PATENTING OF GENETIC INNOVATIONS IN ANIMAL BREEDING

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INTRODUCTION

While herdsmen have practiced the art of animal breeding since the beginning of domestication of livestock, the science of animal breeding is just now entering its second century. From its roots in Mendelian inheritance to the developments in quantitative genetics our field has now grown to include modern molecular sciences. The practical applications of the field have been to genetically improve the animals that produce meat, milk and other products of economic value. Animal breeding as commerce has always "protected" its endeavors commercially by developing breed societies and using pedigrees to protect the intellectual property developed by the master breeders. The advent of molecular biology, sequencing of genomes and the development of cloning, have brought with them large additional investments. These developments have come with the expectation of increased rewards by investing companies and the reality that technical improvements must be protected in order to obtain sufficient return. The purpose of this paper is to discuss forms of intellectual property, in particular patents and patent law, and to suggest ways it might impact the field of animal breeding and genetics.

FORMS OF INTELLECTUAL PROPERTY

Intellectual property (IP) is the property resulting from the creative or "inventive" work of an individual or individuals. The protection of IP is described in a large body of law that includes copyrights, trademarks, trade secrets, and patents. Copyrights protect IP such as articles, books, web pages, computer software and music. Copyright protection applies when the work is in a publishable form. The © symbol is not required, but recommended and enforcement of rights is made easier by federally registering the mark. In trademark law, the ™ claims common law trademark rights, while the ® indicates federal registration. Trademarks are used primarily to identify the source of the owners' goods, products or services. Examples include "Le Label Rouge", "American Berkshire Gold" and the gene marker *HAL*-1843 ™ that is associated with the gene test for porcine stress syndrome. A trade secret represents IP that is not divulged by the owner and confers some competitive advantage. Trade secrets can last as long as the information is kept secret. An example of a trade secret might be specific information to make specialized synthetic lines or calculate breeding values. Trade secret law (in the US called the Uniform Trade Secret Acts) helps protect a technology from theft but the degree of protection is dependent on the type of technology and the means used to keep the information secret.

Patents represent the largest form of IP and their development is rooted in a large body of law both in the US and abroad. Such laws and their interpretation are subject to change, especially when new technology is introduced. The descriptions that follow are meant to be general in nature. Patents were developed to "promote the progress of science and useful arts, by securing for limited times, for authors and inventors, the exclusive rights to their respective writings and discoveries" (Article 1, Section 8, US Constitution) in return for making details of inventions available to the public. Patenting was developed in order to support the development of science and innovation. A patent, once granted, represents a legal monopoly granted by the respective country's government to an inventor (specific to that country), permitting the patent owner to prohibit anyone else from making, using, or selling this invention for a specific period of time (now generally 20 years). Infringement of a patent is a civil wrong and the owner may sue for economic damages or injunction to stop infringement. Patents are intended to protect but not withhold technical information. Patents are very different from published papers. Inventors, unlike coauthors, must take part in the inventive process, not just participate in the research. Patents are not peer-reviewed but instead are assessed by patent examiners to determine the application's patentability. A patent application must disclose sufficient detail to enable "one of reasonable skill in the art" to duplicate the invention. The application must be unobvious, i.e., not a simple, obvious extension of existing technology. Novelty is the next criteria and refers to something created that is new. Lastly, the invention must be useful. The scope of patent rights is determined by the claims. Some patents, like gene marker patents, may enjoy very wide coverage across species while others may be limited to single polymorphisms in one breed. Patents may be related to a process, a product produced by a process or dependent on another patent. Patents are open to interpretation by both examiners and lawyers. In the US, patents can be applied for up to one year after publication or public disclosure but this is not allowed in other countries. Patents in and of themselves do not ensure income. They must be promoted and protected and can be viewed as tradable assets and licensed or assigned to third parties.

Confusion often exists relative to "international" patents (see http://www.cambiaip.org), which actually do not exist. Under the Paris Convention Treaty, a group of countries agreed to work with each other to provide a unified examination process and to make filing in its member countries easier by forming the World Intellectual Property Office (WIPO). In unison they adopted the one-year period in which to file an application in one of the other countries without losing the benefit of the original filing date. Using this procedure avoids the citation against the applicant of any "art" that became known after the original filing date in the country of origin, but before the filing date in another country. Under this Patent Cooperation Treaty (PCT), an applicant is allowed one year to file at the WIPO office and, by designating member countries, holds the legal rights and original filing date in those designated countries without having to file in each country or pay the national expense up front. Although there are fees associated with the PCT application, they are less than one would pay for the foreign national filings at a later date. To obtain a patent in these countries, the application does eventually need to be filed in the national patent offices, fees paid, translations done and the laws and regulations of each country office followed. The applicant may have additional time from the national filing date to request examination, depending on particular country requirements. Delaying examination may provide the time desired to continue development and/or commercialization, however, during this period, fees called "annuities" must generally be paid. Due to the expense involved, applications are generally filed only in countries where protection is really needed.

