



1 of 1 DOCUMENT

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ARTICLE: The Evolution of Patents on Life -- Transgenic Animals, Clones and Stem Cells

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TEXT:

Few areas of intellectual property law have generated more attention than the realization that it is now practical to use utility patents to protect rights in higher animals, such as mice, pigs, sheep and cows, so long as they otherwise meet the criteria for patentability. On April 3, 1987, the Board of Appeals in *Ex parte Allen* refused to grant a patent on a process to make more edible oysters by putting them under pressure. n1 The Board said the claims in question were obvious, but it also said that the mere fact that a multicellular animal was involved was not a bar to patentability. The issue, it ruled, "is simply whether that subject matter is made by man," rather than a product of nature.

Days after the *Allen* decision, on April 21, 1987, the PTO announced that it would accept applications for "nonnaturally occurring nonhuman *multicellular* living organisms, including animals." The PTO stated that, to be patentable, the animals must be "given a new form, quality, properties or combination not present in the original article existing in nature in accordance with existing law." n2

The *Allen* decision got some attention in the press, but the controversy intensified when the Patent Office proceeded to issue U.S. Patent No. 4,736,866 to Philip Leder and Timothy A. Stewart of Harvard University on April 12, 1988. This is the now famous, or "infamous" to many, "Harvard mouse patent." Claim 1 is reproduced below:

1. A transgenic non-human mammal all of whose germ cells and somatic cells contain a recombinant activated oncogene sequence introduced into said mammal, or an ancestor of said mammal, at an embryonic stage.

Two notable features of claim 1 are; (a) it covers all mammals, not just mice, and (b) it specifically covers the progeny of the animals that first received the oncogene. DuPont, who had substantially funded the research, now holds the license to the "oncomouse" and sells the mice to research institutions.

Despite the U.S. Patent and Trademark Office's affirmative ruling, a consortium of animal rights groups brought an action challenging the Office's authority to determine that transgenic animals were indeed patentable subject matter. n3 The district court found that the Patent Office rule was an interpretive one and, as such, was exempt from the public notice and comment requirements of the Administrative Procedure Act. n4 The Court of Appeals for the Federal Circuit affirmed the district court holding stating that the Animal Legal Defense Fund was without standing to challenge the Patent Office's authority to grant animal patents. As a result, no court has yet ruled on whether or not animals are patentable subject matter under § 101.

The Harvard mouse patent has also been at the center of controversy surrounding "patenting life" in Europe. In February 1993, the European Parliament (EU) issued an 'instruction' to the European Patent Office (EPO) directing it to revoke the Harvard mouse patent n5 and to refuse to grant any more patents on transgenic animals until the legal uncertainties have been clarified. n6 Such an instruction, however, is merely advisory. The grant has also been subject to a number of third party oppositions. Meanwhile, environmental activist groups, like the European Green Party and Greenpeace, lobbied the European Parliament and were able to muster enough political clout to defeat the European Parliament's final draft directive on the legal protection of biotechnological inventions in March of 1995. n7 Positive change may yet come from the European parliament. On January 10, 1997, the Parliament approved the proposal with many amendments, including a new Article 1(b), which stated that "inventions which concern plants or animals may be patented if the practicability of the invention is not technically confined to a particular plant or animal variety." n8 Although the EPO is not an EU institution, there is some indication that the EPO will apply the provisions of the relevant EU Directives. n9

The Harvard "oncomice" have not simply been altered by environmental pressures, as were the pressurized oysters in *Ex parte Allen*. they have been genetically engineered. More specifically, the mice are "transgenic," in that at least one *additional* gene has been introduced into the germ cells of the animal. Furthermore, these mice can pass the new gene onto their offspring. The added gene can come from another animal of the same species, from an animal of a different species, or it can be completely synthetic. In this case, the new gene is a recombinant activated oncogene sequence that causes a high percentage of the mice to develop tumors. Thus, the mice are useful to test anticancer drugs. A number of these genes are known, and can be derived from chickens, monkeys or even humans.

