Picture: Testbiotech / Falk Heller/ Argum

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Testbiotech
Institute for Independent
Impact Assessment in
Biotechnology

"Stop investment in animal suffering"

Patents on animals and new methods in genetic engineering: Economic interests leading to an increasing number of animal experiments

Christoph Then for Testbiotech, June 2015

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Summary

This report shows how the rising number of experiments carried out on genetically engineered animals is linked to economic interests. It reveals an increasing number of genetically engineered animals coming onto the market as "animal models", and how patents on animals create additional incentives for investment into animal suffering for monetary gain.

Under present circumstances, the genetic engineering of laboratory animals is becoming a self-serving enterprise. Animal models are traded as profitable products, protected by patents and marketed aggressively. In fact, it has to be assumed that the rising number of experiments with genetically engineered animals is not only driven by medical necessity or seeking medical benefits.

In addition to economic interests, new methods in genetic engineering are playing an important role in these developments. Synthetic gene technologies allow the production of countless numbers of animal models. This huge increase in technical feasibility is rapidly overriding the question of what is deemed to be necessary to find potential medical uses.

These developments are in deep conflict with European animal welfare legislation, which requires that animal experiments are reduced to only what is absolutely necessary.

In the light of these findings, several actions are recommended:

- Patents on animals and their usage in animal experiments should be prohibited;
- animals should be endowed with rights and no longer treated as mere objects;
- international initiatives are needed to stop the trade in genetically engineered animals from escalating out of control;
- the genetic integrity of animals should be legally protected;
- all experiments that aim to genetically engineer the genome of animals should be fully registered;
- both the replacement of animal experiments with alternative methods and the development of suitable alternatives must be given greater priority together with basic research;
- companies and investors should define clear ethical standards to avoid economic interest and investment in animal experiments.

1. Introduction

The number of animal experiments has been increasing for many years now. In Germany, around one million genetically engineered animals are currently used per year[1]. Whilst in Germany the overall number of animal experiments was slightly reduced, the number of genetically engineered animals being used was still increasing.

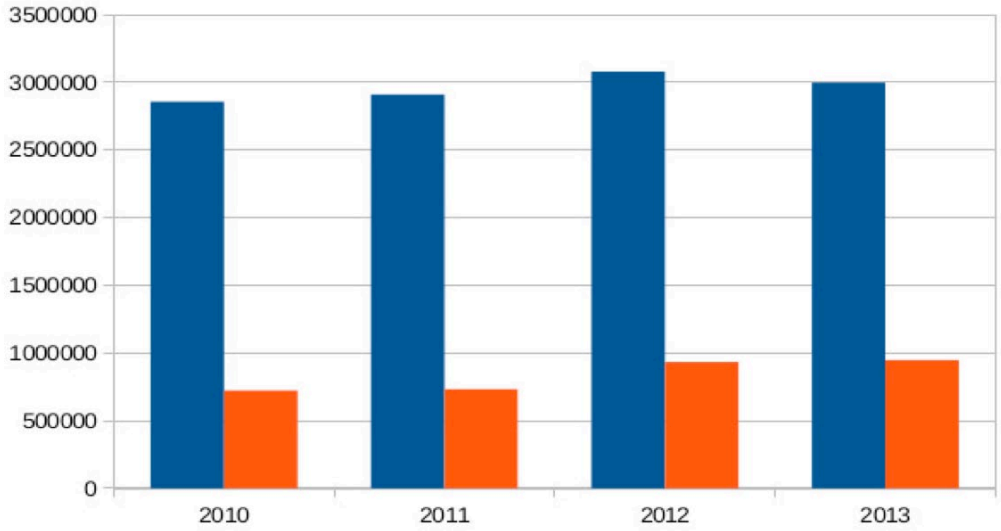


Fig. 1: The number of genetically engineered animals used in experiments has been rising since registration was introduced in Germany.
First column: Overall number of animals used in laboratory experiments.
Second column: number of genetically engineered animals (Source: Bundesministerium für Ernährung und Landwirtschaft, www.bmel.de/SharedDocs/Downloads/Tier/Tierschutz/2013-TierversuchszahlenGesamt.pdf?__blob=publicationFile).

It is mostly basic research that is being carried out with the genetically engineered animals, so these experiments are not required by any legislative framework (such as toxicology testing). It is therefore quite difficult to assess the direct medical benefit in this context.

This development is not only happening in Germany, the EU Commission also states in its latest report on animal experiments that:[2]

> *"Regarding the increase of mice for biological studies of a fundamental nature, Member States indicated that it was due to an increase in research using transgenic mice as specific models (…)"*

In Great Britain, there were more than 4,1 million animal experiments in 2013, which is a slight increase on the previous year, according to official statistics, following an upward trend that has seen the number increase by 1.4 Million since 1995. More than half of the animals were genetically engineered.[3]

This report tries to identify some of the reasons for the steady increase of experiments with genetically engineered animals.

1 This number does not yet include those genetically engineered animals derived from further breeding.
2 http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52013SC0497
3 https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/327854/spanimals13.pdf

2. Patents on animals

The European patents on genetically engineered chimpanzees granted by the European Patent Office (EPO) in 2012 and 2013 are a starting point for this report. It not only deals with these single cases, but also tries to investigate the overall impact that patents on animals have on the balance between economic interests and the aims of animal welfare legislation.

The patent on the so-called oncomouse (EP0169672) was granted by the EPO in 1992. The mice were deliberately genetically engineered to develop cancer within their lifespan. The patent was applied for by Harvard University in cooperation with the US company, DuPont. 17 oppositions were filed against the patent, and discussions went on for more than 10 years. The oppositions were based on Article 53 of the European Patent Convention (EPC), which says that patents on "plant and animal varieties" cannot be granted (Article 53b, EPC). It goes on to say that, "inventions the commercial exploitation of which would be contrary to ‚ordre public' or morality" cannot be granted (Article 53a, EPC). The fundamental legal and ethical questions attached to this case are still not settled.

