human organs for transplants. American laboratories have already made a few mouse-rat chimeras and the oldest one is now 24 months. Juan Carlos Izpisua Belmonte, a biotechnologist at the Salk Institute for Biological Studies in the US, showed a picture of his two-year-old chimeric 'rat-mouse' or 'mouse-rat'. 'In the lab I say mouse, but I really don't know what it is,' he added.

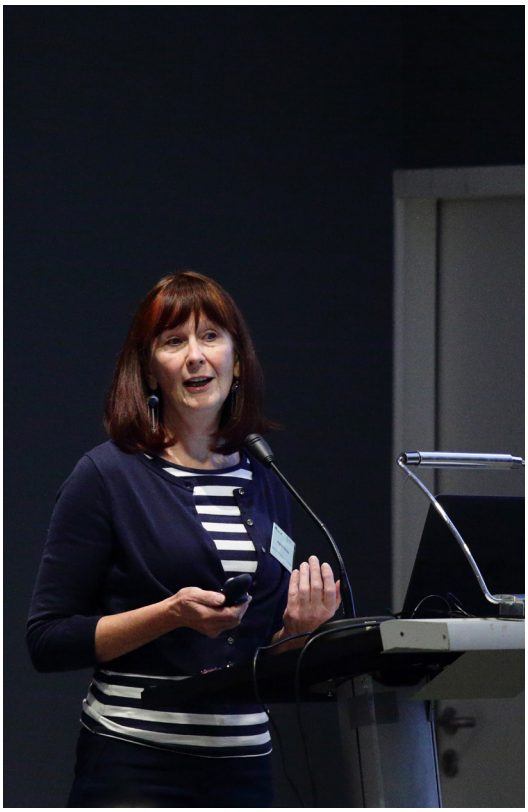
Belmonte explained how his group has created mice embryos that have rat organs. Using the gene-editing tool CRISPR/Cas9, the researchers disabled several genes involved in heart and eye development so that the mice would not grow functioning mice versions of those organs. Rat stem cells introduced into mouse embryos filled in for these, growing functional organs, including one the researchers didn't expect. Rats don't have gallbladders, but rat stem cells introduced into mice embryos are able to form gallbladders.

Belmonte has also succeeded in producing pig embryos that have incorporated a small number of human cells. However no functional organs were formed, possibly due to the shorter development time of the pig embryo compared to human embryos. The group is also trying to introduce human cells into horse embryos. The Salk researchers aim to use CRISPR/Cas9 to engineer farm animals that lack certain organs just as they did with rodents. Human cells able to supply the missing organs might then have a growth advantage and survive better. For ethical reasons, the group is developing genetic tools to prevent human cells from integrating in the brain of the recipient animal.

But how can laboratories monitor the welfare of chimeras, one of the participants asked. 'There are no classifications or protocols for these new animals.' Belmonte agreed that his laboratory has to develop welfare guidelines for chimeras, together with regulators. 'At the moment, however, these first chimeras are perhaps the best treated animals in the world.'

Pigs as disease models

Angelika Schnieke, from the Technical University of Munich, stressed that gene editing improves the possibilities for xenotransplantation, but it can also be used to create farm animals as disease models. 'Large animal models of human diseases can bridge the gap between basic biomedical research in rodents and the translation of new knowledge into clinical practice to improve diagnosis and treatment.' Pigs, horses and cows are anatomically and physiologically more similar to humans than rodents in a number of ways. Their immune systems are more similar and they have a longer lifespan than rodents.



Angelika Schnieke: 'We can have a new animal model in a couple of weeks or months.'

Schnieke showed how laboratories throughout the world have already made twenty porcine models including models for various types of cancers, cardiovascular diseases, diabetes mellitus and neurodegenerative diseases such as Alzheimer's diseases. Gene editing has enormously accelerated the speed of this process. 'We can have a new animal model in a couple of weeks or months.' For the pancreatic cancer model, her group mutated three genes that were known to be involved in pancreatic cancer in humans. They applied the modifications in both pigs and mice. Whereas the CRISPR pig developed this cancer as predicted, mice

with these three mutations did not. This strengthens the argument that animals such as pigs are better disease models for humans.

