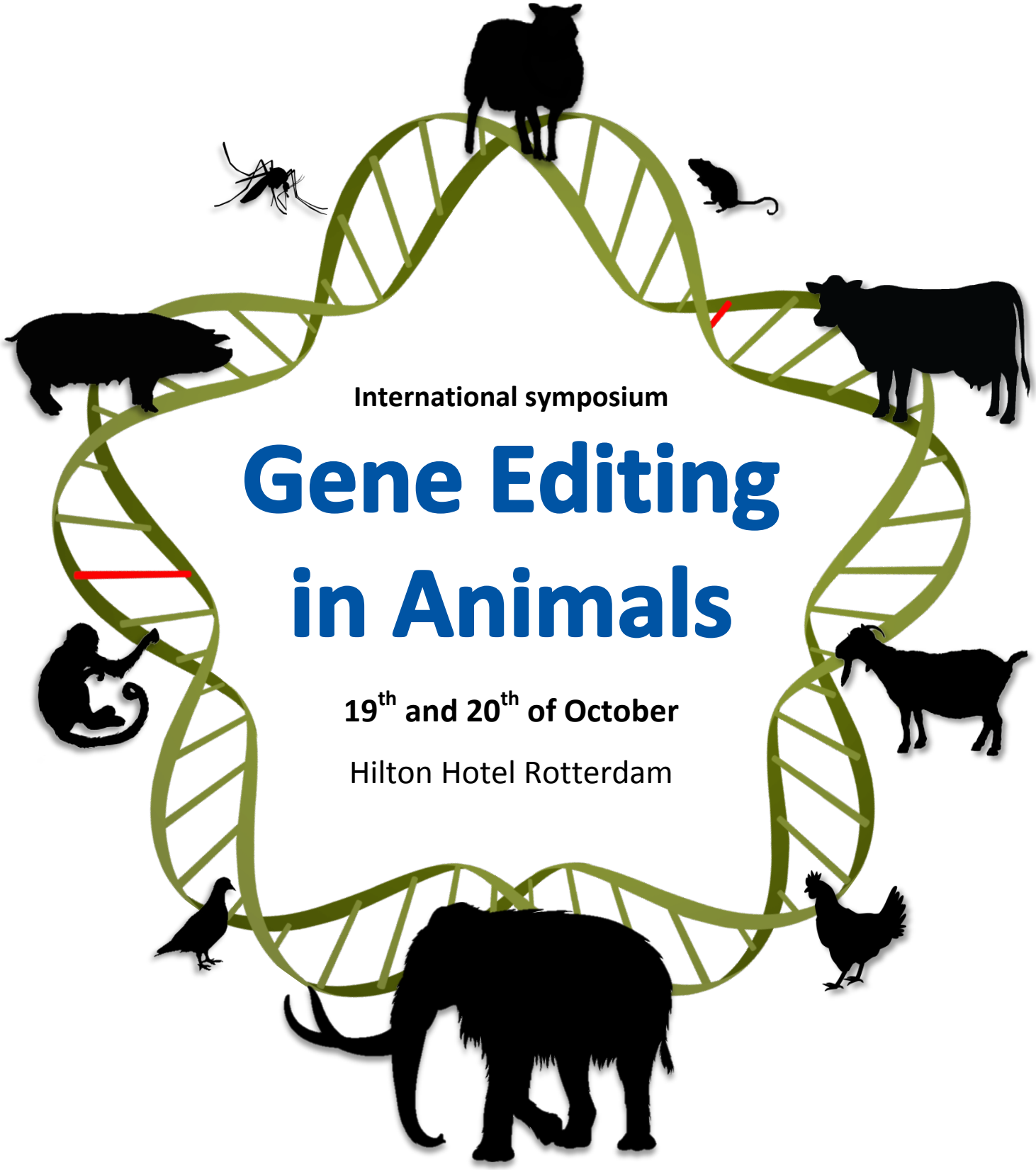

International symposium

Gene Editing in Animals

19th and 20th of October

Hilton Hotel Rotterdam

International symposium

Gene Editing in Animals

Applications & Implications

19th and 20th of October 2017

Rotterdam, the Netherlands

COMMISSIE COGEM GENETISCHE MODIFICATIE

Welcome and Opening

On behalf of the Netherlands Commission on Genetic Modification, I am delighted to welcome you to Rotterdam for this two-day symposium on gene editing of animals.

It is wonderful to see that so many people from the Netherlands and abroad have made an effort to attend this event. I extend a special welcome and thanks to our speakers for their willingness to contribute to this meeting. We are indeed honoured to have you here with us.

The theme of this meeting, gene editing of animals, is both exciting and controversial. Ever since the first transgenic animal was created in 1980, there has been an ongoing public and scientific debate about genetically modified animals, more specifically about the associated risks and ethical implications. In Europe, and the Netherlands in particular, the genetic modification of animals has met with concern and objections from politicians as well as the general public. Consequently, the Netherlands and many other European countries have placed genetic modification under strict regulation.

Although research on transgenesis of livestock and other animals outside Europe has continued, the development of commercial products has largely stalled. Consumers appear to be reluctant, not only in Europe but in other parts of the world too, and research lines have been abandoned due to the poor market outlook worldwide.

The new gene editing tools like CRISPR/Cas9 open up new possibilities for modifying the genome of animals. These tools have the potential to enhance the productivity of major livestock species, introduce disease resistance into livestock, bring back extinct species, make ecosystem modifications by exterminating exotic invasive species, reshape animals as research models for human disease, and to produce human organs for transplantation.

Over the next two days our distinguished speakers will explain the latest developments in these areas. This offers a unique possibility to gain first hand insight into scientific developments in gene editing of animals in China, North and South America, and Australia.