European patent law and patents on animals

The European Patent Convention (EPC), adopted in 1973, provides the legal framework for the European Patent Office (EPO). The EPO has 38 member states. It is not part of the EU and therefore countries such as Switzerland are also members of the European Patent Organisation.

Art. 53b of the EPC prohibits patents on plant and animal varieties. Until the decision on the oncomouse was made, this article was interpreted in such a way that patents on plants and animals could not be granted. Initially, this was the reason why the patent application for the oncomouse was rejected in 1989. In 1992, the patent was granted, but in 1995 the granting of such patents was stopped again (Decision T356/93).

In 1998, the situation changed again. In response to pressure from industry, the EU adopted the directive "Legal Protection of Biotechnological Inventions" (98/44 EC). Even though the EPO is not part of the EU and is not subject to the jurisdiction of the European Court of Justice, the directive was taken into the Implementation Regulations of the EPC, with no change in the wording of the Articles of the EPC. The EU directive allows an interpretation of the prohibition in Article 53b in a way that is only relevant in those cases where a patent on specific varieties is applied for. Article 4 (2) of the EU directive reads:

"2. Inventions which concern plants or animals shall be patentable if the technical feasibility of the invention is not confined to a particular plant or animal variety."

The EPO subsequently used this wording to grant patents such as the one on the oncomouse, because the method of genetic engineering that was used could be used on various species and was not restricted to a specific variety. This meant that the prohibition could be circumvented and rendered largely ineffective.

Ethical boundaries were also redefined: Article 53a of EPC prohibits patents on "inventions the commercial exploitation of which would be contrary to ‚ordre public' or morality". The EU directive narrows this prohibition down: Article 6 (d) excludes patents on animals only under specific circumstances. It reads:

"(d) processes for modifying the genetic identity of animals which are likely to cause them suffering without any substantial medical benefit to man or animal, and also animals resulting from such processes.".

The EPO took its final decision on the oncomouse patent in 2004[4]. The patent was upheld and covers not only the process used to genetically engineer the animals, but also the animals themselves and their offspring. The claims were, however, reduced to just mice – originally the patent covered all non-human animals.

Who is filing patents on animals?

The oncomouse patent was a breakthrough for industry. Meanwhile around 1500 patents have been granted on laboratory animals, and around 5000 application are pending. Many of these patents have been filed by relatively unknown companies or institutions. But pharmaceutical giants are also amongst the applicants. Out of the ten largest global pharmaceutical corporations, Hoffmann La-Roche (and its subsidiary Genentech), Pfizer and Novartis file the highest number of relevant patent applications. According to database research, they have each applied for around 100 to 400 patents that concern animals and its usages.

Company	Espacenet	WIPO
Hoffmann La Roche + Genentech	89 + 402	78 + 225
Pfizer	356	159
Novartis	164	108

Table 1: Number of patent applications on laboratory animals filed by major pharmaceutical companies (source: data bases Espacenet and WIPO, search criteria IPC=A01K67 or A01K0067)

4 Entscheidung T315/03

Grounds for granting European patents

In recent years, more and more 'animal models', mostly genetically engineered mice and rats have been developed. They are engineered to suffer from 'human diseases'. There are animals which will develop cystic fibrosis, dementia, HIV, diabetes, heart diseases and many more conditions – all of which will supposedly help to develop new therapies and medicines. The oncomouse falls within this category. In general, the animal models have so far not fulfilled expectations. (Bailey, J., 2005). This is also true for the oncomouse. The way in which cancer was enforced in these mice does not reflect the complex causes involved in real life conditions in humans.

Nevertheless, the examiners at the EPO explicitly argued that this animal model would help to reduce animal experiments and be useful in developing new medicines. In fact, the examiners more or less followed the arguments of the patent holder, who in a letter to the EPO of 16 April 1991 claimed:

> *"The Applicant's basic position has always been that the present invention is a very moral invention because it offers the possibility of improved and more expeditious clearance of potential new cancer treatments, and in doing so actually provides the basis for a reduction in the overall extent of animal suffering."*

None of these expectations were fulfilled. No pharmaceuticals were developed with the help of the oncomouse (Arthur, 1993; Vogel, 2001). There was no reduction in the number of animal experiments – on the contrary, the numbers have greatly increased since genetically engineered animals were first introduced into research.

The arguments in favour of granting the patent on the oncomouse are still the same today. If some medical benefit is claimed, the patent will not be subject to the prohibition in Article 53a, EPC.

According to the EPO, if an opposition is filed, the burden of proof lies with the opponent to show that there is no medical benefit. But as the example of the oncomouse shows, at the time when a patent is granted, it is not possible to prove or disprove any medical benefit from using an animal model.

It appears that the EPO has chosen an interpretation of patent law that serves its own interests. The EPO budget depends on fees for the examining and granting of patents. It is simply not in the interests of the EPO to reduce the number of patents. In addition, there is no independent court such as the European Court of Justice to scrutinise the decisions of the EPO. The patent office is not part of the EU, but an intergovernmental institution subject only to its own governance.[5]

Patents are driving the increasing number of animal experiments

Patents on animals are driven by the economic interests of the pharmaceutical and chemical industry in treating animals as nothing more than a commodity that can be exploited to maximise profits. Animals are fast becoming a resource for industrial production processes; they are not being treated as fellow creatures but as an invention of industry.

The oncomouse did not help to reduce the number of animal experiments. After the patent was granted, there was, in fact, a marked increase in the number of patent applications filed for animals.