The gene is introduced as linearized plasmid DNA, preferably in combination with an inducible promoter, by injection into the male pronucleus of a fertilized egg. The egg is then transplanted into a host female, where it matures. Interestingly, and distressingly for many researchers, this process was the subject of broad patent claims that issued to an Ohio University group headed by Thomas E. Wagner in October of 1989, well after the issuance of the oncomouse patent. n10 Like claim 1 of the Harvard mouse patent, claim 1 of Wagner et al. covers a method of transforming any mammal with any "exogenous" gene. The broad product-by-process claims were canceled during the 7 years of prosecution.

Since the injected DNA is incorporated into the genome through a process involving disruption and alteration of the chromosomal DNA of the egg at the insertion site, it may result in either lethal mutation or gross morphological abnormalities. Nonetheless, in the case of mice, transgenic animals have been produced which are

indistinguishable from unaltered mice, beyond the effects of the expression of the introduced gene sequence. n11

No other "composition of matter" patents issued in United States classification 800 until December 29, 1992, when the Patent Office issued three more. The patents claim (a) a mouse that develops an enlarged prostate gland (U.S. Patent No. 5,175,383), (b) transgenic mice depleted in mature T-cells (U.S. Patent No. 5,175,384) and (c) a virus-resistant mouse that produces beta-interferon (U.S. Patent No. 5,175,385). The '384 and '385 patents had been pending 4 and 5_ years, respectively. The first claims of the '384 and '385 patents are shown below:

1. A transgenic mouse having a phenotype characterized by the substantial absence of mature T-cells otherwise naturally occurring in said mouse, said phenotype being conferred by a transgene contained in the somatic and germ cells of said mouse, said transgene comprising the V-TCR DNA fragment which encodes a T-cell antigen receptor polypeptide variant, and said polypeptide variant being incapable of mediating T-cell maturation in said transgenic mouse. [GenPharm International (U.S. Patent No. 5,175,384)]

1. A transgenic mouse whose somatic and germ cells contain and express a gene coding for human beta interferon at a level sufficient to provide antiviral activity in said mouse, said gene having been introduced into said mouse, or an ancestor of said mouse at an embryonic stage, and wherein said gene is operably linked to an at least partially constitutive non- interferon promoter. [Ohio University/Edison Animal Biotechnology Center (U.S. Patent No. 5,175,385)]

However, unlike claim 1 of the oncomouse patent which was not even limited to mice, or to any particular oncogene, these claims are both limited to mice and to "single genes" which accomplish a specific function. As in the case of transgenic plants, the early bird gets a transgenic stick of great breadth, while later comers tend to get the narrow end of the stick.

The first patent on a non-murine animal also issued to the U.S. Government DHHS in February of 1993 (U.S. Patent No. 5,183,949). Claim 1 of this patent is directed to "a rabbit infected with HIV-1 virus, said rabbit produced by the infection of human T-cells infected *in vitro* with HIV-1." This rabbit is a potential animal model on which to test anti-HIV drugs. However, this is not truly a transgenic animal, since its genome was not augmented with a preselected construct comprising recombinant DNA.

While the beta-interferon mouse could fairly be described as a lucky mouse, in that it was meant to resist infection, this line of research led mostly to mice afflicted with increasingly exotic pathologies. Such transgenic mice can be used both to test new drugs and to test compounds which might protect them against the effects of natural and synthetic pathogens such as carcinogens or mutagens. Much has been made of the production of giant pigs, fish or chickens by the introduction of growth hormone genes, and, in fact, mice grew to the size of rats when they were transformed in this way. n12 However, attempts to alter whole animal morphology of farm animals, at least by microinjection of zygotes, are both time-consuming and difficult to evaluate from a cost/benefit standpoint in terms of the myriad of other side effects which might occur. Rather, as reflected by the increasing number of issued patents, commercial interest followed two main threads: transgenic animals, mainly mice, as models for human diseases, and transgenic farm animals that can produce valuable compounds, such as human pharmaceuticals, more efficiently than bacteria and yeasts. n13