But while applications of gene editing hold much promise, they also raise questions about governance and societal and ethical concerns. In view of the new possibilities, should governments reconsider and adapt the often strict regulation of animal modification and use of experimental animals?

The Netherlands is one of the few countries in the world with a licensing system for the genetic modification of animals that reviews applications for their ethical acceptability. We consider not only the potential negative effects on the health and welfare of the animals, but also the violation of their genotypic integrity. This system is based on the assumption that genetic modification introduces new traits that cannot be introduced by natural procreation or breeding. From a legal point of view, genetic modification of animals is seen as a violation of

their integrity and can therefore only be allowed for specific purposes for which no alternatives exist. In general, genetic modification of animals is allowed for biomedical research purposes, while applications for breeding animals for recreation and sport are prohibited.

Gene editing questions these premises. Although new traits can be introduced, the underlying modifications of the genome can be extremely small, sometimes consisting of only one nucleotide change. And in many instances no new sequences at all are introduced. As these changes in the genetic material could also be introduced spontaneously in nature, can they be considered to be interference in the identity of these animals? Should these animals still be considered GMOs?

Moreover, the introduced traits can be beneficial for the animal and the environment. For instance, cows have been developed that are resistant to tuberculosis. Besides the benefits for the animals themselves and for other livestock and public health, TB resistance can also benefit wildlife. Badgers are seeding infection into the cattle population and in the UK a culling programme for badgers is in place as part of a bovine TB eradication programme. Is TB-resistant livestock a solution to stop the controversial badger cull, and should this be taken into consideration in the assessment of GM animals?

The new possibilities not only put existing questions about the relation between humans and animals back on the agenda, but also raise new ethical questions. Many animal species have become extinct because of hunting and destruction of habitats by mankind. Gene editing offers the tools to bring back extinct species. Is this a possibility we should embrace, or is reviving endangered and extinct species a human folly?

Our aim in holding this symposium is to provide insight into current developments in the field, and to draw up an inventory of the ethical and societal aspects linked to gene-edited animals. By no means do we expect to answer the questions mentioned earlier, but to provide food for thought about the possible implications of animal gene editing from a governance perspective.

The lectures and debate in this symposium will provide input to a COGEM policy report on gene editing in animals to be published before the end of this year.

I very much look forward to an open and fruitful discussion which will enable us to learn, explore and broaden our perspectives on this challenging topic.

Professor Sybe Schaap
Chair of COGEM

Programme Day 1

Registration

09:30 – 10:00	**Coffee and registration**

Opening & introduction

10:00 – 10:10	**Welcome and opening**
	Sybe Schaap, *Chair COGEM*
10:10 – 10:50	**Introduction**
	Chair: Tjeerd Kimman, *Wageningen University & Research, NL*

Session: Gene editing in livestock

10:15 – 10:45	**Genome editing in livestock breeding programs: opportunities and challenges**
	Han Mulder, *Wageningen University & Research, NL*
10:45 – 11:15	**Genome editing in poultry - opportunities and impacts**
	Tim Doran, *Health & Biosecurity, CSIRO, AU*
11:15 – 11:45	**Heritable multiplex gene editing via CRISPR/Cas9 exhibits low incidence of off-target mutations in sheep and goats**
	Xiaolong Wang, *College of Animal Sciences, Northwest A&F University Yangling, CN*
11:45 – 12:15	**CRISPR experiences in sheep**
	Alejo Menchaca, *Institute of Animal Reproduction of Uruguay, Fundación IRAUy, UY*
12:15 – 12:30	**Discussion**
12:30 – 14:00	*Lunch break*

Session: Ecological interventions: population control

14:00 – 14:30	**Target Malaria: step-wise development of genetic mosquito control, from lab to field**
	Samantha O'Loughlin, *Department of Life Sciences, Imperial College London, UK*
14:30 – 15:00	**The potential and risks of CRISPR gene drive systems**
	Jianghong Min, *Sculpting Evolution Group, MIT Media Lab, US*
15:00 – 15:30	**Gene drive technologies for the control of invasive rodents**
	John Godwin, *Department of Biological Sciences, North Carolina State University, US*
15:30 – 15:45	**Discussion**
15:30 – 15:45	*Coffee break*

Session: Ethical challenges and perspectives

16:15 – 16:45	**Pigs for hearts and mice against ticks**
	Jeantine E. Lunshof, *University of Groningen, NL, and Harvard Medical School, US*
16:45 – 17:15	**Ethical issues in genome editing of non-human animals**
	John Dupré, *Centre for the Study of Life Sciences (Egenis), University of Exeter, UK*
17:15 – 17:30	**Discussion**

Programme Day 2

Registration

09:00 – 09:30	**Coffee and registration**

Opening & Welcome

09:30 – 09:35	**Introduction** Chair: Frans Brom, *Scientific Council for Government Policy, NL*

Session: Developments in xenotransplantation

09:35 – 10:05	**Reprogramming, gene editing stem cells and organ generation: in vitro and in vivo approaches to increase healthspan** Juan Carlos Izpisua Belmonte, *Gene Expression Laboratory, The Salk Institute for Biological Studies, US*
10:05 – 10:35	**Engineering the pig: novel models of human disease and organs for transplantation** Angelika Schnieke, *Livestock Biotechnology, Technical University of Munich, GE*
10:35 – 10:50	**Discussion**
10:50 – 11:15	*Coffee break*

Session: Implications of gene editing for laboratory animals

11:15 – 11:45	**Genetic manipulation – "We can, but should we" … "We can, we will"** Michael V. Wiles, *Technology Evaluation and Development, The Jackson Laboratory, US*
11:45 – 12:15	**Primate gene editing and human complex disease study** Weizhi Ji, *Yunnan Key Laboratory of Primate Biomedical Research, The Institute of Primate Translational Medicine, CN*
12:15 – 12:30	**Discussion**
12:30 – 13:45	*Lunch*