5 For more on the EPO see : www.epo.org/about-us/organisation.html

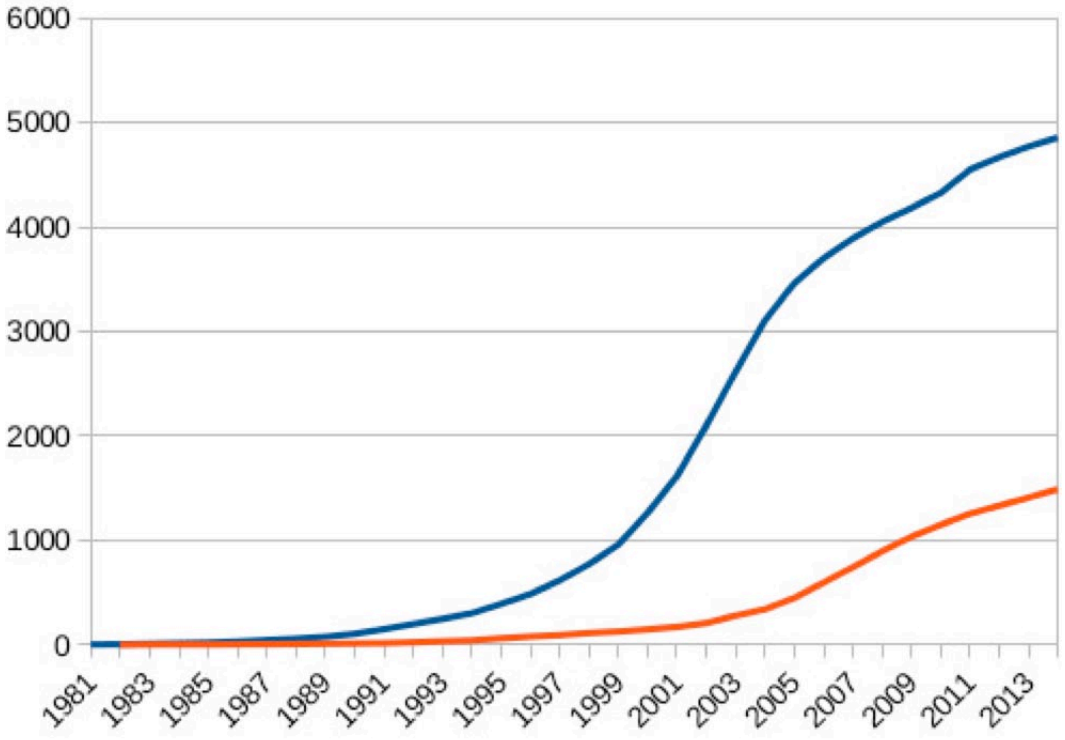
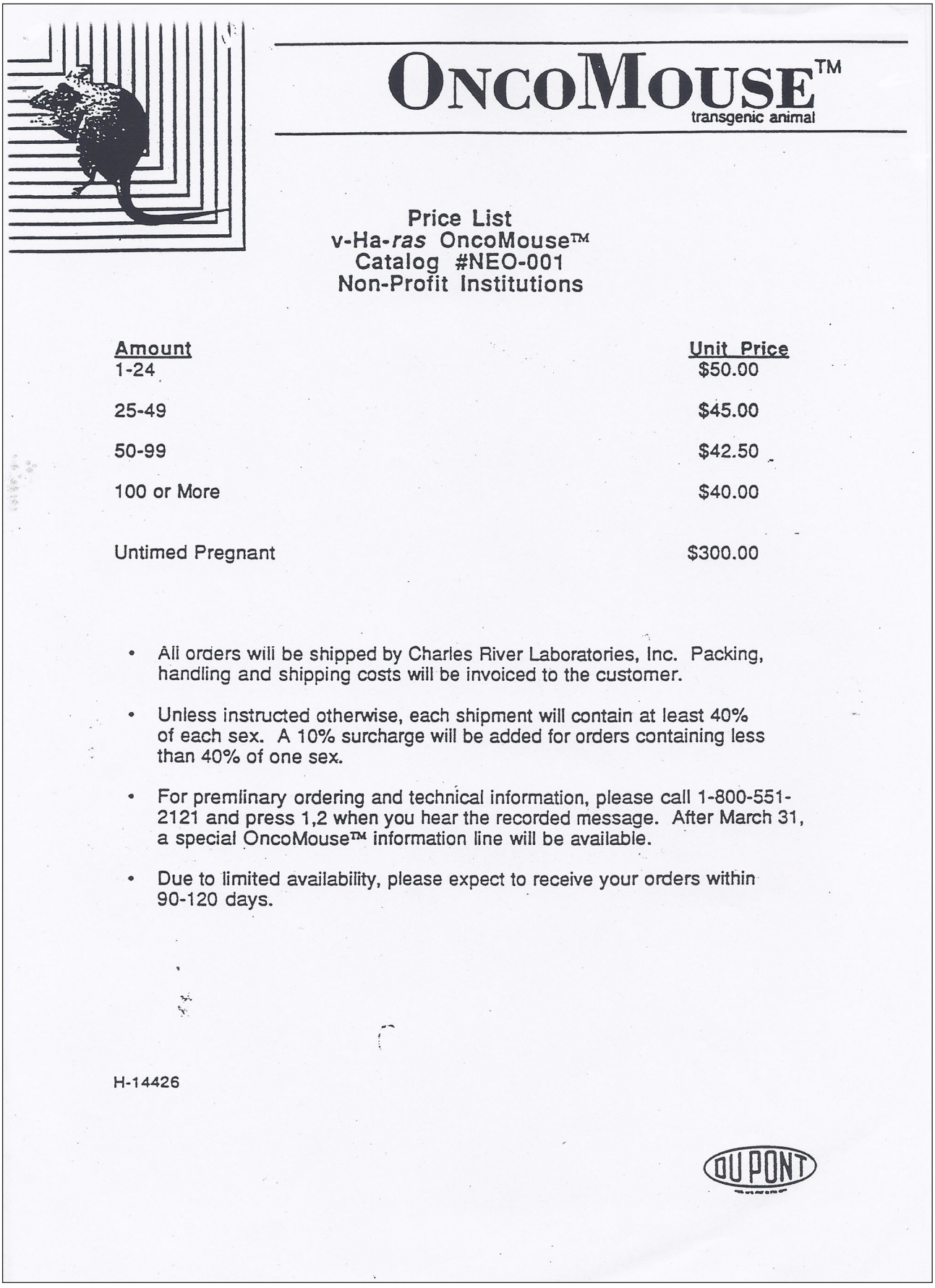


Figure 2: Number of patent applications and patents granted on animals at the EPO since 1981 (accumulated). Source: Global Patent Index, search criteria IPC=A01K67.