A BRIEF HISTORY OF PATENTS

The early protection of intellectual property rights can be traced back to Venice in the Middle Ages when master craftsmen in guilds prohibited competition from former apprentices for a period of 20 years (Waltersheid, 1994). Such laws had considerably different economic effects for the master craftsman, the apprentice and the general public. For livestock, early breed societies were developed and monitored pedigrees to protect the IP of the master breeders.

The first modern patent act is often thought of as The US Patent Act of 1790. There was similar legislation in France in 1791. Patents related to living matter are relatively new. One of the earliest patents for living matter was granted to L. Pasteur for a yeast strain but this was done under the belief that it was an inanimate object and not living (Lesser, 2002). The first specialized patent law applied to living organisms was that of the Plant Protection Act of 1930 in the US and provided what is commonly referred to as Plant Breeders Rights (PBR) to propagate new varieties by asexual methods. In 1961, a similar law was passed in France called the UPOV (International Union for the Protection of New Varieties of Plants - Union Internationale pour la Protection des Obtentions Végétales; http://www.upov.int). Protection in the US was expanded in 1970 with the Plant Variety Protection Act to include sexually reproduced plants. The UPOV was revised in Europe in 1991. Under these laws two principles, "breeder's rights" which allows breeders to use protected varieties without permission of the owner and "farmer's privilege" which allows farmers to collect seeds from their crops and use them, were developed (Lesser, 2002). For years many seed companies have attempted to halt this latter practice by asking farmers to sign contracts prohibiting it. Recent technology, like the "terminator" technology (Kaiser, 2000), biologically prohibits the practice. Santaniello *et al.* (2000) provides an excellent review on all aspects of patent protection for plants.

The dawning and blossoming of the molecular age presented real problems for the protection of IP related to living organisms other than plants. In 1975, a French company failed to patent a "dwarf, egg-laying chicken hen produced by a process" involving a sex-linked recessive gene (Bent, 1989). In 1980, the United States Supreme Court in a 5-4 decision (*Diamond v. Chakrabarty)* declared that "anything under the sun that is made by man" is patentable. This case concerned the patenting of genetically engineered bacteria that destroyed oil sludge. In 1987, the US Patent trade office issued a pronouncement of the patentability, in principle, of non-human multicellular organisms that were not naturally occurring (Bent, 1989). This was quickly followed in 1988 by the landmark patent on the so-called "Harvard mouse" which was engineered to be susceptible to cancer. In Europe, similar laws were passed allowing patenting of animals and animal-related inventions. From 1995 to 2001, a total of 45 animal patents were granted in the US (Lesser, 2002). While these changes in patent law had large economic implications, the social and moral ramifications were also enormous.

ANIMAL BREEDING AND GENETICS – IP PROTECTION

The broad area of biotechnology encompasses many of the patent applications in our field and the US Supreme Court has established guidelines that apply to this technology (Nebel *et al.,* 2002). The Court made it clear in *Brenner v. Manson* that patent utility implied usefulness and not just "any invention not positively harmful to society." The Court expressed reservations regarding a monopoly on compounds with unknown functions, and that utility must extend beyond proving that the product is a result of scientific research (Nebel *et al.,* 2002).

Technologies in the field of animal breeding that may require (or qualify for) IP protection include, but are not limited to: statistical methods for genetic improvement, DNA markers for genetic improvement, transgenic and cloned animals and methods to produce them, new methods to measure traits, methods to identify animals, computer software and other written materials. As previously described, manuscripts, web pages and software can be copyrighted. Other forms of technology can be protected using trade secrets or by patenting. Some companies have employed the trade secret approach, while others have used patents to protect their research and also as marketing tools. Published patents and some applications can be found at the U.S Patent and Trademark Office (http://patents.uspto.gov/), European Patent Office (http://ep.espacenet.com), and the PCT Gazette (http://pctgazette.wipo.int). At one time US applications were not published until they had been granted but they are now published 18 months after the application has been filed (non-foreign filers can opt out of 18-month publication; early publication is also available). A sample list of patents is provided in Table 1.