The Technical University of Munich is doing work on xenotranplantation as well: they transplant pig organs to other species. Schnieke's laboratory has successfully transplanted a pig heart from a gene-edited pig into a baboon. In September, the researchers announced that they had nearly doubled the previous survival record for a life-saving pig heart transplant in a baboon to 90 days – at that age the baboon was still healthy. Three months might be long enough for regulators to permit clinical trials in humans, so the group is therefore working to repeat the results in more baboons. In order to increase the likelihood of the pig organs being accepted by the body of the patient, tens of pig genes have to be edited. The German researchers modify genes that are involved in hyper-acute rejection, vascular rejection and cellular rejection.

More mice models than ever

Michael Wiles from the Jackson Laboratory in the US stressed the many advantages this technology offers for creating disease models in mice. To test a gene-disease hypothesis in mice now costs 90 per cent less and takes less than a quarter of the time that it previously took. Besides, laboratories can now modify any species, they can regulate the expression of genes (epigenetics), and they can refine or adapt the genetics of a mouse model in response to new insights into the disease. 'It is much quicker and more efficient to use CRISPR technology to alter a fertilized egg and thus engineer a mouse than the traditional route, which starts by modifying an embryo cell.' One of the results, however, is that pioneers in garages, with less money and expertise than certified laboratories, can also change the genetics of species. According to Wiles, CRISPR and similar technology will change society. 'Perhaps having our genetic destiny within our hands is a next enabling evolutionary step.' One of the participants asked what role Wiles sees for himself as a biotechnologist in addressing ethical issues. In response Wiles described a project in a small country that he declined to participate in because gene editing did not seem to be the best solution for the problem (diminished fertility due to inbreeding).

To test a gene-disease hypothesis in mice now costs 90 per cent less and takes less than a quarter of the time that it previously took.

Monkeys for disease models

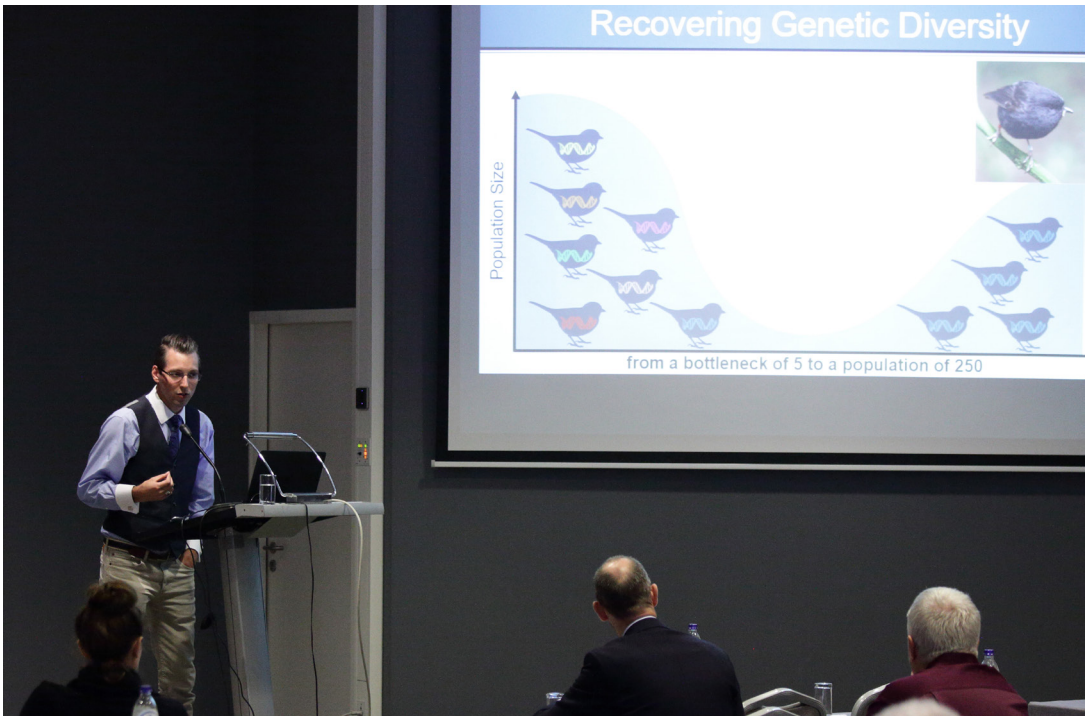
Primates are closely related to humans and known to be probably the most representative disease model for research. In Europe however, the possibilities for using monkeys to develop disease models are limited because of ethical concerns. Weizhi Ji, from the Yunnan Key Laboratory of Primate Biomedial Research in Kunming (China), however, emphasized the importance of using monkeys. He believes Non Human Primates (NHPs) are an ideal model for complex human diseases. 95% of our genome sequence is similar to that of monkeys, whereas we share only 84% of our genome with rodents or pigs. In addition, our minds are more similar to those of primates than to those of rodents, which could help advances in the neurosciences. It is much easier to bring about changes in monkeys by using CRISPR than it is with older genetic technologies. In the five years between 2001 and 2016, only six conventional GM-monkey disease models were published, while 11 gene-edited monkey models have been published in the last three years, including a monkey with autism.