It is difficult to say exactly how these patents are impacting the overall number of animal experiments. But there is no doubt that they are generally providing a commercial incentive leading to a substantial increase in animal experiments. Experiments are conducted before the patents are applied for so that they can be listed as examples in the description of the patent to show that it works. Secondly, there is economic pressure to market the patented animals within the period of 20 years that the patent is valid. The oncomouse is a good example: DuPont started marketing the oncomouse in the 1990s, aiming to sell the animals to the pharmaceutical industry.

Patents on laboratory animals are themselves clear evidence that companies and their investors have very few scruples in making profits from animal suffering. There is a huge gap between what might be considered necessary for future medical benefit and the actual number of animal experiments being performed. Animal experiments are then simply an end in themselves carried out for no clear purpose. This is in deep conflict with European animal welfare legislation, which requires that animal experiments are reduced to only what is absolutely necessary.



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v-Ha-*ras* OncoMouse™
Catalog #NEO-001
Non-Profit Institutions

Amount	Unit Price
1-24	$50.00
25-49	$45.00
50-99	$42.50
100 or More	$40.00
Untimed Pregnant	$300.00

- All orders will be shipped by Charles River Laboratories, Inc. Packing, handling and shipping costs will be invoiced to the customer.
- Unless instructed otherwise, each shipment will contain at least 40% of each sex. A 10% surcharge will be added for orders containing less than 40% of one sex.
- For premlinary ordering and technical information, please call 1-800-551-2121 and press 1,2 when you hear the recorded message. After March 31, a special OncoMouse™ information line will be available.
- Due to limited availability, please expect to receive your orders within 90-120 days.

H-14426

DUPONT

Fig. 3: DuPont was actively marketing the oncomouse in the 1990s.

3. New methods in genetic engineering

In 2007, the Noble Prize was awarded to three researchers who had developed a method to block gene functions in mice ("knock out") in a targeted way. This technique became more widely available in the 1990s making it feasible to investigate various gene functions in mammals. Most of these experiments were conducted as part of basic research from which no direct medical benefit was expected. There was, nevertheless, a substantial increase in the number of experiments using genetically engineered animals.

Synthetic gene technologies

In recent years, other new methods have been developed to genetically engineer mammals. In particular, the ability to synthesise DNA in the laboratory has paved the way for a new dimension in genetic engineering. There are already some microorganisms which have a completely synthesised genome (Gibson et al., 2010). Synthesising DNA means that the structure of the DNA can be radically changed to create organisms with artificial DNA that no longer have a natural template.

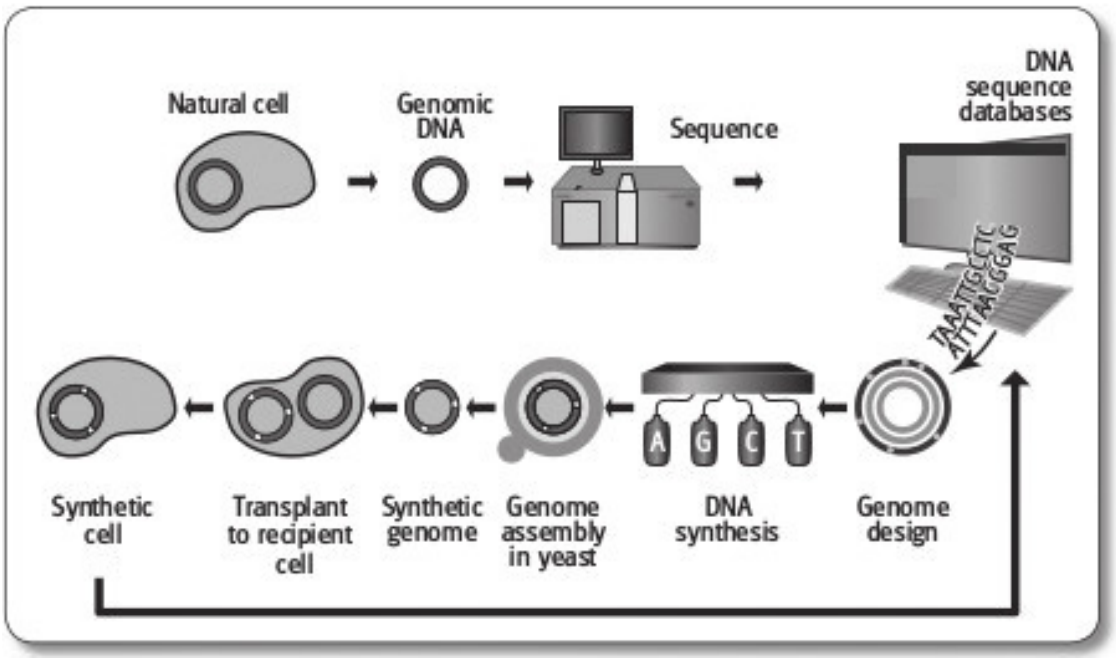

Fig. 4: DNA analysis and DNA synthesis go hand in hand. S
ource: US Presidential Commission for the study of bioethical issues[6]

Other new methods have also been established to genetically engineer laboratory animals. In particular, these include processes using so-called DNA – scissors (nucleases) which can 'cut' the genome at a targeted site to silence genes ("knock out") or to insert synthetic DNA ("knock in").