Table 1. Examples of patents* involving methods and genetic markers in livestock.

Species	Date	Patent No.	Abbreviated Title
Chicken	1998	US 5,707,809	Avian sex identification probes
Cattle	1991	US 5,041,371	Genetic marker for superior milk products …
Cattle	1994	US 5,374,523	Allelic variants of bovine somatotropin gene …
Cattle	1997	US 5,614,364	Genetic marker for improved milk production …
Cattle	2001	US 6,242,191	Methods for assessing the beef characteristics …
Cattle	2001	US 6,284,466	Double muscling in mammals
Cattle	2001	WO9923248**	Assessing lipid metabolism
Sheep	2001	US 6,306,591	Screening for … spider lamb syndrome in sheep
Pig	1994	US 5,358,649	Diagnosis for porcine malignant hyperthermia
Pig	1994	US 5,374,526	Method…genetic marker for increased pig litter size
Pig	2000	US 6,143,880	Pig myogenin gene … related to muscle growth
Pig	2001	US 6,183,955	Methods for determining the coat color …of a pig
All	1987	US 4,683,195	Process for amplifying … nucleic acid sequences
All	1996	US 5,582,979	Length polym. in $(dC\text{-}dA)_n.(dG\text{-}dT)_n$ sequences…
All	2001	US 6,287,564	Method of identifying high immune response …
All	2001	US 6,309,853	Modulators of body weight, …

* See http://www.genome.iastate.edu/resources/patent/table1.html ** Pending application

Two noteworthy patents, US patents 4,683,195 covering PCR and 5,582,979 covering dinucleotide repeats, have extremely broad coverage and affect gene discovery and use of many types of genetic (microsatellite) markers. Perhaps the best known and largest single royalty-generating patent in animal breeding was patent 5,358,649 involving *HAL* 1843™. There was some debate in the scientific community as to the validity of the *HAL* patent since the result seemed quite obvious once the gene became a candidate (see Fujii *et al.,* 1991). Indeed, the *HAL* invention was even predicted in publications where the strategy for finding the mutation was developed (e.g. MacLennan *et al.,* 1990). However, this opinion was based, at least in part, on a misunderstanding of the term obviousness as required for patentability. Patent 5,374,526, which was a method to use *ESR* gene polymorphisms to improve litter size (Rothschild *et al.,* 1994) stirred considerable debate, not only on the scientific merit of the method, as it was the first to claim use of a marker for a quantitative trait, but also because the patent had been exclusively licensed to one breeding company. In addition, some confusion existed early in the development of patents in animal breeding as to whether the genes were patented or whether a process or method involving genes and markers was being patented. This was particularly evident in the discussions that followed the *ESR* patent application (see Rothschild and Plastow, 2002). However, the issue of patenting gene sequences has raised both legal and commercial concerns. This issue came to the forefront when C. Venter, then from NIH, and colleagues applied for a patent on discovered expressed sequence tags (ESTs). In the first review of the application the patent office rejected all the claims for failure to meet the criteria of utility, novelty, and non-obviousness. The ESTs do not specifically define gene function but they provide information for isolation of the entire gene and for determining the gene location in relationship to previously mapped QTL. Considerable patent case law now exists which relates to their utility, non-obviousness, and enablement (Nebel *et al.,* 2002). The patent office has decided ESTs are patentable if it can be shown that they are useful, but if the patent does not claim the entire gene sequence it has limited economic value. Companies, like Incyte Pharmaceuticals, have protected these ESTs by creating proprietary databases that are useful in predicting gene function and in the development of medical and veterinary technologies.

Patent coverage in not just confined to genetic markers. Lines of pigs or chickens have been patented and can be viewed as a specialized extension of early breed development or trademarking for protection of this IP. Other patents exist for methods involving cellular and animal manipulation and involve processes like stem cell development, transgenic production (i.e., US 6,271,436) and cloning (i.e., US 6,215,041 or US 6,258,998). Several advances related to mechanical or electronic devices have been made and include new A.I. or embryo transfer tools, advanced ultra-sound equipment, formulas and methods to measure backfat and other traits in livestock (i.e., see early patent US 4,359,055 and more recent US 5,717,142). The increasing need for traceability of animals and animal products has spawned a number of inventions including electronic ID tags and retinal scanning methods and devices.

