Of mice and men

The Harvard oncomouse drew world attention to the issue of patentability of life forms. Pierre-André Dubois and Kate McCallie explore the divergent approaches of patent authorities in the US, Canada and the EU

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There has been worldwide debate regarding the implications of granting patents on life forms since 1988, when the USPTO issued the first patent for a mammal, the Harvard oncomouse, a genetically modified rodent with a heightened susceptibility to cancer. The reality is that for several years prior to the Harvard oncomouse's US patent application, certain life forms had been patentable in the US, the EU and Canada. But because the Harvard oncomouse was an animal, rather than a microbe or a plant, for many it crystallized the importance of the issues surrounding such inventions.

United States: where the mouse was created

The significant US statutory language relating to all utility patents, including those on life forms, is 35 USC §101, which states: "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title."

Prior to 1980, life forms (even at the level of bacteria but with the exception of plants) were not considered patentable in the US. Courts and the USPTO relied on the "products of nature" principle put forward by the US Supreme Court in *Funk Brothers Seed Co v Kalo Inoculant Co* to disallow patents over life forms. The reasoning behind this principle was that manifestations of the laws of nature should not be the subject of any monopoly; "they are part of the storehouse of knowledge of all men". For example, an attempt to patent a dwarf chicken failed *In re Merat* in 1975.

US law did however protect since 1930 patents on newly discovered or invented, distinct, asexually-reproduced plants by way of the Plant Patents Act and extended such protection in 1970 to new varieties of sexually-reproduced plants by way of the Plant Variety Protection Act.

The 1980 US Supreme Court decision in *Diamond v Chakrabarty* changed the US legal landscape when the divided Court held that a man-made micro-organism capable of breaking down components of crude oil fell within the language of 35 USC §101 and was therefore patentable. Such a micro-organism was a new and useful "manufacture" or "composition of matter".

In 1987, in *Ex parte Allen*, the USPTO Board of Patent Appeals and Interferences, relying on *Chakrabarty*, accepted that certain polypoid oysters (which did not occur naturally) were human made life forms and patentable. Following that decision, the US Commissioner of Patents issued a notice stating that the USPTO would consider non-naturally occurring, non-human, multi-cellular living organisms (including animals) to be patentable subject matter. The notice specifically excluded the patentability of claims directed to or including a human being. The Commissioner stated that any claim directed to humans would be contrary to the US Constitution (most likely as a result of the 13th Amendment prohibiting slavery).

Thereafter, the first US patent for a genetically modified animal was granted in April 1988 for the Harvard oncomouse. This US patent covered any non-human transgenic animal carrying an introduced gene making the animal more susceptible to cancer. Although the grant caused a good deal of controversy in the US, in the ensuing 15 years the USPTO has granted many patents for transgenic animals and the patentability of such animals is not in question. Some of these patents cover not only the genetically modified animals but also those animals' offspring and animals of different races and/or higher taxonomic units, such as species.

Examples of US patents (all transgenic or genetically engineered)

Animal	Use	Patent no
Mice, rats, rabbits, goats, sheep, pigs, llamas, camels and bovine	Secretes a peptide which may be harvested for use in human infant formula	6,222,094
Female farm animals (cows, goats, sheep, rabbits and pigs, also mice and rats)	Produces human Factor VIII or von Willebrand Factor protein for use in the treatment of haemophilic disorders	6,518,482
Mice	Lacks “natural killer” cells that spontaneously kill tumors for use in studying same	6,548,737
Mice, hamsters, guinea pigs and degus	Contains an amyloid peptide for use in studying Alzheimer’s disease	6,172,277
Catfish, koi and bony fish	Disease resistant	5,998,698
Flies	Exhibits adult onset neuro-degenerative phenotype for use in research to cure such diseases	6,489,535
Rabbits	Produces human lipoprotein for use in the study and treatment of high cholesterol diseases	6,512,161
Mice having a genome from a diverse species selected from a group consisting of a cow, sheep, pig, human, chicken, cat and dog	Makes the mouse susceptible to diseases that generally only infect the diverse species animal	5,763,740
Mice	Contains recombinant DNA for use in research and development in the fields of angiogenesis and tumor development	6,262,337
Mice, rats, cows, pigs, sheep, goats, monkeys and rabbits	Expresses heterologous DNA in urothelium	6,339,183
Pigs	For use as organ donors	6,331,658
Mice	For use in studying inflammatory diseases	6,437,216
Mice, rats, rabbits, pigs, sheep, goats and cows	Produces human coagulation factor protein C	5,831,141
Mice	Has epitope-tagged infectious prions that cause CNS spongiform encephalopathies in humans and animals for study and treatment of same	5,789,655