Session: Ecological interventions: revival of species

13:45 – 14:15	**De-extinction: Developing Biotechnologies for Avian Conservation** Ben Novak, *Revive & Restore, US*
14:15 – 14:30	**Discussion**

Session: Regulation & Governance

14:30 – 15:00	**Proposed Regulation of Gene Edited Animals in the US**
	Alison Van Eenennaam, *Department of Animal Science, University of California, US*
15:00 – 15:30	**Genome edited animals: learning from GM crops?**
	Ann Bruce, *School of Social and Political Science, University of Edinburgh, UK*
15:30 – 16:00	**Discussion**

Concluding remarks

16:00	**Concluding remarks**
	Frans Brom, *Scientific Council for Government Policy, NL*

SESSIONS OCTOBER 19th

Genome editing in livestock breeding programs: opportunities and challenges

Dr. ir. Han Mulder
Wageningen University & Research

Genome editing technologies provide new tools for genetic improvement and have the potential to become the next big game changer in animal and plant breeding. The aim of this study was to investigate how genome editing in combination with genomic selection can accelerate the introduction of a monogenic trait in a livestock population as compared to genomic selection alone. A breeding population was simulated under genomic selection for a polygenic trait. Scenarios with and without genome editing were compared for time to fixation of the desired allele, selection response for the polygenic trait, and level of inbreeding. The costs, in terms of the number of editing procedures, were compared to the benefits of having more animals with the desired monogenic trait phenotype.
Genome editing resulted in up to fourfold faster fixation of the desired allele while the loss in long term selection response for the polygenic trait was up to threefold smaller compared to genomic selection alone. With moderate selection on the monogenic trait, the addition of genome editing gave a fourfold reduction of the total number of animals showing the undesired phenotype before fixation. It can be concluded that genome editing strongly decreased the time to fixation for the desired allele compared to genomic selection alone. In addition to ethical and welfare considerations, genome editing in commercial livestock breeding needs careful assessment of technical costs and benefits.

Genome editing in poultry - opportunities and impacts

Dr. Tim Doran
Health & Biosecurity, CSIRO, AU

The application of gene editing in animal agriculture has great potential with many experts predicting that this technology is game changing with respect to breeding of desired traits in livestock species. It enables the rapid introduction of beneficial naturally occurring mutations that already exist within a species or closely related species into elite breeding animals. It is precise and does not introduce deleterious or unwanted traits that arise via traditional selective breeding. We now have the technology to create precise, targeted modifications to the chicken genome. The impacts of this can lead to improved efficiency and sustainability of poultry production to help meet the challenges associated with global food security. Specific innovations that result from gene editing technology will lead to new approaches to managing disease, improving welfare, increasing food safety and enhancing the production and safety of vaccines that are grown in chicken eggs. It is possible that the latest developments in gene editing technology may help to reduce or remove the two major barriers to the acceptance and application of genetic engineering technology in animal agriculture; regulatory approval and public perception. This could pave the way for gene editing and precision breeding to impact on the safe, secure and sustainable production of poultry protein.

Heritable multiplex gene editing via CRISPR/Cas9 exhibits low incidence of off-target mutations in sheep and goats

Dr. rer. nat. Xiaolong Wang
College of Animal Sciences, Northwest A&F University Yangling, CN

The CRISPR/Cas9 system provides an innovative and flexible approach for genome engineering of loci that control economically important traits in livestock. However, off-target mutations that are induced by CRISPR/Cas9 nucleases may lead to unintended negative and undesirable consequences, and are the major obstacle in using this technology in agriculture. We recently generated genetically modified sheep and goats with either one or several genes edited through co-injection of one-cell-stage embryos with Cas9 mRNA and sgRNAs targeting genes (e.g. MSTN for muscle growth, FGF5 for fiber growth, BMPR1B and GDF9 for fecundity) with well-known function. Meanwhile, we carefully analyzed the sgRNAs: Cas9-mediated targeting effects in injected embryos, somatic tissues, as well as gonads via traditional cloning and sequencing approach, demonstrating micro-injection of zygotes as an efficient approach for generating gene-modified small ruminants. We show that the utility of the CRISPR/Cas9 system by gene disruption results in expected phenotypes, for instance, higher body weight in MSTN-disrupted animals and increased hair length in FGF5-disurpted animals. In addition, we performed whole-genome sequencing in three family trios (10×) to assess the potential off-target mutations that where introduced by Cas9 manipulation: no detectable off-target modifications were found that can be attributable to the nucleases. The detection of germline transmission further indicated that the desirable phenotypes have the potential to be transmitted to offspring. We provide the proof of principle that the desirable and heritable phenotypes were acquired in the gene-modified animals, and do not carry detectable off-target mutations. This approach represents a versatile and robust method to produce biologically safe gene-modified small ruminants and other farm animals for breeding.