6 www.bioethics.gov/documents/synthetic-biology/PCSBI-Synthetic-Biology-Report-12.16.10.pdf, überabeitet in "Handbuch Agro-Gentechnik", C. Then, Oekom Verlag 2015.

Nucleases are proteins (enzymes) which can be used to splice DNA, hence the term "DNA scissors" or "gene scissors". The current star of the nuclease family is known as CRISPR-Cas. CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) and consists of a guide-RNA region, which can match with a targeted DNA sequence. RNA is capable of mirroring and 'recognising' DNA structure, so that the CRISPR-Cas system can be directed to specific sequences in the genome. The Cas enzyme, which is coupled with the tracer-RNA, operates as the 'DNA scissor' and can 'cut' a single DNA strand or both simultaneously.

Since the possibilities of the CRISPR-Cas system were first discovered some two or three years ago, publications have grown rapidly and there are already commercial applications for its use in laboratory animals. Other gene scissor systems such as TALEN (Transcription Activator-Like Effector Nucleases) and Zinc Finger Nucleases function along similar lines but have proved more difficult to operate.

The new methods available are very different to the methods currently known as genetic engineering. Some characteristics of these new technologies are:

- It is not necessary to isolate DNA from living beings, the DNA can be directly synthesised in the laboratory.
- The structure of the DNA does not depend on naturally existing genomes, it can be designed in the laboratory without a native template or be a combination of DNA from various organisms.
- Some applications enable direct alteration of the genome in the cells, without isolating or transferring DNA (so-called genome editing).
- The technical possibilities of changing the regulation of the natural genome without changing the structure of the DNA are becoming increasingly important.

There are some scientists who even want to use this method to transform one species into another, going step-by-step, inducing many single changes of the genome. According to George Church, this technology could be used to transform the genome from a human into the genome of a Neanderthal (Church & Regis, 2012):

"The same technique would work for the Neandertal, you would start with a stem cell genome from a human adult and gradually reverse-engineer it into the Neandertal genome or a reasonable close equivalent. … If society becomes comfortable with cloning and sees value in true human diversity, the whole Neandertal creature itself could be cloned by surrogate mother chimp - or by an extremely adventurous female human."

Profitable markets for genetically engineered animals

There are several companies that sell animal models such as mice and rats which have had DNA inserted at a targeted location ("knock-in"). These animals are produced on demand as "custom engineered rodents" and are delivered within a few months. The new technologies are patented, and often include the animals. For example, in February 2014, Cellectis received a European Patent on **all plants and animals** that are engineered with specific DNA-scissors called meganucleases (EP2231697).

Meanwhile there is a profitable market for these animal models. US companies such as Applied StemCell, Creative Animodel and Cyagen Biosciences are aggressively promoting their genetically engineered animals, and even sell them like special offers in supermarkets. These companies might not have their own patents, but will have acquired a licence to use them. Creative Animodels, for example, has on offer new generations of oncomice and apes as animal models to test potency pills. Cyagen Biosciences even makes use of promotional rewards. Customers who place an order for genetically engineered mice will receive a 10 percent discount and can choose between a fluffy mouse and a coffee machine as a reward. If customers recommend new clients they will receive a voucher to spend in an Apple store. Customers can order genetically engineered mice from Cyagen Biosciences for 17 250 US dollars, genetically engineered rats for 18 250 US dollars and so on (prices quoted for 2013). And naturally strict confidentiality applies to all enquiries and orders.

The following pictures were taken from specific websites (www.appliedstemcell.com/, www.creative-animodel.com/, www.cyagen.com/) in May 2015, and quotations were taken from electronic newsletters sent out between 2013 and 2014. This aggressive mode of marketing by companies such as Applied StemCell, Creative Animodel and Cyagen Biosciences shows that producing genetically engineered animals for use in experiments has become a lucrative business. It is very hard to believe that the increase in experiments with genetically engineered animals is driven solely by a desire to increase medical benefits.