The Patent Office did not issue another patent on a transgenic mouse useful as a model for human pathology until February 7, 1995, when it issued Cordell (U.S. Patent

No. 5,387,742), assigned to Scios Nova Inc., which claimed transgenic mice displaying the amyloid deposits typical of Alzheimer's disease. Claim 1 reads as follows:

1. A transgenic mouse whose cells contain a DNA sequence, comprising:

nerve tissue specific promoter; and
 a DNA sequence which encodes a -amyloid precursor protein selected from the group consisting of A751 and A770,
 wherein the promoter and DNA sequence which encodes the precursor protein are operatively linked to each other and integrated in the genome of the mouse and expressed to form -amyloid protein deposits in the brain of the mouse.

The heterologous DNA sequences are limited to those encoding two -amyloid precursor proteins. The DNA sequences must also be operatively linked to a nerve tissue specific promoter. These mice are disclosed to be useful to test drugs as potential candidates to treat various neurodegenerative diseases. However, behavioral degeneration of the mice is not disclosed in the specification. If the mice in fact remain behaviorally unaffected by the - amyloid deposits in their brains, should the Examiner have rejected the claims on the basis of an insufficient disclosure of utility/"how-to-use" the invention? Since issuing Cordell, the Patent Office has issued over 100 patents on transgenic mice, mostly as models of specific pathologies. A representative group is summarized on Table 1, below.

Table 1

U.S. Patent No.	Assignee	Pathology
5,633,425	Columbia University	Polio
5,625,125	DNX	Phospholipase A2 overexpression
5,625,124	Washington University	Ulcers
5,602,309	University of Kentucky	Parkinson's syndrome
5,602,307	Baylor College of Medicine	Inflammation
5,602,306	UAB Research Foundation	Sickle cell anemia
5,602,299	Mount Sinai School of Medicine	Alzheimer's disease
5,569,827	Universite de Montreal	Neuronal HIV infection
5,569,824	Baylor College of Medicine	Cancer susceptible
5,550,316	Fox Chase Cancer Center	Cutaneous melanoma
5,565,186	University of California	Susceptible to prion infection
5,491,283	Children's Hospital of Los Angeles	Leukemia
5,489,743	Amgen Inc.	Thrombocytopenia

Despite the problems of low transformation frequency associated with the microinjection of naked DNA into the pronuclei of higher animals, such as cows and sheep, much effort has gone into patenting animals that can produce valuable heterologous proteins and excrete them into their milk in high levels. One of the first patents to issue in this area contained claims to a transgenic female sheep that expressed the transgene in the mammary gland so as to produce the target protein in its milk. Claim 1 of Clark et al. (U.S. Patent No. 5,476,995), reads as follows:

1. A female transgenic sheep whose somatic and germ cells contain a transgene construct, said transgene construct comprising:

- (a) a DNA sequence encoding a polypeptide which does not naturally occur in the milk of a non-transgenic sheep; and
- (b) a beta-lactoglobulin promoter operably linked to said DNA sequence encoding said polypeptide;

wherein said transgene construct is integrated in such a way that said DNA sequence encoding said polypeptide is expressed in the mammary gland of said sheep to produce a proteinaceous compound comprising said polypeptide in the milk of said female sheep.

The dependent claims recite that the proteinaceous compound is a blood coagulation factor, i.e., factor IX, or alpha-1-antitrypsin, which is useful to treat emphysema or cystic fibrosis patients. The owner of this patent, PPL Therapeutics, has this compound in phase II clinical trials.

This research has led to an Old McDonald's Bioreactor on the hoof, as illustrated by the patents listed in Table 2, below.

