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Patent or perish? An ethical approach to patenting human genes and proteins

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The morality of patents and the system to enforce them has been one of the more controversial aspects of biotechnology.[1] Of all the areas of modern science and technology that involve intellectual property protection, it is the patenting of biotechnology inventions, and specifically genes, that has captured the greatest public attention and controversy. Although early patents on medical products of biotechnology, such as insulin, and early genetic engineering techniques have expired, there is an expanding rate of new patent applications for novel gene and protein discoveries, and new processes.

The patents include claims for genomic DNA sequences, complementary DNAs,[2] individual mutations, expressed sequence tags (ESTs) and single nucleotide polymorphisms (SNPs).[3] The coverage of these patents and their enforcement has global implications, between the private and public sector and between rich and poor countries. Like the technology that intellectual property (IP) protection is applied to protect, IP protection is a system that needs to be subject to ethical analysis to examine whether it is suitable for a moral society.

The question of how many patents were issued has become an annual question asked of academic researchers around the world. Previously, this was an expectation limited to those working in industry, but it has spread through government departments and universities, as witnessed by the distribution of gene patents.[4] We can ask whether the old axiom, 'publish or perish', can be complemented by a new axiom, 'patent or perish'?

While there are many contentious areas of biotechnology regarding IP protection, like stem cells,[5] this article focuses on human genes and proteins because the criteria of human DNA, or human experiments, are objective selection criteria that can be used as markers for ethical review in a patent application. The principles outlined here can be applied to many other areas, and may be cloudy when hydrid genes are constructed between species, but use the model of human genetic information represented in any form: DNA, mRNA, cDNA or protein.

We can ask whether the patenting of genes is an ethical activity, and if so, what conditions might make it more ethical. There have been objections by scientists for the extension of IP protection into areas that were previously in the public domain,[6] with debates over cases such as ESTs and basic research tools like polymerase chain reaction (PCR). The European Biotechnology Directive,[7] emphasizes that patent law is not the forum to make a judgement on what types of research should be conducted or commercialized. However, as for any human activity where decisions must be made, both stages have moral implications. We can consider two distinct stages in the patent system: the process leading up to the award of the patent, and the implementation and enforcement system.

There are grounds already established for the exclusion of patentability based on ethical concerns in a number of patent systems, and these date back to more than a century.[8] Article 53(a) in the European Patent Convention, and Article 6 in the Directive, says 'if the exploitation of the invention would be contrary to morality' a patent shall not be granted.[9,10] These grounds are part of the societal governance of biotechnology, attempting to lead research in ways that are consistent with social values. If patent offices consider the ethical issues relating to inventions, they can provide an additional social mechanism for society to guide research interests, beyond the limits that are already partially imposed on publicly funded research, by limiting the fields of research that can receive public funds.

Ethically, one can start by asking rather simple questions. Is the principle of beneficence, or loving good, served more by having research than by not having research, and do we generate more research into more beneficial areas of science encouraged by the incentive system of patents than we would by not having patents? Are other ethical principles such as justice and doing no harm served by systems of intellectual property protection? Does it make any difference whether the product or process involves living organisms or rocks? Should practical law be expected to share the same goals as that of ethics, namely can we expect laws that reflect social ethics, or should we be satisfied with some compromise?

Ethically, can anyone own a product of their mind, a product of nature, a product of a designed process, a discovery, or even an invention?[11] Intellectual property rights (IPRs) are the rights given to persons over the

creations of their minds. There are several systems of IP protection designed to reward inventors, for example, patents, trademarks, copyright, plant variety rights. To qualify for a patent, an invention must be novel, nonobvious and useful. Patents can generally be sought either on products or processes used to manufacture the product. It is easier to obtain a process patent, but it has been harder to prove that a competitor is using your process, as access to their production facilities may be restricted.

A new use of a known protein can be patented even if it is patented for another use, as can a structure.[12] Patented information may also be used in the study of a particular disease, for example, by the introduction of a gene into an animal to make a model of a particular human disease, and it was for this reason 'Oncomouse' was patented in 1988 in the USA.[13] The Oncomouse patent led to a global debate over the morality of patenting animals, a practice that was continued in the USA after a brief delay, and in Europe after a decade of debate.

Some argue that genomics is no different from other sciences for IPRs.[14] The trend to apply for patent protection on a large number of genes simultaneously has broad socioeconomic impact because a few companies are dominating genomic sequencing. The companies, Celera and TIGR, have sequenced a substantial proportion of the complete genomes to be sequenced,[15] raising questions about whether the new technology really should be subject to the same type of patent system.[16] The extent of this expansion of patents made people ask what are the limits to commercialization of the human body, and some suggested that our species name be changed to 'Homo economicus'?[17]

PREPATENT ETHICAL CRITERIA

I propose the following criteria for ethical issuing of biotechnology patents. Let us consider this as a type of checklist, to elaborate how the criteria of novelty, nonobviousness, utility and pubic morality might be used in practice. I would encourage that this checklist be used by inventors and patent offices to make the system more ethical.