CRISPR experiences in sheep

Dr. Alejo Menchaca
Institute of Animal Reproduction of Uruguay (IRAUy), Fundación IRAUy, UY

After the first report of gene edited mice using CRISPR in 2013, novel KO and KI models had been generated in livestock species such as pigs, goats and sheep. We have been working in genetic engineered animals using SCNT, lentiviral transgenesis and recently CRISPR/Cas9. In December 2014 we produced our first KO lambs for the myostatin (MSTN) gene. The mutation efficiency achieved in this model was 50.0% (10/20) in embryos and 45.5% (10/22) in born lambs after Sanger sequencing, showing indel mutations at the MSTN gene. Absence of myostatin protein was confirmed after western blot analysis of homozygous KO founders, and they showed heavier body weight than their wild type siblings. In another interesting application, sgRNA were generated in order to induce a mutation at the HYAL2 locus (unpublished). This gene codifies for the receptor of the Jaagsiekte sheep retrovirus, a virus causing ovine pulmonary adenocarcinoma. We obtained acceptable outcomes with 41.7% (5/12) mutant blastocysts after Cas9 protein co-injection, and 66.7% (6/9) using Cas9 mRNA co-injection. Blastocyst were vitrified and subsequently transferred to recipient ewes, achieving 38.5% (25/65) of pregnancy rate. Birth is expected for July 2017 and genotyping and phenotyping of mutant lambs will help to validate the possibility to produce virus resistant farm animals using this technology, as well as to have a better understanding of HYAL2 in different target organs and tissues including reproductive function. In addition, sgRNA for a human point mutation in a gene related to deafness was recently designed in order to study this disability in the sheep model (unpublished). Sheep zygotes were microinjected into the cytoplasm with two sgRNA and Cas9 protein, and the produced embryos were vitrified and transferred to synchronized recipients. Pregnancy rate 30 days after fertilization was 31.3% (27/87) and 26 ewes are still pregnant 60 days after transfer. In summary, the models described above confirm that CRISPR/Cas system has become a relevant tool for the generation of gene edited sheep models, making this technology affordable for many more laboratories around the world. The produced models will have practical implications in the field of livestock production, animal health and medicine.

Target Malaria: step-wise development of genetic mosquito control, from lab to field

Dr. Samantha O'Loughlin
Department of Life Sciences, Imperial College London, UK

To achieve elimination of malaria, new interventions are needed to complement the existing ones, particularly in the most heavily affected areas of sub-Saharan Africa. Target Malaria is developing genetic approaches to vector control, including some using gene-drive technology. We have promising proof-of-principle demonstrations in the lab, but the transition from lab to field will require many considerations beyond the technical; facility management, regulatory knowledge, compliance, engagement, communication, quality control, to name but a few. At Target Malaria we are employing a step-wise, multi-disciplinary approach to developing our technology.

The potential and risks of CRISPR gene drive systems

Jianghong Min
Sculpting Evolution Group, MIT Media Lab, Massachusetts Institute of Technology, US

While the idea of a "selfish-gene" that would drive itself to be inherited by all progeny of an obligate sexually reproductive organism have existed since 1960, active attempts to engineer such a system would not be attempted until Austin Burt's work on homing nuclease based gene drives in 2003. Recent advances in targeted genome editing brought on by the discovery of the CRISPR nuclease Cas9 further enabled this technology by giving rise to RNA-guided gene-drive designs. However, these developments also bring concerns that the technology is too powerful, enabling individuals to unilaterally alter our global shared environment. Thus, we are in need of technologies to intrinsically limit the geological spread of CRISPR gene drive organisms, as deployment of global drive systems ought to be reserved for only the most extreme of circumstances.

To that end, we have been developing locally confined drive systems at the Sculpting Evolution group at MIT Media Lab. Simultaneously, we are using nematodes of the genus Caenorhabditis as a model organism for in vivo investigation of a number of parameters concerning real world applications of gene drives: including but not limited to hereditary stability, evolutionary cost, and containment strategies. We believe that it is important to develop such a model as a testing bed for future application driven gene-drive deployment to help us understand the capabilities of this new technology and to minimize the possibility of unwanted ecological ramifications.

Gene drive technologies for the control of invasive rodents

Prof. John Godwin
Department of Biological Sciences, North Carolina State University, US

Invasive rodents impact biodiversity, human health, and food security worldwide. The biodiversity impacts are particularly significant on islands. Islands are biodiversity hotspots, but have also been the sites of 69%, 90%, and 95% of extinctions of mammals, reptiles, and birds respectively. Rodenticide application is the current main control technology and has produced major conservation benefits, but also has impacts that are concerning and use on inhabited islands is extremely challenging. Genetic Biocontrol of Invasive Rodents (GBIRd) is an international partnership that includes North Carolina State University, University of Adelaide, Texas A&M University, USDA National Wildlife Research Center, Commonwealth Scientific and Industrial Research Organization, Landcare Research, and Island Conservation. GBIRd is focused on the responsible collaborative development and evaluation of gene-drive technology for rodent control with equal emphasis placed on technology development, social and cultural license, and the policy/regulatory environment. Our initial focus is the house mouse, *Mus musculus*, with development and testing of both natural (t-allele) and synthetic gene drive systems. These gene drive systems are intended to skew offspring sex ratios towards either males or females with the goal of reducing reproduction and potentially eliminating invasive rodent populations on islands. This effort also includes assessing characteristics necessary for mating success, testing approaches for spatially-limiting gene drive function, mathematical modeling to inform gene drive development and potential deployment approaches, and structured risk assessment. The partnership is committed to stringent biosafety standards, oversight by an external ethics advisory committee, and early and sustained engagement with stakeholders, communities, and regulatory authorities to facilitate evaluation of the social, cultural, and policy acceptability of genetic biocontrol approaches. Gene drive technologies have the potential to produce significant benefits for biodiversity conservation, human health, and food security. Carefully assessing this potential is important and research must proceed in a transparent, responsible, and inclusive manner.

Pigs for hearts and mice against ticks

Jeantine E. Lunshof, PhD
University of Groningen, NL & Harvard Medical School, US

Gene editing in animals has a very wide range of applications. Some of these applications are in wild living animal populations and aim at altering ecosystems, for example the use of genetic engineering with or without gene drives to control human disease vectors. A very different application is the use of gene editing methods to make alterations in the germ line of domesticated animals, for example to make their organs suitable for transplantation into humans. Ethical considerations differ in many respects, one question being the justification of interventions for the benefit of individual and public health versus the highly individual benefits of organ transplantation.