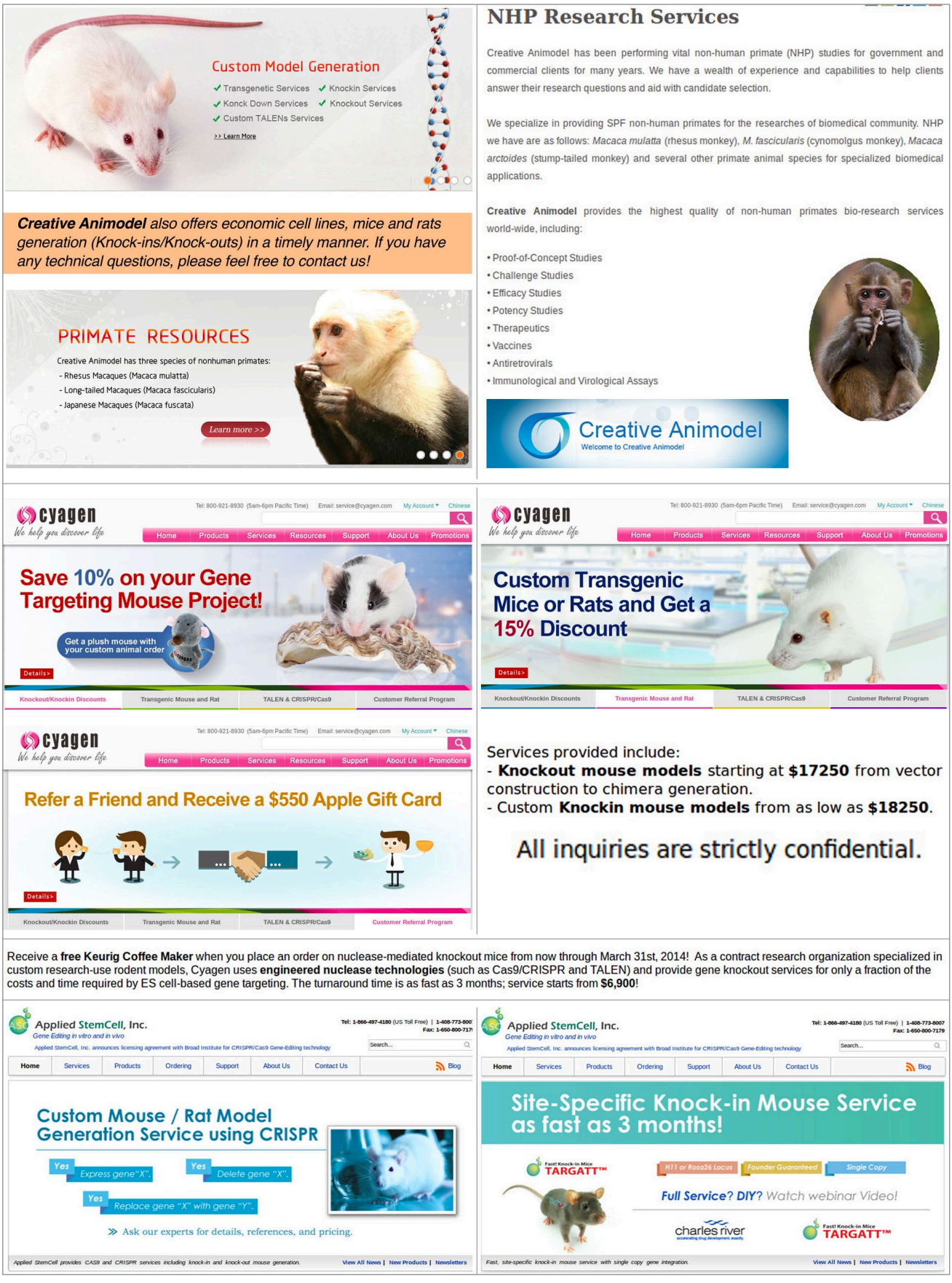

Fig 5: Applied StemCell, Creative Animodel and Cyagen Biosciences promote their animal models on websites and in electronic newsletters. Sources: www.appliedstemcell.com/, www.creative-animodel.com/, www.cyagen.com/

4. Patents on genetically engineered chimpanzees

One particular problem lies in the commercial incentives that could lead to animal experiments with great apes and other non-human primates. Great apes are our closest relatives in the animal kingdom, and increasing research into animal behaviour is making it more difficult to explain the difference between humans and species such as chimpanzees and bonobos. There is, in fact, a strongly emerging debate about whether these non-human and highly protected animals deserve to be given a legal status similar to that of humans (see http://www.greatapeproject.org/).

Experiments with great apes are more or less prohibited under EU Directive 2010/63/EU "On the protection of animals used for scientific purposes". That is because the legislators accepted that causing suffering to great apes (including chimpanzees) in the name of science is ethically unacceptable to EU citizens, irrespective of any benefit from their use.

Nevertheless, the European Patent Office has granted several patents that specifically claim genetically engineered chimpanzees as an invention. Several organisations have filed oppositions against four of these patents held by Altor Bioscience (US), Bionomics (Australien) and Intrexon (US). Amongst those are the following organisations: Albert Schweitzer Stiftung für unsere Mitwelt, British Union for the Abolition of Vivisection (BUAV), Deutscher Tierschutzbund, Gen-ethisches Netzwerk (GeN), GeneWatch UK, Gesellschaft für ökologische Forschung, Jane Goodall Institute (Germany), Kein Patent auf Leben!, Menschen für Tierrechte - Bundesverband der Tierversuchsgegner e. V., Pro Wildlife, Schweizerische Arbeitsgruppe Gentechnologie (SAG), Schweizer Tierschutz (STS), TASSO e.V., Testbiotech and the Wild Chimpanzee Foundation, Germany (WCF). Furthermore, more than 15.000 people signed the oppositions.

According to the text of the oppositions, the patents violate Article 53a, EPC, and are contrary to 'ordre public' or morality". Accordingly, mammals and especially chimpanzees cannot be regarded as a human 'invention'. The following chapters give an overview of the content and the background of these patents.

Case study 1: Patent held by Altor Bioscience

The Altor BioScience Corporation[7] was founded in 2002 and is a spin-off from another company, Sunol Molecular. One of its key products under development is ALT-836, a monoclonal antibody that is meant to bind to human immune factors as an inhibitor. Altor Bioscience holds an exclusive licence from Genentech (a member of the Roche group) to develop and commercialise a class of antibody-based antagonists that are involved in immune reactions. Products of Altor Bioscience (and similar Sunol Molecular products) are tested in animal experiments using great apes such as chimpanzees and bonobos (Jiao, et al., 2010; Welty-Wolf et al., 2006).

The patent EP 1409646 held by Altor BioScience was granted in June 2012. The patent claims transgenic animals whose DNA is manipulated in such a way that their immune system is "humanised". These animals are intended for the study of immune reactions and testing of pharmaceutical substances such as the antibodies mentioned above. The idea is to use a broad range of transgenic animals for this purpose.

