Opposition against European Patent EP 1409646 B1

Title: TRANSGENIC ANIMALS COMPRISING A HUMANIZED IMMUNE SYSTEM

TRANSGENE TIERE MIT HUMANISIERTEM IMMUNSYSTEM

Application number: 01994325.7

Proprietor: Altor BioScience Corporation, Miramar, Florida 33025 (US)

Date of publication of the grant of the patent: 13.06.2012

Date of the opposition: 07.3.2013

Fee for the opposition paid into EPO bank account: Commerzbank München, BLZ (Sort Code) 700 800 00, (Account No.) KtNr. 3 338 80000

List of opponents:

Albert Schweitzer Stiftung für unsere Mitwelt

Deutscher Tierschutzbund

Gen-ethisches Netzwerk (GeN)

GeneWatch, UK

Gesellschaft für ökologische Forschung

Jane Goodall Institut

Kein Patent auf Leben!

Menschen für Tierrechte, Bundesverband der Tierversuchsgegner e. V.

Pro Wildlife

Schweizerische Arbeitsgruppe Gentechnologie (SAG)

Schweizer Tierschutz (STS)

Christoph Then supported by Testbiotech

Wild Chimpanzee Foundation, Germany (WCF)

Further see list of 498 individuals which signed against patent on chimpanzees (attached)

Postal address for communication with the opponents:

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Revocation of the whole patent and if necessary a public hearing of the opposition is requested.

The grounds for opposition are Art 53a, EPC and Art 83, EPC.

1. Background information on the patent

The company, Altor BioScience Corporation, founded in 2002, is a spin-off from another company, Sunol Molecular. One of its key products under development is ALT-836, is a monoclonal antibody that is supposed to bind to human immune factors as an inhibitor (see attached ALT-836 Factsheet, D1). Altor holds an exclusive license from Genentech (a member of the Roche group) to develop and commercialise a class of antibody-based antagonists that are involved in immune reactions.

The patent claims transgenic animals whose DNA is manipulated in such a way that their immune system is "humanized". 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. 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."

- Claims 35 – 57 are claims on the methods to produce the animals as described. These claims also extend to the animals through product by process.

- Claims 58 and 59 again very generally claim transgenic non-human animals.

Products of Altor (and similar Sunol Molecular products) are actually tested in animal experiments using great apes such as chimpanzees and bonobos, as shown by two publications in which some of the experts involved are also named as inventors of the patents filed by Sunol and/ or Altor:

- D2: Jiao, J.A., et al., Inhibition of acute vascular thrombosis in chimpanzees by an anti-human tissue factor antibody targeting the factor X binding site. Thromb Haemost, 2010. 103(1): p. 224-33.
- D3: Welty-Wolf, K.E., et al., Blockade of tissue factor-factor X binding attenuates sepsis-induced respiratory and renal failure. Am J Physiol Lung Cell Mol Physiol, 2006. 290(1): p. L21-31.

Genentech which is licensing exclusive rights to Altor to develop and commercialise a class of antibody-based antagonists that are involved in immune reactions, seems to be aware of the ethical problems related to animal experiments involving great apes such as chimpanzees. In an e-mail message to Testbiotech that was sent on 23 October 2012, a spokesperson of the Roche Group/ Genentech, Nadine Pinell, states:

> “I read your article this morning titled 'European Patent Office issues patents on chimpanzees'.
>
> Below please find a statement from Genentech about the use of chimpanzee in biomedical research . I'd be grateful if you'd consider updating your report to include our perspective.
>
> Genentech Statement
> Genentech researchers are always looking to use fewer animals and possible alternatives to address scientific questions. While the chimpanzee was a useful and necessary animal model in the past, technological advances in monoclonal antibody technology and production overrides the value of limited data obtainable from chimpanzee studies.
> Genentech does not advocate the use of chimpanzees for testing of antibodies, unless there is no alternative or the use of chimpanzees has the potential to provide great benefit in treating life-threatening diseases.
>
> Genentech would support legislation to oppose the use of chimpanzees for biomedical research, unless there is no alternative or the use of chimpanzees has the potential to provide great benefit in treating life-threatening diseases.
> ###
>
> Best regards,
> Nadine
>
> --
> Nadine Pinell
> Senior Manager, External Communications
> Corporate Relations
> Genentech, A Member of the Roche Group

We welcome the statement if it helps to avoid animal experiments. At the same time, we also have to state that filing patents on genetically engineered chimpanzees is a clear signal that not only medical necessities, but also commercial interests play a significant role in the decision making process. Thus, Genentech / the Roche group should also make clear that patents like EP 1409646 should neither be filed nor granted.