Moral debate

Interestingly, even though much of the debate surrounding the patentability of life forms is centred on ethical or moral grounds, US patent law does not include any statutory wording dealing with ethical issues or "ordre public" as is the case of European patent law. A common law doctrine (based on an extension of the utility requirement) did evolve from a line of old cases (starting with the seminal case of *Lovell v Lewis* in 1817) stating that "a new invention to poison people, or to promote debauchery, or to facilitate private assignations" should be considered non- patentable as lacking any utility, as such invention would be deemed to be "injurious to the well being, good policy or good morals of society". This doctrine was used, for example, to try to challenge patents for gambling devices at a time when gambling was considered socially unacceptable, but has had little impact on the patenting of life forms.

Perhaps not surprisingly in view of the absence of statutory wording, US courts have stayed away from the moral debate. In *Chakrabarty*, the US Supreme Court noted in its decision that briefs were filed "pointing to a parade of horribles", including "that genetic research may pose a serious threat to the human race", but specifically stated that such concerns were outside the scope of its permitted review under §101. In 1991, an attempt was made by the Animal Legal Defense Fund to challenge on moral grounds the USPTO's 1987 notice on patenting life forms (*Animal Legal Defense Fund v Quigg*). While the US Court of Appeals, for the Federal Circuit, dismissed the application on lack of standing, it did note

that whether patents are allowable for animal life forms is not a matter of discretion but law. The Court showed no inclination to consider moral issues that were not part of the patent legislation.

More recently, after the publicity generated by the human/animal chimera patent application (a patent application claiming to cover injecting human stem cells into mice and other animals), filed by the interest group Foundation on Economic Trends in order to challenge the USPTO policy of conferring patents on living materials, the USPTO issued a media advisory in 1998 quoting the *Lovell* case and stating that "the existence of a patent application directed to human/non-human chimera could, under certain circumstances, not be patentable because, among other things, they would fail to meet the public policy and morality aspects of the utility requirement". Bearing in mind the great number of US patents that have been granted on life forms, it can be said that it is only in the most controversial cases that the USPTO (and perhaps courts) might consider moral-type related arguments to deny patent protection.

Related to the discussion on patents over life forms proper is the issue of patenting gene sequences. Despite continued public argument on moral and ethical issues surrounding such patents, thousands of patents have been issued on human gene sequences in the US. For example, in 2001, the University of Missouri was granted a patent that covers a method of producing cloned mammals - a category that does include human beings. Partially in response to a massive upsurge in gene patent applications, as well as general public concern regarding the matter (were these mere discoveries or truly inventions having a real use?), the USPTO issued in 2001 stricter guidelines for examining patent applications. These new rules raised the bar for such applications, thus requiring that a gene-related invention present specific, substantial and credible utility to qualify for grant.

Stem cell research and patenting thus remains controversial in the US for fear of human cloning and patents on humans. In February 2003, the US House of Representatives voted to ban all forms of human cloning, either for research or otherwise. The proposed bill will not be debated until later this year. Previous attempts to outlaw cloning and animal patenting failed. US President Bush has stated that he would veto any legislation that does not ban all forms of human cloning.