I will present two examples of studies in which I have been involved as an ethicist. First, the use of genetically engineered mice to combat Lyme disease “Mice against Ticks”, and, second, the successful use of gene editing to remove endogenous retroviruses from pig cells, a first step towards making pig organs suitable for transplantation into humans.

Ethical issues in genome editing of non-human animals

Prof. John Dupré
Centre for the Study of Life Sciences (EGENIS), University of Exeter, UK

Several possible applications of genome editing, notably using CRISPR-Cas9 technology, to livestock are already well-advanced, for example, the production of hornless Holsteins, and of cattle with enhanced TB resistance, and the development of pigs with resistance to African Swine Fever. Editing of Porcine Endogenous Retroviruses from the pig genome greatly advance the possibilities of xenotransplantation. These technologies raise a range of ethical issues that I'll attempt to survey in this talk.

I'll then consider four kinds of ethical issues that are likely to be raised in connection with the technology: (i) the so-called "yuk factor" that was prominent in responses to earlier transgenic techniques; (ii) slippery slope arguments: where is this technology likely to lead? (iii) implications for animal welfare; and (iv) its relation to the wider context of national and global food security. The first seems to me more a problem of communication than of ethical substance, though certainly an issue that must be addressed. The second requires a sophisticated analysis of the nature and function of genomes, and of the limits these provide to targeted modification.

The third and fourth issues raise, I think, the most challenging questions, about the use of animals both as a medium and long term aspect of global food production, and also more widely, for example in medical applications. Serious attention to these issues is, I shall suggest, a precondition for an adequate discussion of the ethical and regulatory challenges presented by these rapidly advancing technologies.

SESSIONS OCTOBER 20th

Reprogramming, gene editing stem cells and organ generation: in vitro and in vivo approaches to increase healthspan

Prof. Juan Carlos Izpisua Belmonte
Gene Expression Laboratory, The Salk Institute for Biological Studies, US

Aging is the major risk factor for many human diseases including organ failure. We will report that partial reprogramming by short-term cyclic expression of Oct4, Sox2, Klf4, and c-Myc (OSKM) ameliorates cellular and physiological hallmarks of aging, tissue and organ physiology and prolongs lifespan in a mouse model of premature aging. The amelioration of age-associated phenotypes by epigenetic remodeling during cellular reprogramming highlights the role of epigenetic dysregulation as a driver of mammalian aging. I will also present recent results on how to genetically modify and reverse the aging process. Finally I will summarize new results of our chimera experiments on how differentiation in vivo, coupled to gene editing, might constitute an avenue for the generation of cell and tissues for transplantation.

Engineering the pig: novel models of human disease and organs for transplantation

Prof. Angelika Schnieke
Livestock Biotechnology, Technical University of Munich, GE

Large animal models of human diseases can bridge the gap between basic biomedical research in rodents and the translation of new knowledge into the clinic to improve diagnosis and treatment. Generating large animals carrying defined genetic modifications has however been hindered for several decades by the lack of embryonic stem cells, but novel technologies including gene editing are now revolutionising the field. Examples of new cancer models (Flisikowska et al., 2012; Saalfrank et al., 2016) will be presented to illustrate technological developments that have enabled us to generate genetically defined livestock models and the improvements and possibilities made possible by gene editing.

Large animals, especially pigs, are also being considered as xenogeneic donors for organ and tissue replacement in humans. This would alleviate the severe shortage of donated human material, but realising this requires overcoming major immunological hurdles and ensuring biological safety of such xenografts. Gene editing has provided tools to solve both issues and help bring xenotransplantation closer to clinical practice. It has allowed us to eliminate both xenoreactive Gal and non-Gal epitopes in a single experiment (Fischer et al., 2016) or, as described by others (Niu et al., 2017), to silence porcine endogenous retroviruses. Beyond xenotransplantation, a yet more radical approach to providing human organs is being investigated; the possibility of growing whole human organs in the pig (Wu et al., 2017).

Recent years have seen unprecedented technical advances, enabling us to modify the genome of many animal species. While these open the way to extraordinary biomedical advances they also raise ethical issues, and the well-being of the animals involved must always be a major consideration.

Fischer *et al*. (2016). Efficient production of multi-modified pigs for xenotransplantation by 'combineering', gene stacking and gene editing. Scientific Reports 6:29081
Flisikowska *et al*. (2012). A porcine model of familial adenomatous polyposis. Gastroenterology 143, 1173-1175.
Niu *et al*. (2017). Inactivation of porcine endogenous retrovirus in pigs using CRISPR-Cas9. Science. pii: eaan4187
Saalfrank *et al.* (2016). A porcine model of osteosarcoma. Oncogenesis 5, e210
Wu *et al*. (2017). Interspecies Chimerism with Mammalian Pluripotent Stem Cells. Cell 168(3):473-486

Genetic manipulation – "We can, but should we" … "We can, we will"

Michael V. Wiles, PhD
Technology Evaluation and Development, The Jackson Laboratory, US

Humankind has progressed from a handful of hunter gathers to ~7.5 billion people and nascent space explorers. This is the result of technology, however all technology is double edged and has a cost. Here I focus on the technological development of genetic engineering, what is and what it can do.

The art of selective breeding to enhance species for man's benefit, ranging from maize, to cattle, to dogs has been used for thousands of years by humans leading to many benefits. In the last 5-10 years this progress has accelerated to the point that now the genome of all species is open to precise genetic modification. In my talk I will briefly review this recent history and explore what these technologies are capable of, their limitations and their potential future.