Weizhi's institute has made a monkey with Rett Syndrome (RTT) by mutating one gene (called

Mecp2). Children with this severe monogenetic disease show impaired development and have a lot of pain; they are prone to infections and they lose language and motor skills. Weizhi showed that the phenotype of the rodent RTT model is different from that of human patients, but the phenotype of the monkey RTT model is comparable to that of humans. For example, most girls and most female monkeys survived, and most boys and male monkeys with the mutation resulted in abortion during pregnancy (in humans RTT affects mainly girls). Rodents showed no gender differences. And compared with humans, rodents displayed completely different social behaviour, whereas monkeys evolved more similar social behaviour. Weizhi: 'Monkey models are therefore very helpful for understanding diseases as well for drug screening and clinical therapy.'

In Europe, however, it is likely to be difficult to obtain permission for performing behaviour experiments with (genetically modified or gene edited) monkeys. Other participants stressed that in all cases laboratories will first need rodents to find out which technologies or therapies are the best.

Bringing back extinct animals



Ben Novak:'The de-extinct passenger pigeon will not be transgenic or genetically modified.'

Many conservation programmes have saved iconic birds and other species from extinction through interventions such as captive breeding and the reintroduction of endangered species in an area. Nature conservationists in the Netherlands, for example, introduced primitive 'Heckrunderen' in the Oostvaardersplassen thirty years ago. These Heckrunderen were created around 1930 by the German breeder Lutz Heck. He crossed indigenous cattle with specific 'primitive' traits in breeds from Hungary, Corsica, Scotland and Spain. CRISPR/Cas could also enable re-introduction of extinct animals.

Reintroducing a pigeon in the eastern US

Ben Novak is a scientist at Revive & Restore, an international organization for the genetic rescue of endangered and extinct species, based in California. He explained how his organization is trying to bring back the North American passenger pigeon and heath hen, using CRISPR and other biotechnologies developed for chickens. The passenger pigeon is an iconic species in the eastern part of the US. Before they were shot down in large numbers in the nineteenth century, the passenger pigeon population numbered billions. Their disappearance from the skies was a sign that even the most abundant of natural resources could be exhausted by unchecked human consumption, heralding a new age of conservation regulation and game management. Reintroduction of the passenger pigeon may also help restore forest biodiversity in the eastern US.

To 'revive' the extinct bird, the organization plans to edit the germ-line of living band-tailed pigeons according to genes for ancestral traits that have been found in the genome of a passenger pigeon from a museum. Next steps will include breeding the edited band-tailed pigeon/passenger pigeon in captivity, reintroducing these new 'hybrids' into the wild after proper conditioning, and monitoring. Novak stresses that 'de-extinct' species will not be transgenic or genetically modified. 'They most closely resemble selectively bred hybrids.' According to Novak, many species and environments would benefit from such restoration.

But who decides what kind of landscape or ecosystem we want, one of the participants asked. Passenger pigeons were once part of a specific natural landscape in the eastern US, but farmers today might regard passenger pigeons as a pest. Moreover, the disappearance of the passenger pigeon might have stimulated the rise of other species which flourish in another natural landscape. 'Our view of nature and what is natural will keep changing,' this participant remarked. Revive & Restore, however, sees the advantage of bringing back the passenger pigeons not in restoring a specific form of ancestral nature, but in providing measurable ecological services such as enlarging the biomass in forests.

