# Opposition against European Patent EP 1364025 B1

Title: A NOVEL GENE BNO1 MAPPING TO CHROMOSOME 16Q24.3

Application number: 02711634.2

Proprietor: Bionomics Limited, Thebarton, S.A. 5031 (AU)

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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 e.V.**
**Gen-ethisches Netzwerk (GeN) e.V.**
**Gesellschaft für ökologische Forschung e.V.**
**Jane Goodall Institut – Deutschland e.V.**
**Menschen für Tierrechte, Bundesverband der Tierversuchsgegner e. V.**
**Schweizerische Arbeitsgruppe Gentechnologie (SAG)**
**TASSO e. V.**
**Wild Chimpanzee Foundation, Germany (WCF)**
**and**
**Dr. Ruth Tippe (supported by „Kein Patent auf Leben!“)**
**Dr. Christoph Then (supported by Testbiotech e.V.)**

**The opposition is supported by 15500 signatures against patents on chimpanzees**

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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 56 EPC.

# Reasons for opposition:

## A) Art 53 a, EPC

### A 1) Claims on animals and usage of animals

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.

### A1.1) Claims 35-37 are not patentable according to Rule 28 (d), EPC.

Patents on genetically engineered animals are restricted by specific ethical boundaries. EU Directive 98/44 (Biotech Directive) and 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.”

The appeal decision on the so-called oncomouse (T0315/ 03) states that substantial medical benefit must ensue from use of the species claimed in the patent ("the necessary correspondence test"). Unsubstantiated claims for species such as oncorodents, oncomammals or even oncoprimates are not therefore patentable. However, the patent we are opposing includes a wide range of species with all kinds of genetically introduced traits.

Existing regulation states that for each species the process as described must be examined to determine whether it is likely to cause animal suffering and whether any substantial medical benefit is to be gained. The EPO did not carry out an examination in the present case. The patent as it stands does not describe any specific medical benefit from any of the specific animal species.

The animals claimed in the patent will most likely suffer since the whole purpose is to induce a higher incidence of cancer. In general, genetic engineering in animals cannot be considered to be neutral in regard to suffering since in every case it is inextricably linked with negative health impacts in the animals. For example, van Reenen et al., 2001 state (D1):

> "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.

**In the light of these findings, claims 35 -37 have to be revoked.**

**A1. 2) Lack of patentability according of Art 53a, EPC:**

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. The claims in this patent as cited do 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 2012, published by German authorities (D2).

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.

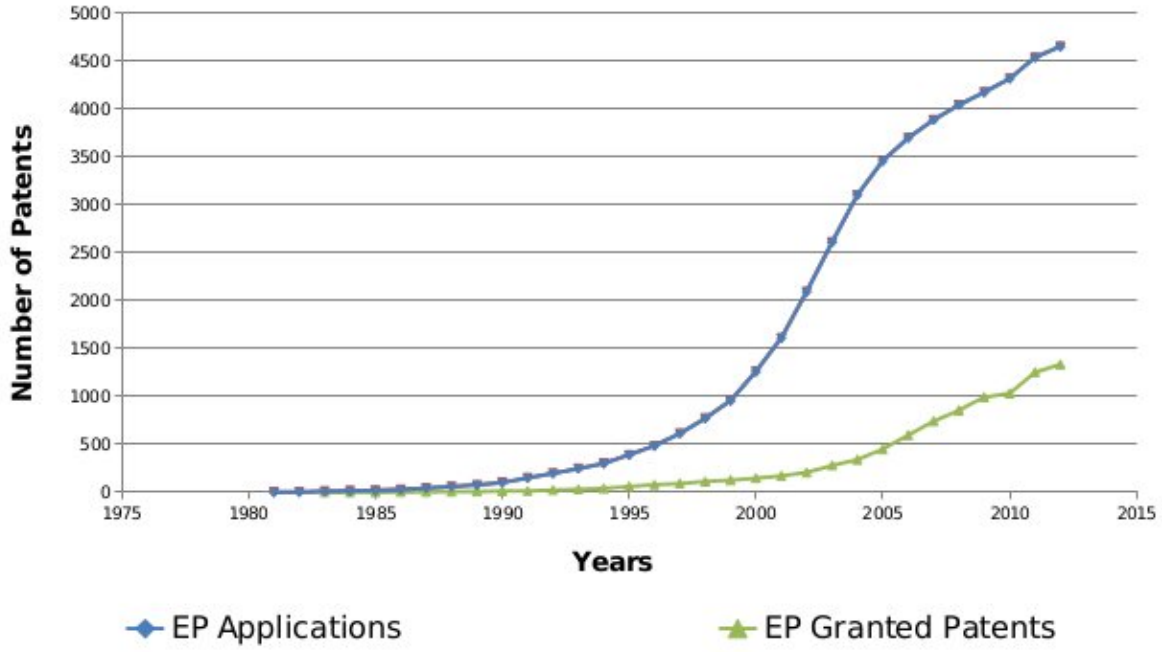


**Figure: Number of patent applications and granted patents on animals at the EPO since 1980**

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.