7 http://altorbioscience.com/

Fig. 6: Protest in front of the European Patent Office (source: Testbiotech / Falk Heller/ Argum)

As described in the patent:

> *"[0020] A preferred non-human transgenic animal host for the present invention is a mouse, however, any animal that can be manipulated transgenically and has an immune system capable of carrying out required recombination and expression events of the present invention may serve as a non-human transgenic animal host. Additionally preferred animals include, but are not limited to, rat, chimpanzee, other primates, goat, pig, or zebrafish."*

The claims of the patent are not restricted to any specific animal species:

Claim 1 very generally claims all non-human transgenic animals that are genetically engineered as described in the patent thereby claiming all kinds of animal species, including great apes e.g. chimpanzees. Claims 28-35 list a number of animals which can be said to be examples of preferred species, but do not restrict the patent to the species as listed:

> *"28. The non-human transgenic animal of any one of the preceding claims, wherein said animal is any animal which can be manipulated transgenically.*
>
> *29. The non-human transgenic animal of any one of claims 1-28, wherein said animal is a mouse.*
>
> *30. The non-human transgenic animal of any one of claims 1-28, wherein said animal is a rat.*
>
> *31. The non-human transgenic animal of any one of claims 1-28, wherein said animal is a primate.*
>
> *32. The non-human transgenic animal of any one of claims 1-28, wherein said animal is a chimpanzee.*
>
> *33. The non-human transgenic animal of any one of claims 1-28, wherein said animal is a goat.*
>
> *34. The non-human transgenic animal of any one of claims 1-28, wherein said animal is a pig.*
>
> *35. The non-human transgenic animal of any one of claims 1-28, wherein said animal is a zebrafish."*

Case study 2: The patent held by Bionomics

Bionomics[8] is based in Australia and has applied for several patents claiming genetically engineered chimpanzees, some of them granted in Europe. EP1364025 was granted in July 2013. The company claims as an invention human genes presumed to play a role in the prevention of cancer. According to the patent, the genes will be used to genetically manipulate the chimpanzees. As a result of the genetic manipulation, the great apes may be more susceptible to developing cancer.

Fig. 7: Protest in front of the European Patent Office (source: Testbiotech / Falk Heller/ Argum)

Claims 35 and 36 of the patent cover mammals in which specific genes linked to cancer have been changed or silenced. The following animal species are claimed: rats, mice, hamsters, guinea pigs, rabbits, dogs, cats, goats, sheep, pigs and non-human primates such as monkeys and chimpanzees.

The wording of the claims is as follows:

> *"35. A genetically modified non-human animal selected from the group consisting of rats, mice, hamsters, guinea pigs, rabbits, dogs, cats, goats, sheep, pigs and non-human primates such as monkeys and chimpanzees, transformed with an isolated nucleic acid molecule as defined in any one of claims 1 to 5.*
>
> *36. A genetically modified non-human animal selected from the group consisting of rats, mice, hamsters, guinea pigs, rabbits, dogs, cats, goats, sheep, pigs and non-human primates such as monkeys and chimpanzees, in which homologous BNO1 gene and gene function has been knocked out."*

Further in claim 37, usage of the animals is claimed as follows:

> *"37. The use of a genetically modified non-human animal as defined in either one of claims 35 or 36 in screening for candidate pharmaceutical compounds."*

At the end of 2014, in response to the oppositions, the company informed the EPO that it was withdrawing the controversial claims.

8 www.bionomics.com.au/

Case study 3: Patents held by Intrexon

Intrexon sees itself as "a leader in synthetic biology". According to the Intrexon website (2014[9] their business is about to take control of the biological functions of all kinds of species:

"Intrexon Corporation is [...] focused on the industrial engineering of synthetic biology [...] The company's advanced bioindustrial engineering platform enables [...] unprecedented control over the function and output of living cells."

The new technologies will also be used to produce animals for food: Intrexon is active in pharmaceuticals as well as in agriculture. Some members of its management team worked for Monsanto before joining Intrexon. It has also acquired companies that, for instance, clone livestock or produce genetically engineered salmon.

Fig. 8: Protest in front of the European Patent Office (source: Testbiotech / Falk Heller/ Argum)

Intrexon holds two European patents that include genetically engineered chimpanzees:

Patent EP 1572862 was granted in August 2012. In claims 45 to 50 all non-human organisms manipulated with synthetic DNA produced by Intrexon are patented as described. Other animal species that are claimed include a mouse, rat, rabbit, cat, dog, bovine, goat, pig, horse, sheep, monkey, chimpanzee.

The wording of the claims is:

"45. A non-human organism comprising the host cell of claim 39.

46. The non-human organism according to claim 45, wherein the non-human organism is selected from the group consisting of a bacterium, a fungus, a yeast, an animal, and a mammal.

9 www.dna.com/

47. The non-human organism according to claim 46, wherein the mammal is selected from the group consisting of a mouse, a rat, a rabbit, a cat, a dog, a bovine, a goat, a pig, a horse, a sheep, a monkey, and a chimpanzee.

48. A non-human organism comprising the host cell of claim 42.

49. The non-human organism according to claim 48, wherein the non-human organism is selected from the group consisting of a bacterium, a fungus, a yeast, an animal, and a mammal.

50. The non-human organism according to claim 49, wherein the mammal is selected from the group consisting of a mouse, a rat, a rabbit, a cat, a dog, a bovine, a goat, a pig, a horse, a sheep, a monkey, and a chimpanzee."

A very similar patent, EP 1 456 346 was granted in February 2012. In claims 48 to 53 all non-human organisms manipulated with synthetic DNA produced by Intrexon are patented as described. Amongst others, the following animal species are claimed: a mouse, rat rabbit, cat, dog, bovine, goat, pig, horse, sheep, monkey and chimpanzee.

5. Politics, industry and investors have to take responsibility

This report describes some parallel and largely synergistic developments:

- The number of animal experiments with genetically engineered animals has been increasing for several years.
- New techniques in genetic engineering allow radical changes in the genome of laboratory animals.
- There is evidence of a lucrative market for genetically engineered animals offered for sale as "animal models".
- Granting patents on animals generates additional financial incentives for investing in animal suffering.

As a consequence, there is a growing trend towards an increasing number of animal experiments that is not solely driven by what might be deemed necessary to achieve future medical benefits, but also by economic interests in marketing genetically engineered animals.