Considerable discussion has ensued recently from a patent entitled "Method of Bovine Herd Management" granted in the U.S. in 1994 and later in Canada (Schaeffer, 2002). The invention is for the “test-day model” and includes the gathering, mathematical treatment, and the use of the modified data by dairy producers. The novelty and unobviousness of the patent has been seriously questioned. It was pointed out that the practices of gathering, manipulating and using data by dairy producers have existed for nearly 100 years. The patent therefore claims rights to a practice that has been public knowledge for a long time. The novel idea within the patent was the specific mathematical model and procedures that Everett and co-workers developed for the analysis of test day yields. Everett was also not the first researcher to apply a model to test day records and as has been demonstrated, the model as described in the patent, is not necessarily the best model that could be applied (Schaeffer, 2002). This patent generated considerable discussion. It has been argued “what would the field of animal breeding be if the selection index or Henderson’s BLUP had been patented?” Yet while quantitative geneticists see the thought of such protection as sacrilege, molecular scientists accept (but may not like) that in a similar way the foundation patent for PCR exists and royalties must be paid for its use.

OTHER LEGAL CONSIDERATIONS

In the US and some other countries, there is no clear exception to infringement for research use of patented inventions, even in non-profit or educational institutions. Researchers are required to obtain a license or permission from the patent owner to use a protected invention for research purposes. In other countries, there is either an exemption for educational or non-commercial research or research on improving the invention. Research using the invention, however, is not allowed. Researchers should also be concerned with possible claims for “contributory infringement,” i.e., assisting someone else to infringe on a patent. For example, due to a claim of possible contributory infringement, the US Genome Coordinators were asked to halt the practice of supplying primers for microsatellite analysis to other researchers. To resolve the issue the Coordinators began buying the primers from a company with a research license.

ETHICAL, SOCIAL AND ECONOMIC ISSUES

Many ethical and social issues have been raised related to patenting of animals and genes (Bent, 1989; Brody, 1989; Dresser, 1988; Evans, 2002). These include: 1) patenting of animals or genes will be destructive to nature and allows man to play "God"; 2) patenting will devalue animal life and hence human life; 3) patenting will increase animal suffering; 4) patenting will lead to a decline in genetic diversity of animals and threaten species; 5) patenting speeds the trend toward commercialization of academic research and 6) patenting will undermine conventional farming and lead to increased industrial farming systems. Early humans domesticated animals and master breeders and geneticists have transformed them into productive species. Was this playing "God" or interfering with nature? The use of transgenics for making specialized animal lines for disease research is certainly adapting nature but does it devalue life and is it unethical or immoral? These are value judgements that most in society have decided are acceptable (Brody, 1989). Certainly some lines have been (and need to be) drawn to delineate what is acceptable and unacceptable. For example, most people and governments have concluded that while cloning of animals is acceptable (at least for research purposes), cloning of humans, for whatever reason, is immoral, unethical and to be avoided.

Animal welfare and animal rights issues continue to be at the forefront of livestock production and biomedical research (Evans, 2002). Individuals who believe that animals have "rights" will likely be opposed to patenting any invention derived from animal research. The most commonly cited examples are those relating to transgenic animals (i.e., early transgenic pigs) in which some animals had health problems. Production and patenting of specialized lines of rodents for biomedical research that have a tendency to develop specific diseases is also considered unethical by animal rights activists (Brody, 1989). If, however, individuals believe that animal rights are subordinate to those of humans, but that they deserve proper care and welfare then the issue of patenting is much less of a concern.

It has been suggested that through the use of gene markers and highly selective breeding, or through the use of transgenics and cloning, that genetic diversity will be greatly reduced. Certainly these methods have the potential to remove within-line variation but they are likely to increase between-line variability. However, it may be argued that the patent system in fact encourages diversity as it promotes and helps establish, via patent-related deposits of biological materials, a broader genetic diversity (Bent, 1989). Related to this issue is the issue of patenting of products from animals or plants from developing countries. Should companies be allowed to sample and alter wild stocks and to subsequently earn great sums of money by then selling them to both developed countries and back to the countries from where they were obtained? Some individuals say this so-called biopiracy is encouraged by patenting and some countries are moving to address these concerns (Evans, 2002). An extension of this is the issue of species integrity. The development of transgenic pigs for xenotransplantation and other species with human genes for human protein production threatens the genetic lines that determine species. While consideration of xenotransplantation has slowed due to fears of retroviruses and diseases like mad cow disease and AIDS, as Evans (2002) points out this dispute over species integrity "is not empirical" but it is tied up in the individual and societal views on nature and "the notion of awe and wonder." It is likely, no matter how repugnant this process is to some, there will be development of transgenic lines of animals for biomedical research (not food production) and applications that do encompass genes from other species.