Prohibit if the Research Leading to the Patent Involved Unethical Research

The first question is to judge whether the research leading to the patent application itself is ethical.[18] This requires a social consensus on the tolerable limits of doing harm to research subjects, either animals on humans, but a parallel is seen in the policy of scientific journals to refuse to publish the results of unethical research. The issue of animal welfare was of major debate in the 1990s, with the test case of Oncomouse in Europe, but is not specifically related to genetic material.

Ensuring that human participants in research gave informed consent would seem to be one of the easier ethical criteria for the patent office to examine, and I would urge patent offices to require the same data that a scientific journal would require for publication of the paper, namely proof of consent and a letter from the relevant ethics committees that any research was conducted following ethical practices. This does not necessarily mean that specific consent is required from the genetic donor for filing the patent application, but at a minimum there should be consent for the procedures that resulted in provision of the biological sample to the researchers. In Article 26 of the European Biotechnology Directive, consent to removal of genetic material is said to be desirable, but it is left up to national governance. Each country has its own specific legal obligations for human rights laws and international conventions.

Prohibit if There is Likely Harm to Human Moral Order Including the Environment

The exclusions to inventions relate to those judged contrary to *ordre public* or morality, but the difficulty is how to interpret these. Public opinion surveys may find little support for patenting genes or living organisms.[19,20] There are mixed religious views on the issue.[21] However, the ethical debate has not led to a consensus that there is any special nature of human genetic material that precludes patenting.[22] In Article 36 in the European Biotechnology Directive, inventions that cause 'serious prejudice to the environment' are excluded from patentability, but this does not directly relate to gene patents.

'The Genome in its Natural State Shall not be Patented'

There is global agreement with Article 4 of the Universal Declaration on the Human Genome and Human Rights, passed by the UNESCO General Assembly in 1997, and adopted by the UN General Assembly in 1998, which states: 'The human genome in its natural state shall not give rise to financial gain.'[23] Interpretations of what 'natural state' means are subjective, given that what is being patented is not a chemical substance but the information included in the sequence. Is complementary DNA really a man-made substance, whereas the same sequence information in the mRNA is 'natural'? It can be compared to distinguishing a virus that was entirely chemically synthesized from a virus made in a cell. The Nuffield Council on Ethics report on patenting recommended that 'the identification of DNA sequences through the use of computational techniques should not be regarded as 'inventive'.[24]

Even if we accept that cDNA and ESTs are patentable, they may not be useful in the patent sense. The Human Genome Organization (HUGO) in 1997 and 2000 urged patent offices to rescind decisions that allowed ESTs to be patented based on the utility of the gene sequence as mere probes to identify specific DNA sequences, and to strictly limit their claims to specified uses, since it would be untenable to make all subsequent innovations in which EST sequences would be involved in one way or other dependent on such patents.[25] HUGO also '*maintains* that SNPs, as a rule, *cannot meet the requirement of inventiveness* (nonobviousness)' that is necessary for issuing patents. SNPs are common DNA sequence variations among individuals and concerns about patenting led to

the cooperative SNPs Consortium[26] to make a map of SNPs publicly available and freely accessible, which by its openness could not be patented.

Award Patents Only to Inventions

There has also been extensive debate on whether a gene sequence is an invention or merely a discovery. In the latter case, the discovery of a star does not allow exclusive use, so why should the discovery of a gene entitle someone to exclusive use? If the claimed invention is the next most logical step that is clear to workers in that field, then it cannot be inventive in the patent sense. If a protein sequence is known, then the DNA sequences that code for it will not in general be patentable, unless there is a sequence that is particularly advantageous, and there is no obvious reason to have selected this sequence from the other sequences that code for the protein. In the case of natural products, there are often difficulties because many groups may have published progressive details of a molecule or sequence, so it may have lost its novelty and nonobviousness. However, recently, genomics companies have applied for patents on previously published sequences from databases, and in the United States a policy seems to be emerging that will favour reward of research investment and interpret novelty in such a way so as to encourage industry.

Another example is patents on short oligonucleotide probes used in genetic screening.[27] If someone can demonstrate the use for a larger piece of DNA such as its use as a genetic marker, then they can theoretically obtain a patent on it. The doctrine of equivalents prevents inventors from making only minor changes to a patented invention and then claiming it to be a new invention, but the interpretation of this doctrine is somewhat subjective. One of the arguments patent offices have used to claim that they are not an appropriate body to adjudicate on the morality of inventions is that it is a subjective process. However, the nonobviousness and novelty criteria are subjective decisions in the age of the incremental development of knowledge, especially when researchers are under pressure to patent or perish.