The first targeted gene modification was limited to mouse embryonic stem cells, however with the development of Zinc Finger Nucleases the genome of all species were opened to precision genetic editing. With the subsequent development of CRISPR these capabilities were further extended. These and similar gene editing tools now give us the capability to knock out (disrupt) genes, execute subtle base modifications perfectly, or even replace large domains or complete genes with base perfect levels of accuracy. These approaches are now being used in academic research, human health (directly and indirectly) and increasingly in agriculture. They are also being considered as a tool to eradicate entire species (e.g. malaria).

"Should governments reconsider and adapt the often strict regulation of animal modification and use of experimental animals?" perhaps – however, I would suggest that like Pandora's box, the box containing CRISPR and similar technologies is already open and cannot be closed.

Lastly, life including human life on this planet is fragile and that perhaps having our genetic destiny within our hands is a next enabling evolutionary step.

Primate gene editing and human complex disease study

Prof. Weizhi Ji
Yunnan Key Laboratory of Primate Biomedical Research, The Institute of Primate Translational Medicine, CN

Human beings have been long facing the challenges of curing complex human diseases. Knowing the mechanism behind the diseases is important but limited due to the lack of suitable animal models. Nonhuman primates (NHP) are believed as an ideal model for complex human diseases since the species have similar genetic background to humans. Precision gene editing technology (TALEN, CRISPR/Cas9) is an efficient tool that has been successfully used to generate monkey models for human diseases. The models show high similarity of disease phenotypes as that of human. Using monkey models, we could understand the process of the disease development that may not be directly observed in patients. However, precision gene editing in primates has to be improved as the efficiency is still lower compared with other species, such as for gene recombination. Though there are reports on the success of gene editing in human embryos using CRISPR technology, the safety and efficiency remain the major concerns for human disease therapy. Given that, NHP models can be ideal model to resolve these problems at this stage.

De-extinction: Developing Biotechnologies for Avian Conservation

Ben Novak, MSc
Revive & Restore, US

Birds are the cornerstone of the modern conservation movement, and continue to inspire passions and scientific interests today. Many innovative programs have saved iconic bird species from extinction, implementing varying levels of intervention including translocation between populations, captive breeding and reintroduction, the use of puppets to raise chicks and planes to teach migration, and now avian conservation is leading the development of genetic guided management.

While birds are at the forefront of conservation concerns and interventions, they have lagged considerably behind other model organisms in biotechnology applications. New advances in biotechnologies make it possible to pursue solutions to intractable problems that can lead to sustainable resilience for ecosystems in the face of growing human influences (i.e. increased agricultural demands, global transportation and trade, and climate change). Biotechnology, in particular genome editing, offers a diverse array of applications for avian conservation from combatting disease, facilitating adaptation, controlling invasive species, aiding population recovery, to de-extinction. De-extinction is arguably the most widely known recently proposed methods for resilience conservation.

Revive & Restore's avian de-extinction programs are among the world's leading endeavors working to unite the proven laboratory biotechnologies for domestic chickens with the genomics and ecological sciences necessary to bring back the environmental roles of extinct birds - the North American passenger pigeon and heath hen. With diverse partners academic, institutional, and aviculturists our projects are outlining the steps to implement genetic rescue for birds from the lab to the environment.

Proposed Regulation of Gene Edited Animals in the US

Alison Van Eenennaam, PhD
Department of Animal Science, University of California, USA

The 1980s US "Coordinated Framework for the Regulation of Biotechnology", is technically agnostic towards the breeding method under review. According to the Office of Science and Technology Policy, "Exercise of oversight should be based on the risk posed by the introduction and should not turn on the fact that an organism has been modified by a particular process or technique". In practice, this is not what happens.
The trigger for U.S. Food and Drug Administration (FDA) regulation of genetically engineered (GE) animals as drugs based on their 2009 "Guidance for Industry #187" is those animals modified by recombinant DNA (rDNA) techniques, including the entire lineage of animals that contain the modification. The rDNA construct in the resulting GE animal is the regulated article that meets the drug definition; the GE animal itself is not a drug. All GE animals trigger regulation, regardless of their intended use. In January 2017, an updated draft Guidance #187 was released which proposed that the presence of ANY "intentionally altered genomic DNA" produced using "modern molecular technologies" in an animal should trigger mandatory, premarket animal drug evaluation, irrespective of product risk or novelty of the genomic alteration. The Guidance includes nucleotide insertions, substitutions, or deletions; however, it clarifies selective breeding and random mutagenesis followed by phenotypic selection are not included as triggers.
There is no science-based rationale for regulating animals exhibiting a genetic trait produced using classical breeding techniques differently from those exhibiting that same trait and DNA sequence as a result of modern molecular techniques like gene editing. The proposed draft Guidance is neither risk-triggered nor process agnostic. It has the potential to capture products with proven safety records (e.g. polled cattle) based solely on the fact alterations were introduced using modern molecular technologies, potentially forestalling useful genetic advances in food animal breeding programs.

Genome edited animals: learning from GM crops?

Dr. Ann Bruce
School of Social and Political Science, University of Edinburgh, UK

Scientific developments have enabled genome edited livestock to come closer to commercial reality, yet questions remain around appropriate regulation, potential impact on the industry sectors and public acceptability of products. This talk will aim to place genome edited livestock into a wider context and to view developments with the lens of lessons learned from GM crops in Europe, in particular the extent to which genome edited livestock satisfy aspirations for social benefits.
I will argue that i) genome edited livestock should not all be considered the same. Risks as well as ethical and social concerns will vary with species and application; ii) slow introduction is more likely to build confidence in 'novel' products, rather than assume that risk assessments by government bodies will be sufficient to engender trust; iii) given that many of the current applications relate to disease resistance, the epidemiological implications of tolerance/resistance in different diseases, particularly for notifiable diseases or zoonoses, should be considered, as should the implications on vets in practice and government veterinary services; iv) current developments in genome editing are being driven by free-market economics, where speed to market will be important, but may not necessarily provide the most socially beneficial applications; v) developments are likely to be driven by large breeding companies, raising questions about food security and impacts on other stakeholders; vi) to what extent can genome edited livestock relate to aspirations to transform global food production systems to become more sustainable?