In a perfect world, public support of research would be 100% of required funding and all IP would be publicly available in the country of origin. Many US public institutions are now funded at about 40% of total budgets and pressures to obtain outside funding are growing. Companies supplying funding expect to "own", through licensing agreements or otherwise, the IP that results. Protection of IP can provide research partners a greater basis for trust and exchange of ideas and help insure that public institutions focus research on areas of high relevance and payoff. Commercial relationships also aid in technology transfer, employment opportunities for students and may allow for research opportunities not available in the public sector. Fretz and MacKenzie (2002) have suggested that: 1) such activities serve the public good; 2) short term, low quality research should not be favored in order to obtain funding; 3) managing of IP must be a balance of serving the institution, funding agency and public; 4) independence of the researcher and institution must be maintained; 5) the mission of the public institution is not altered and 6) conflicts of interest should be avoided. Institutions must be proactive in balancing funding, IP protection and commercialization.

Does patenting increase the likelihood of "industrial farming?" Economic and governmental issues certainly play a role in the size of the average farm and the level of commercialization of farming. It can be argued that if large companies have exclusive licensing arrangements for genetic tools then small breeders will be disadvantaged. Market pressures related to size of operation and efficiency of production are much larger influences on the industrialization of farming and livestock production than patenting.

Other issues regarding patenting that have an economic basis can be discussed. Langinier and Moschini (2002) provide an excellent review of the economics of patenting and the benefits and costs that are derived. While inventors would prefer broader claims, limited claims encourage competition and further innovation. Complex products often require building on other patents. Unfortunately, development does become blocked by other patents (especially at the leading edge) and this has negative effects on both the developer as well as the public. Licensing of patents exclusively to one company may benefit that company and segments of the public but might also limit further innovation and not be in all the public's best interest. Langinier and Moschini (2002) concluded "that continued efforts are required to improve the workings of the patent system" to improve the economic performance of the system.

CONCLUSIONS

In the 21st century sequenced genomes, transgenic livestock and cloned animals will become the norm. These discoveries and their uses represent the intellectual property of individuals and teams. Bruce Lehman, former US Commissioner of Patents and Trademarks, has said, "The only wealth there is in the world is the wealth that comes from the human mind." Animal breeders have begun to patent their IP and this has raised economic, legal and ethical concerns that might affect the support of public education and research. Patents do not block the spread of knowledge but instead can aid technology transfer. The "landscape" of agriculture has changed with increased vertical integration of production and there is more control from the farm to the consumer's table. Inventions move more quickly into the market place but certain production sectors may be disadvantaged. While the public is concerned about the safety of products and access to them, it must be assured that patenting will continue to promote progress and not prevent it. Patent applications must not be frivolous and the real costs of patenting must be reasonable. A reasonable percentage of profits from patenting must be reinvested into research to promote future discovery. Finally, scientists must work to see that the IP that is produced has usefulness, does not harm animals or humans and promotes the public good.

ACKNOWLEDGEMENTS
The author expresses his sincere appreciation for the invitation to speak at the 7 th WCGALP. Suggestions by Graham Plastow, Scott Newman, Donna Johns and Heidi Nebel are appreciated. Partial financial support for grants was provided by PIC USA, Sygen International and the IAHEES, paper no. J-19688, project no. 3600, as well as by Hatch Act and State of Iowa funds.

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Animal breeding and genetics changed markedly in the 20th century and changes in the 21st century should likely be larger with sequenced genomes, transgenic livestock and cloned animals becoming the norm. These discoveries and their uses represent the intellectual property or "inventive" work of individuals and teams. Animal breeders in universities and in governmental research labs have begun to protect their inventive works through patenting. This change has alarmed and threatened some of the public and raised economic, legal and ethical concerns. Patents do not prevent the spread of knowledge but have aided technology transfer. Patent applications must not be frivolous and the real costs of patenting must be reasonable. Profits from patenting must be reinvested into the research system to promote future discovery. As scientists and inventors we must work to see that inventions that are produced have usefulness for society, do not harm animals or humans and do the most to promote the public good.