2. Patents and animal welfare

Patents are seen as an incentive to promote technology via trade monopolies. In this case, the technology involves living matter, most especially mammals that can suffer from pain and stressful conditions. This patent does not provide an incentive to develop pharmaceuticals, but rather to perform animal experiments.

From a scientific perspective, animal experiments are not of commercial interest per se, but a tool for scientific research. This patent, however, introduces a commercial aspect into the production of transgenic animals and decision-making on animal experiments. In other words, the transgenic animal itself becomes a product that can be produced and commercialised over a period of 20 years (the duration of the patent) at maximum profit – just like any other patented product.

Therefore, this patent creates a severe ethical conflict with animal welfare issues, which needs to be dealt with in patent law and cannot be resolved by general animal welfare legislation. While it is true that patents do not allow or forbid animal experiments, and that animal welfare legislation has to be obeyed when relevant experiments are conducted, it is not true that this legislation can prevent commercial abuse of the patent at stake. There are several ways to escape regulation if sufficient financial incentives are created. For example, transgenic great apes could be produced in countries with lower animal welfare legislation standards. Further, it has to be taken into account that the patent covers all kind of animal species less regulated by law. Thus, there is no doubt that the patent can be seen as providing incentives for additional animal experiments, and can contribute to an increase in the use of laboratory animals.

To assess the true range of problems associated with these kinds of patents, a more general perspective can be useful. The European Patent Office has been granting patents on genetically engineered animals since 1992. Since that time, not only have more than a thousand patents on animals been granted, there has also been a steady increase in the number of animal experiments in this area. This is highlighted in a recent statistical overview for the year 2011, published by German authorities (D4).

Following the logic behind the system, far from having a neutral effect it is likely that patents are a driving factor. For example, it can be assumed that animal experiments had to be conducted in order to apply for several thousand of the patents filed at the EPO. Further, it is likely that at least some

patent holders were trying to push the marketing of their patented animal models, and as such have a particular commercial interest in enhancing the use of these animals.

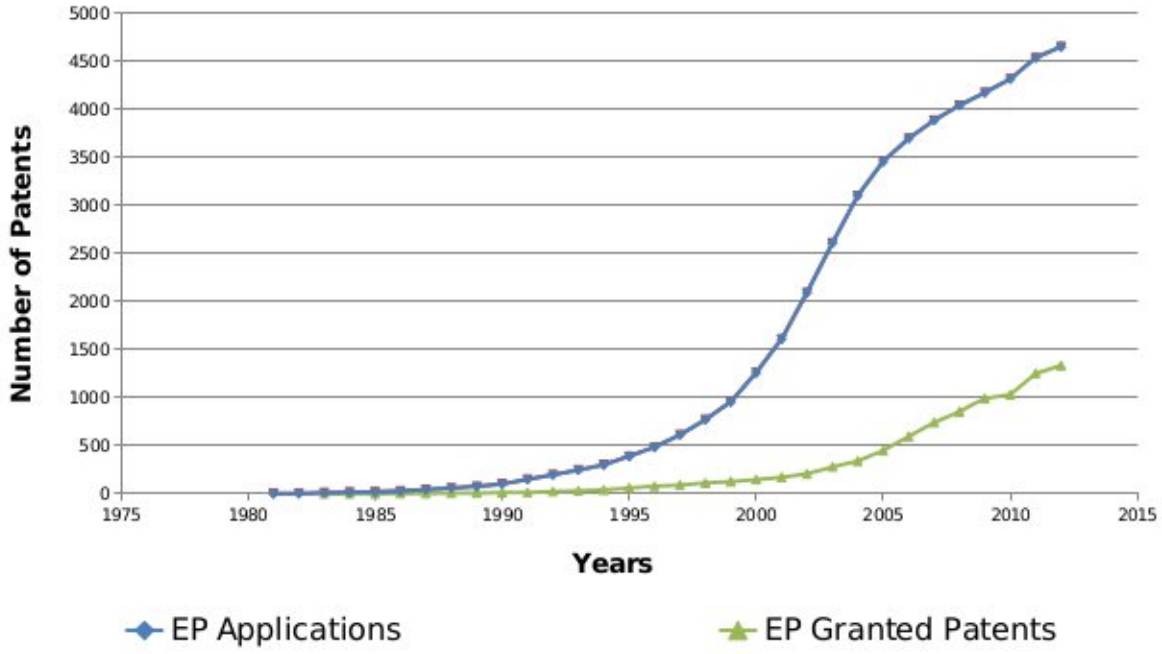

Figure: Number of patent applications and granted patents on animals at the EPO since 1980