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' (D3).

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.

**This patent must be revoked because it violates Art 53a, EPC.**

**A2) The patent claims isolated human DNA sequences as an invention**

Claims 1-5 are directed at DNA sequences isolated from the human body. For example, the wording of claim 1 and 5 is:

> 1. An isolated BNO1 nucleic acid molecule mapping to human chromosome 16q24.3 and comprising the nucleotide sequence set forth in SEQ ID Numbers: 1 or 3.
>
> 5. An isolated nucleic acid molecule consisting of the nucleotide sequence set forth in SEQ ID Numbers: 1 or 3.

**A2. 2) Claims 1-5 lack patentability according to Art 53a, EPC (also with relevance for Art 56, EPC):**

Human DNA sequences as claimed in the patent might concern a broad range of diseases. For example page 7 of the patent gives the following explanation:

> Examples of such disorders include, but are not limited to, cancers, immune/inflammatory disorders and neurological disorders. Cancers include adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma, teratocarcinoma, and, in particular, cancers of the breast, prostate, liver, ovary, head and neck, heart, brain, pancreas, lung, skeletal muscle, kidney, colon, uterus, testis, adrenal gland, blood, germ cells, placenta, synovial membrane,

> tonsil, cervix, lymph tissue, skin, bladder, spinal cord, thyroid gland and stomach. Other cancers may include those of the bone, bone marrow, gall bladder, ganglia, gastrointestinal tract, parathyroid, penis, salivary glands, spleen and thymus. Immune/ inflammatory disorders include acquired immunodeficiency syndrome (AIDS), Addison's disease, adult respiratory distress syndrome, allergies, ankylosing spondylitis, amyloidosis, anemia, asthma, atherosclerosis. autoimmune hemolytic anemia, autoimmune thyroiditis, autoimmune polyenodocrinopathy-candidiasis-ectodermal dystrophy (APECED), bronchitis, cholecystitis, contact dermatitis, Crohn's disease, cystic fibrosis, atopic dermatitis, dermatomyositis, diabetes mellitus, emphysema, episodic lymphopenia with lymphocytotoxins, erythroblastosis fetalis, erythema nodosum, atrophic gastritis, glomerulonephritis, Goodpasture's syndrome, gout, Graves' disease, Hashimoto's thyroiditis, hypereosinophilia, irritable bowel syndrome, multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, osteoarthritis, osteoporosis, pancreatitis, polymyositis, psoriasis, Reiter's syndrome, rheumatoid arthritis, scleroderma, Sjogren's syndrome, systemic anaphylaxis, systemic lupus erythematosus, systemic sclerosis, thrombocytopenic purpura, ulcerative colitis, uveitis, Werner syndrome, complications of wound healing (eg scarring), cancer, hemodialysis, and extracorporeal. Circulation, viral, bacterial, fungal, parasitic, protozoal, and helminthic infections, and trauma. Neurological disorders may include Parkinson's disease and Alzheimer's disease.

In fact chromosome 16 does seem to be related to a genetic predisposition to several diseases (see for example http://ghr.nlm.nih.gov/chromosome/16). The patent holder does not however actually describe any causal connection of the DNA sequence to the diseases or conditions listed in the patent. There is only one short explanation on page 21 of the patent:

> From these expression studies we propose that BNO1 is a protein responsible for the development of breast and prostate cancer.

It was already known that some DNA sequences localised in the specific region of Chromosome 16 are involved in causing breast and prostate cancer. As explained on page 4 of the patent:

> Cytogenetic studies have implicated loss of the long arm of chromosome 16 as an early event in breast carcinogenesis since it is found in tumours with few or no other cytogenetic abnormalities. Alterations in chromosome 1 and 16 have also been seen in several cases of ductal carcinoma in situ (DCIS), the preinvasive stage of ductal breast carcinoma. In

addition, LOH studies on DCIS samples identified loss of 16q markers in 29 to 89% of the cases tested (Chen et al., 1996; Radford et al., 1995). In addition, examination of tumours from other tissue types have indicated that 16q LOH is also frequently seen in prostate, liver, ovarian and primitive neuroectodermal carcinomas. Together, these findings suggest the presence of a gene mapping to the long arm of chromosome 16 that is critically involved in the early development of a large proportion of breast cancers as well as cancers from other tissue types, but to date no such gene has been identified.

In this regard, the patent did not add any unexpected or surprising knowledge or inventive technology to that that was available before. Furthermore, the patent does not reveal any specific link between the DNA sequence as claimed and the diseases listed on page 7. The only findings presented in the patent are DNA sequences that might be useful in diagnosing breast and prostate cancer. These were discovered by simply mapping those regions which were the most likely.