Table 2

U.S. Patent No.	Assignee	Animal	Protein
5,589,604	American Red Cross	Pig, sheep, goat, cattle	Protein C
5,322,775	PPL Ltd.	Sheep	Blood coagulation factors
5,639,940	PPL Ltd.	Sheep, pig, goat, cow	Fibrinogen
5,625,126	GenPharm	Mouse	Human antibodies
5,602,306	UAB Research Foundation	Pig	Human hemoglobin

All of these transgenic animals were produced by variations of the now proven technique wherein recombinant DNA segments are introduced into fertilized eggs of mammalian species and the embryos are implanted into surrogate mothers to obtain transgenic offspring. Apart from the low transformation frequency, this process is slow; in cows, their long gestation period can mean that up to three years is required before a protein can be harvested from the milk. The other phenotypic properties of a transgenic animal are also up for grabs, because the genome is being altered at the very early developmental stage, while producer animals are selected at the end of the process.

A procedure that is potentially more predictable and more efficient, "adult cell cloning" was first reported by a group at Roslin Institute (Edinburgh) and PPL Therapeutics in February of 1997. n14 "Dolly" or lamb number GLL3, was produced by enucleating an unfertilized oocyte from a Scottish Blackface ewe. Cells from the mammary gland of a 6-year-old Finn Dorset ewe in the last trimester of pregnancy were used as nuclear donor cells. The cells were induced into quiescence by reducing the serum in the culture medium. A cell was then electrofused to an enucleated oocyte. The reconstructed oocytes were also activated by electrical pulse and cultured in ligated oviducts of sheep. The morula or blastocysts that developed were transferred to recipient ewes and Dolly was eventually born, exhibiting the same genotype as the Finn Dorset ewe that was the nucleus donor.

As the authors rather dryly conclude:

The dissemination of the genetic improvement obtained within elite selection herds will be enhanced by limited replication of animals with proven performance by nuclear transfer from cells derived from adult animals. In addition, gene targeting in livestock should now be feasible by nuclear transfer from modified cell populations and will now offer new opportunities in biotechnology. n15

Here is a representative claim constructed from the independent and dependant claims of Roslin Institute (PCT WO 97/07669):

An animal prepared by a method comprising:

- (a) reconstituting an animal embryo by transferring the nucleus of a quiescent adult somatic cell into an enucleate oocyte;
- (b) causing an animal to develop to term from the embryo; and
- (c) optionally, breeding from the animal so formed.

With respect to patentability, consider whether or not Dolly is novel over the lamb version of the donor that certainly existed prior to the invention of Dolly. n16 However, Dolly is not absolutely identical to the donor sheep. As stated by the inventors:

Animals produced by transfer of nuclei from a source of genetically identical cells share the same nucleus, but are not strictly identical as they are derived from different oocytes. The significance of this different origin is not clear, but may affect commercial traits. Recent analyses of the mitochondrial DNA of dairy cattle in the Iowa State University Breeding Herd revealed [changes] associated with milk and reproductive performance [citation omitted]. It remains to be confirmed that similar effects are present throughout the cattle population and to consider whether it is possible or necessary in specific situations to consider the selection of oocytes. n17

Dolly was not transgenic. However, on July 24, 1997 the Roslin/PPL group announced the birth of five more lambs cloned using fibroblasts as nuclei donor cells. The fibroblasts included a selectable marker gene and an undisclosed human gene. One lamb, "Polly," was confirmed to have the human gene. n18 Although the reproducibility of these experiments was questioned, cloned mice have been reported that were produced using a similar procedure in which enucleated oocytes were injected with nuclei from cumulus cells. n19 In 2000 Advanced Cell Technology reported cloning six healthy Holstein heifers and PPL then reported cloning pigs. n20

On August 7, 1997, ABS Global Inc. of DeForest, Wisconsin, announced the successful cloning of a bull calf named "Gene." n21 The calf was produced by establishing an embryonic stem cell line, then introducing a cloned stem cell into an enucleated calf egg and fusing the two cells to yield a "nuclear transfer embryo." The embryo was induced to replicate and allowed to develop into an immature embryo. The embryo was implanted into a surrogate mother cow, and developed to term. n22 A similar experiment recently yielded cloned transgenic goats expressing a gene encoding recombinant human antithrombin in their mammary glands. n23