In Germany, animal welfare is part of the constitution and rigorously enforced. Animal experiments are only possible within narrow legal boundaries. They have to be authorised and are assumed to be in accordance with ethical standards only if they are reduced to what is absolutely necessary. However, current laws do not seem to be sufficiently robust to reverse the trend towards more and more animal experiments, especially in the field of genetic engineering.

New methods of genetic engineering are largely responsible for current trends. Synthetic gene technologies allow the production of a limitless number of animal models. The question is how to counteract this development, for example, how do we justify the serial production of genetic defects in animals ("knock out")? The huge increase in technical feasibility is rapidly overtaking the question of what is really necessary in regard to potential medical benefit.

We need to rethink and set new priorities. Ethical questions deserve more attention and existing laws need updating to be sufficiently robust. The purpose of animal welfare legislation is to weigh up animal suffering against potential medical benefit. But the existing legal framework is insufficient to deal with the dynamics of highly profitable markets. These markets will create new ways and means to circumvent existing laws. For example, international companies can conduct their experiments in countries with lower legal standards. It is also quite probable that the authorities will not be informed about all the experiments requested by European companies since all enquiries and requests are treated as "strictly confidential". Thus, the real number of animals used in experiments might be much higher than officially registered. International initiatives would be required to regulate the trade in genetically engineered animals, similar to those regulating the trade of endangered species.

Further possible legal action would be a prohibition of patents on animals and a change in the legal status of animals, which should no longer be regarded as mere objects but be respected as having their own rights. In this context, the protection of the genetic integrity of animals could be established in law. Further, the replacement of animal experiments by alternative methods has to be given much higher priority.

The responsibility for reducing animal experiments has to be shared by the companies that conduct or commission animal experiments and investors in this field. But as far as we know, in this regard, there is almost a complete lack of standards for ethically acceptable investment.

The problem goes beyond the genetic engineering of laboratory animals. In April 2015, the public was alarmed about experiments conducted in China. For the first time a scientific publication reported the application of DNA-scissors (CRISPR-Cas) on human embryos (Liang et al., 2015). In point of fact, the scientists themselves were warning against taking these experiments any further. However, in this case it will be decisive whether or not binding international regulations can be established.

6. Conclusions

There are good reasons to assume that the increasing number of animal experiments is at the very least partially due to economic interests. Animal models (genetically engineered laboratory animals such as mice) have become a profitable product, protected by patents and marketed aggressively. Animal experiments are becoming a self-serving enterprise, with increasing numbers driven by supply and demand. The balance, between what is considered necessary for future medical benefit and the number of animal experiments actually being performed has become heavily distorted.

Developments are in deep conflict with the aims of European animal welfare legislation, which requires that animal experiments are reduced to only those that are absolutely necessary. Existing laws do not seem to be sufficiently robust to reverse the current trend of ever more animal experiments, especially in the field of genetic engineering.

In the light of these findings, several actions are recommended:

- Patents on animals should be prohibited;
- animals should be endowed with rights and no longer treated as mere objects;
- international initiatives are needed to stop the trade in genetically engineered animals from escalating out of control;
- the genetic integrity of animals should be legally protected;
- both the replacement of animal experiments with alternative methods and the development of suitable alternatives must be given greater priority together with basic research;
- companies and investors should define clear ethical standards to avoid economic interest and investment in animal experiments.

References

Arthur C. (1993) „The oncomouse that didn't roar. New Scientist, Nr. 1879, 26. Juni 1993.

Bailey, J. (2005) Man Or Mouse: Genetically Modified Animals in Medical Research. A Critical Review. Animal Aid

Church, G., Regis, E. (2012) Regenesis, how synthetic biology will reinvent nature and ouselves. Basis Books, New York.

Gibson, D. G., Glass, J. I.,Lartigue, C., Noskov, V. N., Chuang, R. Y., Algire, M. A., Benders, G. A., Montague, M. G., Ma, L., Moodie, M. M., Merryman, C., Vashee, S., Krishnakumar, R., Garcia, N. A., Pfannkoch, C. A., Denisova, E. A., Young, L., Qi, Z. Q., Segall-Shapiro, T. H., Calvey, C. H., Parmar, P. P., Hutchison, C. A., Smith, H. O., Venter, J. C. (2010) Creation of a Bacterial Cell Controlled by a Chemically Synthesized Genome, Science, 329(5987): 52-56.

Jiao, J.A., et al. (2010) Inhibition of acute vascular thrombosis in chimpanzees by an anti-human tissue factor antibody targeting the factor X binding site. Thromb Haemost, 103(1): 224-33.

Liang, P., Xu, Y., Zhang, X., Ding,C., Huang, R., Zhang, Z., Lv, J., Xie, X., Chen, Y., Li, Y., Sun Y., Bai, Y., Songyang, Z., Ma, W., Zhou C. Huang, J. (2015) CRISPR/Cas9-mediated gene editing in human tripronuclear zygotes. Protein Cell 6(5): 363–372.

Vogel, B. (2001) Oncomouse TM, eine Recherche zur medizinischen und kommerziellen Bedeutung der Harvard-Krebsmäuse. Greenpeace Report.

Vogel, G. (2015) Embryo engineering alarm, researchers call for restraint in genome editing. Science, 347(6228): 1301.

Then, C. (2015) Synthetische Gentechnik und ihre Anwendung bei Pflanzen und Tieren in der Landwirtschaft, Testbiotech Basis-Text 22-1-2015, www.testbiotech.org/sites/default/files/Testbiotech_Basis_Text_Synthetische%20Gentechnik.pdf

Welty-Wolf, K.E., et al. (2006) Blockade of tissue factor-factor X binding attenuates sepsis-induced respiratory and renal failure. Am J Physiol Lung Cell Mol Physiol, 290(1): L21-31.