One particular problem stems from the claims targeting great apes and non-human primates included in this patent. 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/). This debate has to be taken seriously, and is a strong signal that great apes must be treated with very high ethical standards.

3. Grounds for opposition

A) Article 53 a, EPC

Article 53a, EPC prohibits patents on the grounds of their commercial exploitation violating public order and morality. Without doubt, the protection of animal welfare has to be respected, and is of fundamental importance for public order and morality in Europe.

For this reason, animal experiments with mammals are restricted by animal welfare legislation in Europe. In particular, experiments with great apes are prohibited under EU Directive 2010/63/EU "On the protection of animals used for scientific purposes" (save in truly exceptional circumstances). 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. A survey in six EU countries - Germany, the UK, France, Italy, Sweden and the Czech Republic - in 2009 found that 81%, 77% and 73% of respondents thought that the new EU directive on animal experiments then under consideration should prohibit all experiments causing pain or suffering to primates, dogs and cats respectively. This is a very strong expression of opinion by EU citizens' (D5).

Granting this patent would constitute a violation of the provisions of Art. 53 a, EPC because it could provide incentives to conduct animal experiments for commercial reasons using primates, great apes and also species such as dogs, cats and rodents.

Genetic engineering in animals cannot be seen as neutral in its effect on animal suffering, since it is inextricably associated with negative health impacts. For example, van Reenen et al., 2009 (D6) state:

> "As discussed in previous sections of this paper, there are convincing arguments to support the idea that treatments imposed in the context of farm animal transgenesis are by no means biologically neutral in their effects on animal health and welfare. On the contrary, several treatments seem to directly threaten the pre- and postnatal survival of transgenic farm animals, and there is every reason to assume that overt pathogenicity and lethality merely represent the very extremes of a wide range of possible detrimental effects of experimental manipulations and phenotypic changes related to transgenesis on animal health and welfare."

In regard to Rule 28 (d) it has to taken into account that the patent does not provide substantial medical benefit to humans or animals. The claims are not directed at any medical purposes that could benefit patients. The production or commercialisation of transgenic animals does not have any direct advantage for patients. The patent might contribute to research, however, this cannot be regarded as a direct medical benefit to humans or animals. In result the patent is in contravention of rule 28 (d) of the EPO.

In result this patent must be revoked because it violates Art 53a, EPC.

B) Examination of patentability under Art 83, EPC

In the patent, there are no examples provided of how and if great apes and animal species named in the patent can be genetically engineered successfully with the constructs of DNA as described in the patent.

Because the different biological functions can have various effects on many levels within the different species, it has to be assumed that a skilled person cannot make use of the invention as claimed. Examples for relevant technical problems are described in van Reenen et al., 2009.

As a result, the patent must also be revoked in regard to Art 83 (EPC).

Attachments:

- 498 signatures from individuals against patents on chimpanzees
- D1: Factsheet of Altor on product ALT-836
- D2: Jiao, J.A., et al., Inhibition of acute vascular thrombosis in chimpanzees by an anti-human tissue factor antibody targeting the factor X binding site. Thromb Haemost, 2010. 103(1): p. 224-33.
- D3: Welty-Wolf, K.E., et al., Blockade of tissue factor-factor X binding attenuates sepsis-induced respiratory and renal failure. Am J Physiol Lung Cell Mol Physiol, 2006. 290(1): p. L21-31.
- D4: Statistical overview on animal experiments conducted 2011 in Germany.
- D5: Results of a survey showing that large majority of EU citizens is in favour to prohibit all experiments causing pain or suffering to primates, dogs and cats respectively.
- D6: Van Reenen, C.G., Meuwissen, T.H., Hopster, H., Oldenbroek, K., Kruip T.H., Blokhuis, H.J., 2001, Transgenesis may affect farm animal welfare: a case for systematic risk assessment, J Anim Sci 79:1763-1779