If differentiated human donor cells can be successfully induced into quiescence, and there is no reason to think that they cannot, "adult cloning" of human beings should be possible. Some of the less farfetched reasons to do this that have been proposed include replacing a terminally ill child or providing the donor with a source of matched tissue for transplantation. In fact, in November 1998, Advanced Cell Technology briefly made headlines when it announced it had made a "human" embryo by fusing a nucleated human somatic cell with an enucleated cow cell. Such proposals have further fueled the moral outrage that has led certain religious coalitions, environmental groups and bioethicists to oppose almost every aspect of biotechnology, from patenting genes and transgenic plants to cloning humans. n24 Their concerns will probably not be alleviated by the recent report from the Oregon Regional Primate Center that two rhesus monkeys have been cloned. The stated goal of the research is to produce genetically identical rhesus monkeys for experimental use. The production of genetically identical animals should lead to fewer being needed for research purposes, to average out individual variations, and also to more accurate results.

Following a report by the National Bioethics Advisory Committee that called cloning humans "morally unacceptable," President Bill Clinton banned the use of federal funds for human cloning research, and called for a law that would ban human cloning but allow cloning of genes and animals that advance medicine and agriculture. In July 1997 the House Science Committee approved a bill to prohibit funding to produce cloned human embryos. In 2001, the full House voted to ban all human cloning experiments, both reproductive and therapeutic. While the Biotechnology Industry Organization (BIO) has opposed cloning humans, BIO opposed this bill. BIO realizes that bills intended to bar "somatic cell nuclear transfer" to produce a child could inadvertently ban cloning genes in microorganisms or research on processes involved in early human development.

In December 1997, Dr. Stuart Newman, the founder of the Council for Responsible Genetics, filed a patent application claiming, *inter alia*, human-animal chimeras. Dr. Newman, a cellular biologist at the Medical College of New York, stated that he would use any patent granted to block research of this type. The Patent Office recently rejected the claims as encompassing human beings. Dr. Newman has said he will appeal the ruling, in order to obtain a higher court decision that humans are not patentable. n25

The debate about reproductive or therapeutic cloning of individuals has become interlocked with the ethical controversy that has accompanied a new area of science broadly termed "stem cell technology." This area of research is based on the discovery that cells of the early mammalian embryo, including those from the blastocyst, can be cultured *in vitro* so as to proliferate indefinitely in an undifferentiated state. More importantly, the cells are pluripotent, in that they can be induced by various cytokines to form derivatives of all three embryonic germ layers -- endodermal (e.g., hepatocytes), mesodermal (e.g., blood and bone) and ectodermal (e.g., neuronal cells). These "embryogenic stem cells" (ES) have enormous potential for both drug discovery and direct therapeutic applications.

Isolation and differentiation of human embryonic stem cells (hES) was first reported by J. A. Thompson et al. at the University of Wisconsin in 1998. n26 The Wisconsin Alumni Research Foundation has now received a number of patents on human and primate ES technology, including U.S. Pat. No. 6,200,806, which claims the cells *per se*.

1. A purified preparation of pluripotent human embryonic stem cells which
 - (i) will proliferate in an in vitro culture for over one year,
 - (ii) maintains a karyotype in which the chromosomes are euploid and not altered through prolonged culture,
 - (iii) maintains the potential to differentiate to derivatives of endoderm, mesoderm, and ectoderm tissues throughout the culture, and
 - (iv) is inhibited from differentiation when cultured on a fibroblast feeder layer.

Combined with cloning techniques, the use of ES theoretically permits an individual to clone him/herself in early embryonic form in order to obtain and differentiate stem cells into tissue that could be used for an autologous transplant, such as a liver, heart or islet cell transplant, or even to create synthetic organs. See, R. A. Pederson, *Scientific American*, 69 (April 1998).