List of attendees

First name	Surname	Institution/Organisation	Country
Henk	Aanstoot	UMC Utrecht	The Netherlands
Eric	van den Akker	Bureau GGO / RIVM	The Netherlands
Mohammed	Alsultan	College de Heemlanden	The Netherlands
Ator	Ashoti	Hubrecht Institute	The Netherlands
Burak	Atesyurek	Hogeschool Rotterdam	The Netherlands
Cathy	Bakker	Erasmus MC Rotterdam	The Netherlands
Andrew	Bean	CSIRO/VaXIMISER	Australia
Sijne	van der Beek	CRV	The Netherlands
Axel	Beier	Hubrecht Institute	The Netherlands
Hans	van den Berg	VandenbergAdvies	The Netherlands
Sikko	Beukema	Ministry of Economic Affairs	The Netherlands
Marti	Borkent	Erasmus Medisch Centrum Rotterdam	The Netherlands
Jacqueline	Bos	Wageningen University, Social Sciences Group	The Netherlands
Jorik	Bot		The Netherlands
Bernice	Bovenkerk	Wageningen University and Research	The Netherlands
Marjan	Bovers	COGEM	The Netherlands
Wilbrord	Braakman	NLG-Holland .. Braakman bv	The Netherlands
Jan	Braakman	Boerderij	The Netherlands
Annelien	Bredenoord	UMC Utrecht / Eerste Kamer der Staten Generaal	The Netherlands
Didier	Breyer	Scientific Institute of Public Health (WIV-ISP)	Belgium
Danique	Broere	HRO	The Netherlands
Frans	Brom	Scientific Council for Government Policy (WRR)	The Netherlands
Ann	Bruce	University of Edinburgh	United Kingdom
Marion	di Bucchianico	ILT	The Netherlands
Liting	Chen	UMC Utrecht, Regenerative Medicine	The Netherlands / Taiwan
Karin	de Cock	Erasmus MC	The Netherlands
Marion	Cornelissen	Academic Medical Center Amsterdam	The Netherlands
Rene	Custers	VIB	Belgium
Ruqaya	Darweesh		
Ciska	De Ruyver	Faculty of Veterinary Medicine - Ghent University	Belgium
John E.	Degener	UMCG	The Netherlands
Merel	van Dijk	Hogeschool Rotterdam	The Netherlands
Wybo	Dondorp	Maastricht University	The Netherlands
Tim	Doran	Health & Biosecurity	Australia
Clemens	Driessen	Wageningen University	The Netherlands
Jasper	Dumas	Hogeschool Rotterdam	The Netherlands
John	Dupré	University of Exeter	United Kingdom
Dominika	Durechova	Takara Bio	The Netherlands
Puck	Eicher	Utrecht University	The Netherlands
Anne	van den Ende	Utrecht University	The Netherlands

First name	Surname	Institution/Organisation	Country
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Ron	Fouchier	Erasmus MC	The Netherlands
Daryl	Geers	Hogeschool Rotterdam	The Netherlands
Niels	Geijsen	Hubrecht Institute	The Netherlands
Sophie	van Gemeren		The Netherlands
Rogier	van Gent	COGEM	The Netherlands
John	Godwin	North Carolina State University	USA
Catherine	Golstein	Haut Conseil des biotechnologies / High Council for Biotechnology	France
Joana	Gomes Neto	Rijksuniversiteit Groningen, IGEM team 2017	The Netherlands
Danny	Goovaerts		Belgium
Nienke	de Graeff	Utrecht University	The Netherlands
Astrid	Groot	University of Amsterdam	The Netherlands
Elise	Grootscholten	Student Hogeschool Rotterdam	The Netherlands
Bente	Haartsen		The Netherlands
Michelle	Habets	Rathenau Instituut	The Netherlands
Ghazaleh	Hajmousa	AMC (Academic Medical Center)	The Netherlands
Lucien	Hanssen	Member of COGEM	The Netherlands
Sjors	Heijboer	Hogeschool Rotterdam	The Netherlands
Robert	Hoek	Human Environment and Transport Inspectorate	The Netherlands
Petra	Hogervorst	National Institute for Public Health and the Environment (RIVM)	The Netherlands
Lilian	van Hove	Rathenau Instituut	The Netherlands
Ivo	Huijbers	The Netherlands Cancer Institute	The Netherlands
Juan Carlos	Izpisua Belmonte	The Salk Institute for Biological Studies	USA
Ashfaak	Jagga	Hubrecht Instituut	The Netherlands
Weizhi	Ji	The Institute of Primate Translational Medicine	China
Tom	de Jong	Leiden Universiteit / COGEM	The Netherlands
Karin	Jongsma	UMGU	The Netherlands
Darnell	Kammeron		
Eric	Kamst	Hogeschool Rotterdam	The Netherlands
Suus	van de Kar	Utrecht University	The Netherlands
Jozef	Keulartz	Radboud University	The Netherlands
Muhammad Imran	Khan	Radboud University Medical Center	The Netherlands
Tjeerd	Kimman	Wageningen University & Research	The Netherlands
Gijs	Kleter	RIKILT Wageningen University & Research	The Netherlands
Lisette	van der Knaap	COGEM	The Netherlands
Egbert F.	Knol	Topigs Norsvin Research Center BV	The Netherlands
Esther	Kok	RIKILT Wageningen University & Research	The Netherlands
John	Komen	Program for Biosafety Systems	The Netherlands
Bart	Kooi	Wageningen Bioveterinary Research	The Netherlands
Maria	Koster	COGEM	The Netherlands