Examples of pending European patent applications (all transgenic or genetically engineered)

Animal	Use	Patent no
Rats and mice	Serve as models of human diseases in order to test agents for treating brain and nerve disorders such as depression, sleep disorders, schizophrenia and autism	EP 1 276 371 A2
Rats and rabbits	For use in studying Alzheimer's disease	EP 1 255 437 A1
Mice	Expresses syndecan in the hypothalamus region for use in studying obesity and weight control and for screening drugs that can regulate weight gain	EP 0 942 967
Rats, mice, cows, sheep, goats and pigs	For use in studying HIV host cell interactions and to evaluate anti-HIV drugs	EP 0588816
Fish	Has certain transgenes for use in studying development processes, cell lineage relationships and the effect of specific genes and compounds	EP 1 240 824 A1
Rodents	Has a disrupted gene for the study of thermoregulation, obesity and maternal behaviour, olfaction, male behaviour, apoptosis, cell survival and degeneration, and infectious diseases	EP 1 090 116
Flies	Can spontaneously develop metastatic tumours for use in studying and treating same	EP 1 207 751
Rats	Have been modified so the expression of the gene coding for insulin is deleted for use in determining medicines that act on pathologies involving insulin	EP 0 972 018

Europe: where the mouse had a tough time

After 10 years of debate, the EU adopted Directive 98/44/EC on the legal protection of biotechnological inventions in 1998 (Directive). In contrast to the situation in the US, the Directive has clear provisions stating that certain inventions will not be patentable because their commercial exploitation would offend against "ordre public" and morality. The Directive was incorporated into the European Patent Convention (EPC) in June 1999 and therefore impacts the EPO's examination of European patent applications relating to biotechnology inventions.

The Directive directly addresses patenting life forms. Under the Directive (and the EPC and EPC Rules amended as a result of the Directive), plants or animals may be patentable if the technical feasibility of the invention is not technically confined to a single plant or animal variety. This changed the EPC's prior wording that explicitly excluded plant and animal varieties from patentability.

The Directive states at Article 6 that the human body at the various stages of its formation (including the embryo and sequences or partial sequences of genes) is not patentable. However, the Directive states that an element of the human body (including the sequence or partial sequence of a gene) that has been isolated from the body by means of a technical process may be patented even if the structure of the element is identical to that of a natural element. To be patentable under the Directive, as was previously true in the EU, the isolated element must still be novel, involve an inventive step and be capable of industrial application. Article 6 recognizes the patentability of animals but specifically excludes from patenting any process for modifying the genetic identity of animals (and animals themselves) which are likely to cause them suffering without any substantial medical benefit to man or animal.

Evolving position

The Harvard oncomouse illustrates well the EU's evolving position on life form patentability. The application for a European patent on the Harvard oncomouse was originally rejected in 1989 by the EPO's Examining Division on the ground that animal varieties were excluded from patentability under Article 53(b) of the EPC, which prohibited patents on plants and animal varieties. On appeal to the EPO's Technical Board of Appeal in 1990, the case was returned to the EPO's Examining Division with the finding that animals generally (as opposed to animal varieties) were not excluded from patentability by the EPC. As a result of that reassessment, the EPO's Examining Division in 1992 granted a European patent. This landmark decision marked the first time a transgenic animal patent was granted under the EPC. At least part of that decision was also made on the basis that granting the patent would not offend the ethical exclusion in Article 53(a) of the EPC prohibiting patents that would be contrary to "ordre public" or morality. The invention's purpose - to facilitate cancer research and prevention - was viewed to outweigh any disadvantage of the invention, including any risk to the environment and possible animal suffering. Several third parties opposed the patent grant, and the EPO resumed opposition proceedings that continued onward for nine years, during which time the Directive was implemented into the EPC, and parties were asked to submit further submissions based on the Directive.

Finally, in November 2001, the EPO Opposition Division issued a European patent in amended form, limiting the patent to transgenic rodents containing an additional cancer gene. Significantly, this narrowed the patent from its original claim (which covered any non-human transgenic mammal carrying the introduced gene). The Opposition Division considered in detail the issue of "ordre public" and analyzed the issue based on Article 53(a) EPC and Rule 23d EPC as amended by the Directive:

- Was the invention contrary to "ordre public"? Statutory law allows for the use of animals for testing and as such, is highly indicative that the exploitation of the invention cannot be said to be de facto prohibited. Therefore, the invention could not be said to offend "ordre public".
- Will the invention cause animal suffering? Suffering will occur from the moment that the test animals develop tumors.
- However, will the invention have substantial medical benefits? While the animals will suffer, this must be balanced with the bona fide belief of the inventor that the invention will have substantial medical benefits. It simply cannot be denied that the invention will help progress in cancer research.