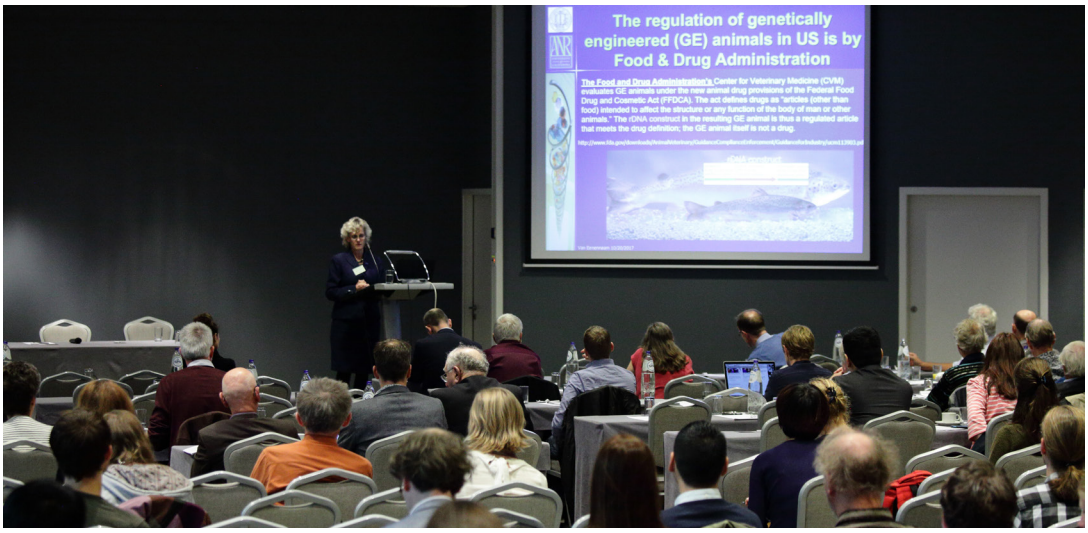
How should we regulate gene-edited animals?

Definition of GMO

One of the major questions that arose during the symposium was how: should we define a GMO? 'It is really tough to come up with a definition,' one of the participants declared. 'Using CRISPR you can change just one or two base pairs, but also tens, hundreds or thousands of base pairs. The mutations may be similar to what could happen in nature, but they can also result in brand new organisms.'

According to Alison Van Eenennaam from the University of California, regulators should restrict themselves to the risks of a product, regardless of the way they are made. But that is not the way it works in the United States, she explained. In January, the FDA announced a draft guideline that classifies all gene-edited animals that have had their genomes intentionally altered as drugs. This means that the authorization process can take years. That was the case with the AquaBounty's fast growing GM-salmon, so far the only GM-animal that has made it to the agricultural world market. It took almost 30 years from the initial production of this salmon at the University of Toronto to obtaining Canadian Government approval for its sale in Canada. The company has already spent 16 million dollars on the regulation processes.

Because it will often be impossible to distinguish between natural mutations and intentionally altered base pairs, the new FDA guidelines will be unworkable, Van Eenennaam predicted. Her own group has also created CRISPR cows without horns. The mutations in these cows are similar



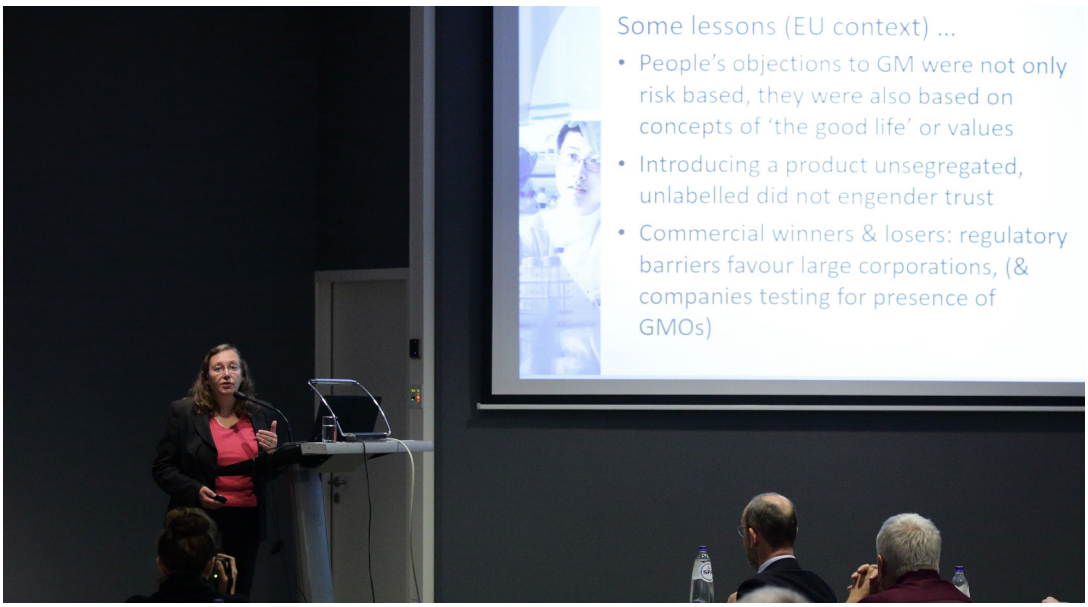
Alison Van Eenennaam: 'Regulators should restrict themselves to the risks of a product, regardless of the way they are made.'