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First name	Surname	Institution/Organisation	Country
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Lianne	Kraaier	Hubrecht Institute	The Netherlands
Olga	Krabbe	Hubrecht Institute	The Netherlands
Melissa	van Kranenburg	Hubrecht Institute	The Netherlands
Bram	Kuppens	Erasmus MC	The Netherlands
Jan-Karel	Kwisthout	Ministerie Infrastructuur en Milieu	The Netherlands
Luc	van der Laan	Erasmus MC Rotterdam	The Netherlands
Nienke	van Leeuwen	LUMC	The Netherlands
Lin	Lin	Hubrecht Institute	The Netherlands
Marjolein	Lugtigheid		The Netherlands
Jeantine E.	Lunshof	University of Groningen & Harvard Medical School	The Netherlands / USA
Gert	van Maanen	Bionieuws – Netherlands Institute for Biology	The Netherlands
Ruth	Mampuys	COGEM	The Netherlands
Clara	Martinez Mir	Utrecht University	The Netherlands
Shadee	Martis	HR	The Netherlands
Anastasia	Matthies	Federal Office of Consumer Protection and Food Safety	Germany
Miriam	van der Meer	Universiteit van Amsterdam	The Netherlands
Gerrit	Meester	Member COGEM –ScEMA	The Netherlands
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Alejo	Menchaca	Institute of Animal Reproduction of Uruguay	Uruguay
Shazia	Micheal	Academic Medical Centre	The Netherlands
Nemanja	Milićević	Academic Medical Center (AMC)	The Netherlands
Jianghong	Min	MIT Media Lab	USA
Roosmarijn	Minnema	Radboud University Nijmegen	The Netherlands
Hedwig	te Molder	Wageningen University	The Netherlands
Jeanine	van Nieukerken-de Wilde	Stg. Natuurwetmoeders	The Netherlands
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Samantha	O'Loughlin	Imperial College London	United Kingdom
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Ruud	Out	Ntrans Technologies	The Netherlands
Giovanni	Palla	Utrecht University	The Netherlands
Luke	Pattiwaël	Hogeschool Rotterdam	The Netherlands
Miranda	Pellenkoft	LUMC	The Netherlands
Gorben	Pijlman	Wageningen University	The Netherlands
Daniel	de Poel	College de Heemlanden	The Netherlands
Wim	van der Poel	Wageningen University	The Netherlands
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Elise	Rens	HRO	The Netherlands

First name	Surname	Institution/Organisation	Country
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Dick	Roelofs	Vrije Universiteit, Science Faculty, Ecological Science	The Netherlands
Fanny	Sage		The Netherlands
Zeliha	Sahin		The Netherlands
Sybe	Schaap	Chair COGEM	The Netherlands
M.H.W.	Schakenraad	Council on Animal Affairs (RDA)	The Netherlands
Danny	Schildknegt	Netherlands Cancer Institute	The Netherlands
Angelika	Schnieke	Technical University of Munich	Germany
Floor	Schukking		The Netherlands
Astrid	Schulting	COGEM	The Netherlands
Peng	Shang	Hubrecht Institute	The Netherlands
Kari-Pekka	Skarp		The Netherlands
Astrid	Skarp	Hogeschool Rotterdam	The Netherlands
Ulrich	Sperling	SAFOSO AG	Switzerland
Armin	Spök	Alpen-Adria Universität Klagenfurt, Wien, Graz	Austria
Diederick	Sprangers	Genethics Foundation	The Netherlands
M.H.	Spreuwenberg	ILT	The Netherlands
Jan	Staman	Staman advies en verkenning	The Netherlands
Rob	Steenmans	WUR	The Netherlands
Kerwin	Steevensz	School of Engineering and Applied Science	The Netherlands
Anne-Xander	van der Stel	Utrecht University	The Netherlands
Nico	van Straalen	Vrije Universiteit Amsterdam	The Netherlands
Sjaak	Swart	RUG	The Netherlands
Frank	Swartenbroux	European Commission	Belgium
Phoei Ying	Tang		
Alison	Van Eenennaam	University of California	USA
Huub	van der Velden	UMC Utrecht	The Netherlands
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Karlien	Veldscholte	Erasmus MC	The Netherlands
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Irma	Vijn	HollandBio	The Netherlands
Dorien	Vinke		The Netherlands
Marieke	Visscher	Ntrans technologies	The Netherlands
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Huib	de Vriend	LIS Consult	The Netherlands
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Randall	de Waard	HRO	The Netherlands
Arend Jan	Waarlo	COGEM	The Netherlands
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First name	Surname	Institution/Organisation	Country
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Justus	Wesseler	Wageningen University	The Netherlands
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Frank	van der Wilk	COGEM	The Netherlands
Gijsbert	van Willigen	Leiden University Medical Center	The Netherlands
Rob	Wolthuis	Cancer Center Amsterdam	The Netherlands
Zhou	Wu	Wageningen University & Research	The Netherlands
Siyuan	Xing	Wageningen University & Research	The Netherlands
Zhihan	Zhao	Hubrecht Institute	The Netherlands

Note: Attendee list contains registrations until October 9th, 2017

The Netherlands Commission on Genetic Modification (COGEM)

The Netherlands Commission on Genetic Modification (COGEM) is an independent scientific advisory body that provides advice to the government on the potential risks to human health and the environment of the production and use of genetically modified organisms (GMOs) and informs the government of ethical and societal issues linked to genetic modification. COGEM's remit covers all fields from agriculture to medicine and from contained use to deliberate release of GMOs. COGEM advises on environmental risks but not on feed or food safety of GMOs, animal welfare or patient safety (e.g. in relation to gene therapy).

Further information on COGEM and its publications can be found at www.cogem.net

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