Consequently, allowing the patent for animals that are candidates for laboratory testing is in line with the Directive and Article 53(a) EPC, but allowing broad claims without amendment to non-human mammals would not.

An important post-Directive case regarding stem cell patenting in the EU involves what is known as the Edinburgh Patent which was issued in late 1999 for an invention entitled 'Isolation, Selection and Propagation of Animal Transgenic Stem Cells'. This was the invention that brought into the world Dolly the Sheep, the first animal cloned from a stem cell. The invention described a method of genetic engineering to isolate stem cells (including embryonic stem cells) to obtain pure stem cell cultures. Because the word "animal" in the English language encompasses human beings, the patent grant engendered severe protests; it was argued in oppositions filed by third parties that this patent could be interpreted to cover the cloning of human beings. Following grant and in response to the opposition, the patentee amended on a voluntary basis the claims to clearly state that the method was directed to "non-human" animals. In July 2002, the patent was maintained by the EPO Opposition Division in amended form. The EPO concluded that such a patent would not offend Article 53(a) EPC.

While the Directive has not been implemented as of this date by all EU member states (only the UK, Denmark, Finland, Ireland, Greece and Spain have), it can be said that at the EPO level there is now a clear framework for the patenting of life forms that allows both traditional patent law considerations and ethical issues to be considered. There is however only a very limited number of European patents that have been granted to date on life forms.

Canada: where the mouse was vanquished

In late 2002, the Supreme Court of Canada rejected the Harvard oncomouse's patentability, signalling Canada's distinctly different approach toward patenting life forms as compared to the US and the EU. While Canadian law allows patents on single-celled organisms, such as yeasts and bacteria, on genetically modified crops, and on modified human genes and cell lines, the Supreme Court has now confirmed that "higher" life forms are not patentable in Canada.

Section 2 of the Canadian Patent Act states that a patent will only be granted for an invention which is defined as "any new and useful art, process, machine, manufacture or composition of matter, or any new and useful improvement in any art, process, machine, manufacture or composition of matter". While the wording of Section 2 is near identical to the corresponding US provision, the Canadian Patent Office and courts have traditionally taken a less expansive view of the meaning of those categories than has the US.

UK position

The UK has been more open to biotechnology patenting in recent years than some other EU member states, despite aggressive lobbying by various interest groups. This is an interesting development considering that the UK was the first country in the world to pass legislation heavily controlling (and thus arguably stifling) genetic modification in a laboratory setting in 1978. The UK was one of the first member states to implement the Directive. The UK Patent Office in September 2002 issued Examination Guidelines for Patent Applications relating to Biotechnological Inventions providing further clarification of the UK Patent Office's pro-biotechnology patent stance. These guidelines emphasize that while many focus on the controversial issues surrounding biotechnology patents, the majority of such applications in the UK will be decided upon the usual issues of novelty, inventive step and industrial application. On a related front, stem cell research is legal in the UK and regulated. Furthermore, despite the European Parliament's vote in April 2003 to ban all forms of stem cell research across the EU, after that vote the UK Patent Office outlined the stem cell research areas it will continue to grant patents in. It did also state that it would not grant patents on cells that could develop into a complete human body.