Is the Principle of Beneficence, or Loving Good, Served More by Issuing the Patent and the Production of the Product, or Provision of Services, Included in the Patent?

A patent should produce benefit for society beyond the inventor. This is linked to one of the criteria for awarding a patent, utility. There is debate over whether ethical principles that apply to individuals, like beneficence, also apply to organizations.[28] Article 27 of the Universal Declaration of Human Rights states that everyone has the right 'to share in scientific advancement and its benefits'. This is a general criterion, not specific for gene patents; however, the argument is often used in the patent debates to support IPRs.

The principal benefit claimed for patents is that rewarding an inventor creates a positive and open environment for progress of research, which leads to the betterment of society.[29] Economists call this the invention inducement theory. History suggests that the financial interest in a free market creates more funding for research, and faster overall progress in important areas has been the result of intense research efforts. In the case of the human genome project, it led to not only a faster completion data but also to a reduction in estimated costs of the project. However, some suggested that recent patents may even inhibit research by discouraging investment into areas where there are already many broad patents,[30] and policy changes to make stricter criteria have been suggested as one means to counter this.[31]

The disclosure theory argues that a patent guarantees the publication of the results and the deposit of the product, or modified organism, in a central repository, for use in the future development of research to create better inventions. An alternative system for protecting an invention against being used by a competitor is keeping it as a trade secret. Research results may not be published at all if an inventor, and the company that produces the products of the invention do not think they can keep to themselves the benefits of the research costs invested, or the money used to purchase the rights to the use of results. The closing of results from other workers is against the principle of scientific openness, but is a common feature of certain forms of industrial research, especially when the process used to create a product could be expected to be kept a secret for some years. However, this latter possibility is small, given the current state of molecular biological technology that easily allows protein, RNA and DNA sequencing. However, there has been controversy over the trends for some journals to allow scientific papers to be published without submission of all the DNA data to a database that permits immediate and unlimited access by researchers, like the Celera human genome sequence paper and the Syngenta rice genome sequence paper.[32]

Limit the Scope of Patents

One approach that can work to encourage inventiveness, and to reflect the amount of work that went into an invention, is to limit the scope of a patent. There has been controversy over the claims made for some patents, for example, Myriad Genetics patents over the BRCA1 and BRCA2 genes. Myriad has used its patents to attempt to limit any other company from conducting breast cancer gene tests for these two genes, and they cover both genes and proteins and are claiming to cover the modes of action of the genes as well. This issue is still to be resolved, despite strong criticism.[33]

Is Justice Served by this Patent?

Global inequity is not a new problem, but it is of central importance. Because of the importance of international protection of IPRs for technological and cultural exchanges and promotion of free trade, there is an international system for IPRs. In 1883 the Paris Convention for the Protection of Intellectual Property was established, and in 1886, the Berne Convention for the Protection of Literary and

Artistic Works was established. The European Patent Office (EPO) in Munich was established to coordinate IPRs inside some European countries. In 1970, the World Intellectual Property Organization (WIPO) was established as the appropriate specialized United Nations agency to administer conventions and promote the worldwide protection of IPRs. IPRs regarding biotechnology have been discussed at various international forums including WIPO, WTO, UNESCO,[34] and UPOV, as well as at each national patent office. By April 1998, 132 countries had signed the Trade Related Aspects of Intellectual Property Rights (TRIPs) agreement, discussed under the General Agreement on Tariffs and Trade (GATT) and the WTO. There have been possible conflicts observed in Article 27 of the TRIPs agreement by the United Nations Commission on Human Rights.[35]

The discussion has often become political and heated, with some viewing patents as a source of legitimate national wealth and others viewing them as the epitome of exploitation of the poor. There are always winners and losers in trade, both within a local community and within the global community. The ethical principles of justice and nonmaleficence need to be considered not only by the global community but also by all responsible government agencies. Since 99%+ of human genetic material is shared by all persons, in a sense the genome is the property of all,[36] justice would give everyone some right to a sense of 'ownership' of any common sequence.

The right of governments to impose compulsory licensing in medical interventions to protect public health was affirmed by WTO in the Doha Declaration, which specifically mentioned measures against 'exclusive rights to the diagnostic use of a DNA sequence'.[37]

Does Issuing a Patent Reflect Proportionately the Prior Art and Indigenous Knowledge?

Research is often incremental, involving contributions from many persons, so a monopoly upon the use of a gene or protein structure may not reflect proportionately the work spent in obtaining the 'invention'. Should only the final step be rewarded? It would not seem to be fair. This issue has been raised in agriculture, considering rewards to farmers for their innovations in the development of plant and animal varieties. Is there knowledge that should be the global commons?[38]

Is the Patent Consistent with the Provisions of the Convention on Biological Diversity (CBD), which Give Nations Sovereignty over Plant and Animal Genetic Resources Collected after 1992?