Apart from the ethical issues that led President George W. Bush on August 9, 2001 to block federal funding for research on newly created hES, the use of hES to generate tissue useful for transplantation has encountered technical difficulties. For example, the fibroblast feeder layer recited in claim 1 of the '806 patent is commonly

murine and the operative cytokines are largely unknown, thus raising the specter of possible viral contamination.

However, research is also progressing on isolating, expanding and characterizing so-called adult stem cells. These are undifferentiated cells with the potential to self-renew and differentiate that have been identified in a number of tissues, including adult bone marrow and fetal brain. For example, hematopoietic stem cells from bone marrow or blood can reinitiate hematopoiesis for the life of a recipient and can regenerate multiple hematopoietic lineages. This research has opened the door to patenting specific types of stem cells. For example, Johns Hopkins university owns Civen (U.S. Pat. No. 4,714,680) which claims a preparation containing hematopoietic stem cells:

4. A suspension of human cells from blood comprising pluripotent lymphohematopoietic stem cells substantially free of mature lymphoid and myeloid cells.

This claim points out both legal difficulties in claiming stem cells and the scientific problems of isolating them. Adult stem cells are a tiny percentage of the cells of any given organ type, including blood. Therefore, a putative stem cell population is obtained by depleting the cells of non-stem cells, i.e., by negative selection by use of monoclonal antibodies that bind to markers on cells that are more mature. Alternatively, the '680 patent discloses using a monoclonal antibody specific for a marker on immature cells to isolate stem cells from mature cells.

Thus, stem cells are often claimed in terms of what they are not, as well as by functional characteristics. MorphoGen Pharmaceuticals, Inc. has obtained a patent claiming "purified pluripotent mesenchymal stem cells" obtained from cultured muscle cells. n27 These cells are defined in terms of their morphology and their ability to differentiate. From a legal standpoint, the terminology used to describe stem cells is in flux. Claim 4 of the '680 patent and claim 1 of the '735 patent use the term "pluripotent," This term is defined in the '680 patent as the capability to repopulate the blood and lymph cell populations (erythrocytes, T cells, etc.). This term is defined in the '735 patent as the ability to differentiate into tissues of the mesenchymal lineage, such as muscle, bone and fat. However, today, the term "pluripotent" more commonly refers to the ability of a stem cell such as an ES to differentiate into tissues derived from all of the major stem cell lineages -- ectodermal, endodermal and mesenchymal. This is the holy grail of adult stem cell research, and researchers are beginning to home in on the prize.

It has already been shown that one type of adult stem cell can yield at least one or two other tissue types *in vivo*. Such cells are now termed "multipotent," and some populations may well be convincingly shown to be truly "pluripotent." Two recent PCT applications have been published claiming multipotent stem cells isolated from bone marrow that can differentiate into at least 3-4 tissue lineages, including neuronal, bone and endothelial cells, as well as muscle and blood. These cells are defined as much in terms of the markers that they lack as the markers they retain. For example, claim 1 of published PCT application WO/01/11011 is reproduced below:

It has already been shown that one type of adult stem cell can yield at least one or two other tissue types in some cases. See, e.g., Gussoni et al., *Nature*, 401, 390 (1999). Such cells are termed "multipotent," and some populations may well be convincingly shown to be "pluripotent." This line of research may eventually close the loop suggested by adult cell cloning and stem cell technology. For example, it may soon be possible to isolate stem cells that are then genetically engineered to express a gene that is non-functional in mature cells of the donor. For example, transgenic *mdx* mice have been produced as animal models for Duchenne's muscular dystrophy (MD). Gussoni et al. demonstrated that, if the mice are irradiated to suppress their bone marrow and then injected with stem cells containing a functional

gene expressing dystrophin, partial restoration of dystrophin expression in muscle cells of the mice is observed. See, Gussoni et al., cited above. While these stem cells were not transgenic, this work suggests that a MD patient's cells could be cloned and stem cells recovered from the dividing embryo. The stem cells could then be transformed with a dystrophic gene and reintroduced into the patient, possibly following total body irradiation to destroy defective stem cells in the marrow. The transgenic cells would be a match to the patient's own immune system, and would go on to differentiate into functional muscle cells.