Mixed messages

In 1982, in *Re Abitibi Co*, the Canadian Patent Appeal Board held that certain genetically modified microbial cultures used in sewage treatment did constitute patentable subject matter. To be patentable, the organism cannot be a mere laboratory curiosity and it must be sufficiently different from known species that it can be said that its creation involved the necessary element of inventive ingenuity. The Appeal Board did however state that the patentability of higher life forms would be "debatable". In 1986, in *Pioneer Hi-Bred Ltd v Canada* (*Commissioner of Patents*), the Canadian Supreme Court ducked the life form patentability issue in a decision involving an application to patent a new variety of soybean plant produced by traditional cross-breeding techniques. The Federal Court of Appeal had rejected the

soybean patent application on the ground that a plant variety produced by cross-breeding did not fall within the definition of an invention. The Court concluded that the plant could not be considered a "manufacture" nor a "composition of matter" as the claimed plant could not be said to have been produced from raw materials or to be a combination of two or more substances united by chemical or mechanical means. In partial reaction to the Canadian *Pioneer Hi-Bred* decision, Canada's Parliament enacted the Plant Breeders' Rights Act to provide patent type protection to plants.

Into this matrix the Harvard oncomouse began its quest for a Canadian patent. In 1985, an application was made for two sets of claims: (1) a transgenic, non-human mammal containing the artificially introduced gene, and (2) a method of inserting the gene into a plasmid, and then injecting that plasmid into a mouse egg. The Canadian Patent Office allowed the second set of claims for the method, while rejecting the claims for the mouse itself as outside the scope of invention under the Patent Act. Harvard appealed this decision to the Federal Court of Canada, which found the mouse non-patentable essentially because the inventors did not have enough control over the overall characteristics of the mouse or its reproduction. Harvard again appealed, and was successful when in 2000 the Federal Court of Appeal found the mouse patentable as a "composition of matter". The Court held that control over all the mouse's characteristics was not a necessary pre-requisite to patentability.

However, the oncomouse's victory in Canada was short lived. In December 2002, in *Commissioner of Patents v President and Fellows of Harvard College*, a sharply divided Supreme Court of Canada held that the mouse was not patentable. The Supreme Court's decision turned on the definition of invention and found that the Canadian Parliament did not intend to include higher life forms within that definition.

The Court concluded that while the definition of invention in the Patent Act is broad, it could not be considered to be unlimited in the sense of including, as the US decision in *Chakrabarty* referenced, "everything under the sun made by man". The Court held that, even if one gives the word "manufacture" a broad meaning, it would commonly be understood to denote a non-living mechanistic product or process, but not a higher life form. As to the words "composition of matter", the Court concluded:

> Injecting the oncogene into a fertilized egg is but for the cause of a mouse predisposed to cancer, but the process by which a fertilized egg becomes an adult mouse is a complex process, elements of which require no human intervention … Thus, I am not satisfied that the phrase "composition of matter" includes a higher life from whose genetic code has been altered in this manner.

Distinction between life forms

The Court found that the Patent Act was not drafted to address the issues relevant to the patenting of higher life forms, including the ethical considerations. It found illustrative that the EU had (partly) resolved the debate by adopting the Directive. The Court also found conclusive (as supporting its conclusion that the Patent Act was never intended to protect higher life forms) that Parliament had passed the Plant Breeders' Rights Act to protect plants. The Court however confirmed that lower life forms should continue to be patentable under the Canadian Patent Office practice. The distinction between lower and higher life forms, while not explicit in the Patent Act, was considered defensible by the Court on the basis of the common sense differences between the two.

The decision will no doubt impact substantially the estimated 1500 plant and animal Canadian patent applications that had been on hold pending the Court's decision. However, it is important to realize that biotechnology inventions can still be protected in Canada through patent claims directed at subject matters the Canadian Supreme Court and the Patent Office refer to as lower life forms. Canadian patent protection for the components that make up a transgenic plant or animal, such as for the gene sequences used, the genetically altered eggs and the ensuing cell lines, should still be available. Furthermore, the biotech industry has been outspoken in its disappointment with the ruling and there are calls for Canada's Parliament to amend the Patent Act to allow for such patentability and bring Canada into greater alignment with the EU and the US.

Tip of the iceberg

The patenting of life forms remains controversial and governments worldwide continue to struggle to balance advances in technology and industry with the moral and ethical issues presented by biotechnological innovations. The Harvard oncomouse and its literal and figurative progeny, which now number in the thousands, will continue to energize the ongoing debate.

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