to the mutations that produce hornless cows when traditional breeding techniques are used. In the Netherlands regulation on animal biotechnology is also based on ethical and social issues. Van Eenennaam, however, sees no advantage to including these issues. 'That would open up a lot of uncertainty. Ethical and social issues should be part of broader discussions about food production, and companies can use labels to let the public choose.'

Regulation that stimulates innovation

Ann Bruce, an innovation researcher at the University of Edinburgh, proposed another idea for regulation: 'adaptive governance'. 'CRISPR/Cas9 is a first step in a new direction', she explained. 'It is a novel technology, and, as scientists and companies are unlikely to have exhausted all ideas for its use, we might underestimate the impact in the long term.' Regulatory authorities could therefore go for stepwise regulation including 1) pre-regulatory standards; 2) pre-regulatory guidelines (these are already more formal); 3) regulation, and 4) post-regulatory standards and guidelines to support compliance with regulation. According to Bruce, a regulatory system for a 'new' technology should take into account four aspects: the innovation strategies of companies, the extent to which innovations could respond to currently unmet social needs, innovativeness of particular sectors of industry, and geographic location and scale of operations. In this way, the regulation process could encourage positive changes in industry and distinguish between products on the basis of social and economically relevant criteria.

Bruce also mentioned some disadvantages of not regulating CRISPR animals. 'Companies could then be open to accusations of 'hiding' the new technology, and if you are hiding something, it must be bad.' From the debates on GM plants she learned that the first products to reach the market are likely to frame the CRISPR technology. Unfortunately, the first products are not necessarily the most socially desirable applications, the first GM plant being a good example: Monsanto's herbicide soy. What might make it even more difficult to introduce CRISPR animals onto the market is that conventional livestock farming already has a bad image, at least in the UK.



Ann Bruce: 'The first products to reach the market are likely to frame the CRISPR technology.'

This can lead to unexpected reactions: biotechnologists show the advantages of hornless cows, and the public is shocked to learn that horn-cutting is a practice and starts criticizing current, industrialized farming. Bruce: 'So my question is also: how might gene editing help deliver alternative systems, with an emphasis on local production and breeds adapted to local conditi-ons, and with an emphasis on animal welfare and reduced environmental impact? Are there alternative, innovative pathways for the current pathways?'

GM animals back on the agenda

'I don't dare to summarize what we have discussed,' concluded Frans Brom, chair for the day and member of the Dutch Scientific Council for Government Policy at the end of the symposium. He therefore came up with three remarks: The first one was that gene editing could be a game changer: it can lead to new laboratories, new companies, new people and new discussions in animal breeding, medicine and nature conservation. The second one? The relationship between animals and humans is back on the agenda. 'Some of the ethical issues are new', Brom said, 'and they are being discussed on a global level.'

His third remark, finally, was that regulation is back on the agenda too. Rules and practices developed in the early phase of genetic modification are no longer suitable for the current DNA-technology in its mature state: in the early phase, genetic modification was only feasible for a few prosperous laboratories; now CRISPR can be used much more widely and by anyone. Brom: 'So the question we have to answer again is how should we organize the regulation of this kind of technology?'

Text: Marianne Heselmans, science writer
Production: ImpactReporters
Layout: Tineke Kooistra, Studio 10