This observation is not only relevant in regard to Article 56, EPC but also Art 53a, EPC: If the patent is upheld, the usage of the DNA sequences as claimed would be monopolised in regard to all medical uses and for all diseases as listed, although the patent holder did not present any relevant findings. Thus the patentees would receive an unjustified reward for something they did not invent. The question of whether the grant of a wide ranging patent is justified or not is one of the most relevant in patent law and is strongly interrelated with morality and public order as mentioned in Article 53a. Unjustified patents have to be interpreted as fraudulent where the public interest is concerned. This is in clear contradiction of morality and public order, especially in this case. It is known that research and innovation can be hampered or even blocked by patents on human DNA sequences, something which can in turn be detrimental to the needs of patients (see for example the report ACLU, American Civil Liberties Union forwarded to USPTO, 2012, D4).

In this context it is highly relevant that in 2005 the European Parliament adopted a resolution on this issue. The resolution states that according to the EU Directive 98/44 which was integrated into the Implementation Regulation of the EPC, there should be no comprehensive patents on human gene sequences (P6_TA(2005)0407, Patents on biotechnological inventions, PE 364.125, (www.europarl.europa.eu/sides/getDoc.do?pubRef=-//EP//TEXT+TA+P6-TA-2005-0407+0+DOC+XML+V0//EN). On the contrary, such patents should be clearly restricted to specific functions:

5. Calls on the European Patent Office and the Member States to grant patents on human

DNA only in connection with a concrete application and for the scope of the patent to be limited to this concrete application so that other users can use and patent the same DNA sequence for other applications (purpose-bound protection);

This interpretation is taken into account for example in the national adoption of the EU Directive 98/44 by the German Parliament and French law on bioethics. Thus, the EU Parliament and German patent law as well as French law on bioethics aim to avoid unjustified reward for patent holders and avoid blocking research caused by absolute patent protection of human DNA patents.

It is also obligatory for the EPO to take into account these requirements under Article 53a: Unjustified rewarding of patent holders as well as blocking medical research have to be considered to be contrary morality and ordre public.

**In consequence the patent has to be revoked under Art. 53 a, EPC.**

## B) Scrutiny of patentability of claims 1-5 under Art 54 (2) (discovery) and Art 56 inventiveness

Claims 1-5 are based purely on discovery and not on inventiveness. A human DNA sequence is claimed as isolated from the human body. The patent covers the DNA sequence directly isolated from the human body using known methods. As described in the patent, the link between diseases and Chromosome 16 and its involvement in breast and prostate cancer were known before this process to the same extent as described in the patent. It also evident from a comparison between documents D5 and D6 (or the document D5 and the patent), that the link between the specific region of the Chromosome and the emergence of breast and prostate cancer was already known. The only step that was accomplished between 2001 (D5) and 2002 (D6 and the patent) was a physical mapping of the specific region on the chromosome that was considered most likely. This cannot be regarded as being inventive.

According to the International Search Report, many parts of the DNA sequence as originally claimed were already known. For this reason, several claims had to be deleted before the patent was granted. In effect, no argument can be made for the inventiveness of the remaining claims as granted. This is especially relevant in regard to the "raising the bar" initiative which was started by the EPO some years ago to avoid patents being granted that are not really inventive. Consequently, this patent should not have been granted.

Further, it also has to be taken into account that in 2013 the US Supreme Court drastically restricted the patentability of human DNA sequences (Myriad case). If the decision of the Supreme Court were to be applied to claims 1-5, it would doubtlessly be revoked since they are based purely on discovery. As the Supreme Court decided:

> „A naturally occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated..."

This US Supreme Court judgement is also in accordance with the EU Patent Directive 98/44 that was integrated into the Implementation Regulation of the EPC. The Directive states that an isolated part of the human body may be regarded as an invention if an industrial application is identified. But, of course, this does not mean that isolation of a human DNA sequence becomes an invention just because it has a commercial application. In this case the commercial application was known before the sequence was discovered.

**Claims 1-5 have to be revoked due to lack of inventiveness.**

**Attachments:**

15.500 Signatures against patents on chimpanzees

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: Statistical overview on animal experiments conducted 2012 in Germany.

D3: 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.

D4: ACLU, 2012

D5: Anne-Marie Cleton-Jansen, David F. Callen, Ram Seshadri et al., 2001, „Loss of Heterozygosity Mapping at Chromosome Arm 16q in 712 Breast Tumors Reveals Factors that Influence Delineation of Candidate Regions“, *Cancer Res* 2001;61:1171-1177.

D6: Powell, J.A., Garnder A.E., et al., 2002, Sequencing, Transcript Identification, and Quantitative Gene Expression Profiling in the Breast Cancer Loss of Heterozygosity Region 16q24.3 Reveal Three Potential Tumor-Suppressor Genes, GENOMICS Vol. 80, Number 3, September 2002, 303-310.