Although Gussoni et al. used known murine hematopoietic stem cells, at least two PCT applications have been filed claiming mesenchymal-type stem cells isolated from bone marrow that can differentiate into at least 3-4 tissue lineages, including neuronal, bone and endothelial cells, as well as muscle and blood. These cells are defined as much in terms of the markers that they lack as the markers they retain. For example, claim 1 of published PCT application WO/01/11011 is reproduced below:

1. An isolated multipotent mammalian stem cell that is surface antigen negative for CD44, CD45, and HLA Class I and II.

This line of research may eventually close the loop suggested by adult cell cloning and stem cell technology. For example, it may soon be possible to isolate stem cells that are then genetically engineered to express a gene that is non-functional in mature cells of the donor. For example, transgenic *mdx* mice have been produced as animal models for Duchenne's muscular dystrophy (MD). Gussoni et al. (*Nature*, 401, 390 (1999)) demonstrated that, if mice are irradiated to suppress their bone marrow and then injected with hematopoietic stem cells containing a functional gene expressing dystrophin, partial restoration of dystrophin expression in muscle cells of the mice is observed. While these stem cells were not transgenic, this work suggests that a MD patient's cells could be cloned and stem cells recovered from the dividing embryo. The stem cells could then be transformed with a dystrophic gene and reintroduced into the patient, possibly following total body irradiation to destroy defective stem cells in the marrow. The transgenic cells would be a match to the patient's own immune system, and would go on to differentiate into functional muscle cells.

Claims to stem cells highlight most of the challenges involved in patenting "life" and enforcing such patents, including determining the novelty and unobviousness of claims to cell lines isolated and characterized by different methods and described using different terminologies, and the scope and enforceability of claims to relatively impure cellular populations versus later, "purer" populations. Issues of patentable subject matter enter the field when claims are drawn to manipulating embryonic material and ultimately regenerating embryos and even transgenic humans.

For example, the grant of European patent 695,351 in August of 1999 caused an outcry among anti-biotech activists when they discovered it containing claims to a method of making a transgenic animal by regenerating a blastocyst comprising a transgenic stem cell. The term "animal" was defined in the patent to cover transgenic humans. As reported in *BioWorld International*, 5, 1 (March 1, 2000), the inventor asserted that "he and his company did not intend to develop or apply technologies to manipulate human beings." However, the U.S. Patent Office has already issued over 1,000 patents on aspects of "gene therapy," many that would yield transgenic humans, if the therapy were to accomplish its goal. n28 In fact, extrapolating the Gussoni et al. methodologies to a method of curing muscular dystrophy with transgenic stem cells would yield a transgenic human, although he or she would be closer to a "normal person" than the transformant was at birth(!).

Whether or not Congress ultimately supports full or partial bans of cloning or stem cell research, it is clear that there has been a fundamental shift in thinking

concerning "patenting life." As late as the mid-70's, the primary concerns voiced by opponents of biotechnology were that no one should be allowed to patent "God's handiwork" -- that no one should be allowed to go into the jungle of nature and own the new organisms that were discovered there. Today, the opponents of biotechnology seem to be more worried about "man's handiwork" -- the plants and animals and even the people which our inventors propose to create and to release into the world. n29

Legal Topics:

For related research and practice materials, see the following legal topics:
Healthcare Law Treatment Reproductive Technology General Overview Patent Law Claims & Specifications Description Requirement General Overview Patent Law Ownership General Overview

FOOTNOTES:

n1 2 USPQ2d 1425 (Bd. App. 1987), affirmed in unpublished opinion 846 F.2d 77 (Fed. Cir. 1988).

n2 1077 OG 24.

n3 *Animal Legal Defense Fund v. Quigg*, 710 F. Supp. 728 (N.D. Cal. 1989) affirmed, 932 F.2d 920 (Fed. Cir., 1991) (finding animal rights groups lacked standing to challenge the Patent Office ruling).