Under the CBD, states have a sovereign right to exploit their own plant and animal genetic resources, and to determine access to genetic resources. This means that the state where the patenting occurs will have to prove that prior informed consent of the state where the genetic resources were obtained, before the research was carried out was obtained. In addition, it should be shown that a mutually agreed fair and equitable sharing of the results of research, which is carried out on the genetic resources of the source state is facilitated. CBD has been interpreted by member states not to cover human DNA. However, as more hybrid DNA sequences are used in protein engineering, the boundary between species will be less clear. This question is complicated because some countries, like the USA, have not signed or ratified the CBD.

POSTPATENT PROCEDURES AND GOVERNANCE

One of the arguments expressed when supporting patenting of biotechnology inventions is that patent law regulates inventiveness, not commercial uses of inventions. Some claim that the patent process itself is ethically neutral, but all agree that the commercial use of inventions is not dependent upon the patent itself, rather it is subject to social demands. Therefore, some of the ethical concerns relating to economic issues resulting from IPRs may be more appropriately dealt with by postpatent implementation measures, voluntary or not. These could be legitimately said to be within the mandate of good governance of a society because of their broad implications.[39] There are similar issues for international governance, for example, by the World Intellectual Property Organisation (WIPO); however, politics may make consensus less likely. Some of the ethical concerns of governance include the following:

Measures to Share the Benefits with the Communities Whose Ideas Gave Rise to the Pursuit of a New Product, for Example, with Medicinal Plants

These could be legally binding upon parties to international treaties, as have been agreed in the benefit-sharing schemes for plant and animal resources, the so-called Bonn Guidelines.[40] For human genetic material, voluntary measures have been suggested by the HUGO Ethics Committee for a contribution to be decided by each company using human genetic resources of between 1 and 3% of net profit to humanitarian purposes.[41] The ethical principle of justice supports returning benefits to the community involved in the development of a product, or in the subsequent clinical trials that showed whether a product was safe and efficient to use.

Set Limits to the Rigid Enforcement of Patents if Price Becomes a Barrier to Use of a Product by Persons in Need

TRIPs Article 31b has been interpreted that a state can produce drugs at low price when there is a condition of national emergency, as seen in the AIDS crisis facing Africa. There are numerous other examples of diseases in the world, where price is an insurmountable barrier to access drugs for sick persons. There are a variety of ethical positions that have been argued for this case, but the ideal resolution of the conflicts will be for reciprocity and cooperation between pharmaceutical companies and developing nations.[42]

The global pharmaceutical industry sales reveal that most companies make close to half their profits in the US market, which raises the ethical ques-

tion of whether high drug prices in the OECD countries should be used to pay for the research and development of new medicines and technologies, and other countries whose economies cannot support the same prices should be offered drugs at low prices. A practical ethics would concur with the ethical principle of beneficence — that the poorest countries in the world cannot be expected to pay the same price for drugs or technology.

Government Price Controls

Given the already extensive history of discussion of the gap between the poor and rich, regulation by governments, and international society, may be the only way to ensure equity.[43] There are direct and indirect methods of control used by governments. An indirect method is a limit set by a government for reimbursement of drugs or devices used in the health system. The ethical question is what is a reasonable profit for a company? Some argue that there should be no limit to profit except the free market,[44] although there may be good reasons to check the prices charged, especially if one suspects that different companies have adopted agreements designed to inflate prices, as has been found in the pharmaceutical industry.[45]

CONCLUSIONS

In conclusion, it is time to move from the rhetoric of debate, and uncertainty for industry and the public, towards using many measures already in the system in a more defined framework for assessing the morality of patent applications. While the difference between an ethical and an unethical application of intellectual property law is not easily assessed by objective criteria, the above steps could be used by inventors, patent offices and regulatory systems empowered by governments to make the system more ethical. I call upon patent offices to devote sufficient human resources to examine the morality of patent applications in order to better represent the concerns of society, and not to hide beyond the false argument that it is too subjective. To start with, the issues associated with human genetic information, and those inventions that involved human experiments, could be an objective criterion for patent offices to use to fulfil the moral expectations that society, including scientists, expects of them.

While some have suggested that special ethics review boards be established to assess the morality of selected biotechnology patents that present social and ethical questions,[46] I would argue that the patent office should be prepared to assess the morality of any patent application by having ethics experts among their staff. Sufficient resources should be given to allow patent offices to exercise good and ethical governance of the task society expects of them. In fact, as at the beginning, there are ethical and moral issues involved in research that lead to patents in many fields of science, and in the utilization of many patents, and the societal trend is to have more concern over these issues and their governance.

DUALITY OF INTEREST

None declared.

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