Opposition against European Patent EP 1 456 346 B1

Title: NOVEL ECDYSONE RECEPTOR/INVERTEBRATE RETINOID X RECEPTOR-BASED INDUCIBLE GENE EXPRESSION SYSTEM

Application number: 02714955.8
Proprietor: Intrexon Corporation Blacksburg, VA 24060 (US)
Date of publication of the grant of the patent: 15.02.2012
Date of the opposition: 14.11.2012

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
British Union for the Abolition of Vivisection (BUAV)
Deutscher Tierschutzbund
Gen- ethisches Netzwerk (GeN)
Gesellschaft für ökologische Forschung
No Patents on Life!
ProWildlife
Schweizerische Arbeitsgruppe Gentechnologie (SAG)
Schweizer Tierschutz (STS)
Testbiotech
Wild Chimpanzee Foundation, Germany (WCF)

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

Reasons for the opposition:

A) Article 53 a, EPC

In claims 48 to 53 all non human organisms manipulated with synthetic DNA of Intrexon are patented as described. Amongst others, the following animal species are claimed: mouse, rat, rabbit, cat, dog, bovine, goat, pig, horse, sheep, monkey, chimpanzee.

The wording of the claims is:

> "48. A non-human organism comprising the host cell of claim 45.
>
> 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.
>
> 51. A non-human organism comprising the host cell of claim 45.
>
> 52. The non-human organism according to claim 51, wherein the non-human organism is selected from the group consisting of a bacterium, a fungus, a yeast, an animal, and a mammal,
>
> 53. The non-human organism according to claim 32, 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."

Following usages are described in the patent:

> "Such improved systems would be useful for applications such as gene therapy, large scale production of proteins and antibodies, cell-based high throughput screening assays, functional genomics and regulation of traits in transgenic animals." (Page 4)

A1) Examination of patentability according to Rule 28 (d), EPC.

Patents on genetically engineered animals are restricted by specific ethical boundaries. EU Directive 98/44 (Biotech Directive) as well as Rule 28 (d) of the implementing regulations of the European Patent Convention (EPC) prohibit patents on:

> "(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."

Also according to appeal decision on the so called oncomouse (T0315/ 03) it has to be shown that substantial medical benefit will flow from use of the species included in the patent ("the necessary correspondence test"). Unsubstantiated claims for species such as for example oncorodents, oncomammals or even oncoprimates were not patentable in that case. But the patent as opposed includes such a wide range of species with all kind of genetically introduced traits.

In conclusion, according to the existing regulation there has to be an examination of the process as described to determine whether it is likely to cause animal suffering and if any substantial medical benefit is to be gained, for each species included.

This examination was not carried out by the EPO in the present case. In fact, the EPO completely ignored Rule 28 (d).

If upon examination the examiners were of the opinion that the patent described some potential medical benefit then the suffering of the animals would become irrelevant. This kind of reasoning is unacceptable.

The patentee does indeed refer to potential medical benefit:

a) On page 18 there is a reference to gene therapy as a potential usage of the synthetic DNA.

b) On page 21 there is a reference to potential applications of the DNA constructs (gene expression cassettes) as described:

> "therapeutically desirable polypeptides or products that may be used to treat a condition, a disease, a disorder, a dysfunction, a genetic defect, such as monoclonal antibodies, enzymes, proteases, cytokines, interferon, insulin, erythropoietin, clotting factors, other blood factors or components, viral vectors for gene therapy, virus for vaccines, targets for drug discovery, functional genomics, and proteomics analyses and applications, and the like."

c) On page 24, the patentee describes potential usage of genetically engineered cells:

> "Applicants' invention provides for modulation of gene expression in prokaryotic and eukaryotic host cells. (…) Expression in transgenic host cells may be useful for the expression of various polypeptides of interest including but not limited to therapeutic polypeptides, pathway intermediates (...)."

It only describes the usage of single cells, which is also in accordance with the experiments as given in the examples in the patent.

d) On page 25 of the patent, genetically engineered animals are actually mentioned („HOST CELLS AND NON-HUMAN ORGANISMS OF THE INVENTION"). It does not, however, describe any substantial medical benefit in regard to a patentable invention.

In none of these cases there is *any* evidence of substantial medical benefit derived from the genetic engineering as described of *any* of the species included in the claim.

In summary, it must be concluded that no relevant substantial medical benefit is described in the patent.

It is possible that the examiners did not believe that that Rule 28 was applicable because there is no reference to animal suffering in the patent. This kind of reasoning would be unacceptable.

Since no experiments with animals are described in the patent, there is also no evidence for suffering of the animals provided by the patentee. But according to the wording of rule 28 (d) evidence of animal suffering is not the decisive factor. In fact, under rule 28 (d) it is only necessary that the technical process is "likely to cause … suffering". The likelihood of *any* suffering is enough to engage rule 28(d).

Genetic engineering in animals cannot be considered as being neutral from the point of view of suffering, but is inextricably associated with negative health impacts in animals. For example, van Reenen et al., 2009 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."

Further it has to be taken into account that the animals concerned suffer as a result of being housed in confined and unnatural accommodation, even apart from the suffering associated with the genetic engineering itself. Finally, if used in experiments to test new treatments, suffering also would be inevitable in most cases.

It must be concluded that the processes as described in the patent are likely to cause suffering in animals.

In conclusion to A1) the patent processes described are likely to cause suffering in animals, although no substantial medical benefit from the genetic engineering of the species included is provided.

The EPO did not perform any assessment of the relevant claims in regard to Rule 28 (d) nor did the patentee fulfill the requirements of Rule 28 (d) to show any substantial medical benefit of genetically engineered species as claimed. Thus the patent has to be revoked because of violating Rule 28 (d).

A2) Examination of patentability under general wording of Art 53a, 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.

That is why animal experiments with mammals are restricted by animal welfare legislation in Europe. Especially 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) and other primates 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'.

Because the grant of this patent could give incentive to conduct animal experiments for commercial

reasons on great apes and other primates (one has to take into account also countries which are not EU Member States) and also species such as dogs, cats and rodents it is a violation of the provisions of Art 53 a, EPC.

In conclusion, the 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 animals can be genetically engineered successfully with the constructs of synthetic 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 described under claims 48-53. 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:

D1: 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

D2: 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.