n4 5 USC § 551 et seq.

n5 Granted European patent 169,672 (May 13, 1992).

n6 For a discussion of the examination of the Harvard mouse patent in the European Patent Office, see R. K. Seide et al., *Chemistry & Industry*, 656 (Aug. 21, 1995).

n7 COM(95)0661 final/2. The directive as presented would have harmonized the protection of biotechnological inventions among member states and provided encouragement of biotechnology and genetic engineering efforts in the European Union. The European Parliament voted 240 to 188 with 23 abstentions against the adoption of the draft directive, even after the European Council and the European Parliament had settled on a compromise version in January 1994.

n8 COM(95)0661-C4-0063/96-95360(COD). Under Article 27 of TRIPS: "Members may also exclude from patentability . . . (b) plants and animals other than microorganisms...."

n9 EPI Information, President' letter re biotechnological inventions, Winter, 1996 Mitteilungen der deutschen Patentanwälte 270-77; Lange, 1996 GR.U.R. Int. 586-59; discussed by I. Voelker, *IP Worldwide*, 21 (July/Aug. 1997).

n10 T. E. Wagner et al. (U.S. Pat. No. 4,873,191). See also, T. E. Wagner et al., *PNAS USA*, 78, 6376 (1981). This rapid publication should have alerted the art to the possibility that a "submarine" patent application was lurking.

- n11 R. Jaenish, *Science*, 240, 1468 (1988).
- n12 R. D. Palmiter et al., *Nature*, 300, 611 (1982). Query: do these mice meet the utility requirement of 35 U.S.C. § 101?
- n13 For a thorough survey of trade publications and other literature relating to transgenic animals, see T. T. Muga, *J. Patent and Trademark Office Soc'y*, 76, 511 (1995).
- n14 I. Wilmut et al., *Nature*, 385, 810 (1987).
- n15 *Id.* at 812.
- n16 35 U.S.C. § 102(a).
- n17 PCT WO 97/07669 at page 19.
- n18 *Science*, 277, 631 (1 August 1997).
- n19 T. Wakayama et al., *Nature*, 394, 369 (1998).
- n20 *BioWorld Today*, 11, (83), 1 (April 28, 2000); *op. cit.*, 11 (50), 1 (March 15, 2000).
- n21 <http://www.absglobal.com>.
- n22 ABS Global, Inc. (PCT WO 95/17500).
- n23 A. Baguisi et al., *Nature Biotechnology*, 13, 456 (1999). The generation of transgenic animals that have identical genetic backgrounds increases the ease of studying the expression and secretion characteristics of recombinant proteins by the mammary gland.
- n24 On June 17, 1997, the Islamic Educational, Scientific and Cultural Organization held a meeting in Casablanca, Morocco, that urged Muslim countries to ban human cloning but to allow the process to be used for cloning animals and plants. On June 19, 1997, delegates at the annual Southern Baptist Convention reached essentially the same conclusion. In January 1998, thirteen member countries of the Council of Europe signed an agreement forbidding human cloning, while permitting the cloning of cells for research purposes. See, 17 *Biotechnology Law Report*, 256-257 (March-April 1998).
- n25 *Science*, 284, 19 (1999); 17 *Biotechnology Law Report*, 534-535 (July-August 1998).
- n26 See, J. A. Thompson et al., *Science*, 282, 1145 (1998).
- n27 Young et al. (U.S. Pat. No. 5,827,735).

n28 For example, see Gregory et al. (U.S. Pat. No. 5,670,488) (method of treating a cystic fibrosis patient).

n29 Given that the average human possesses an adrenal gland which secretes no more than about 0.01 mg of adrenalin per kilogram of body weight per hour, does the following claim define patentable subject matter?

1. A human being possessing an adrenal gland capable of secreting 1-10 mg/kg/hour of adrenalin into the bloodstream of said human.