Gene patents in Europe

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History of gene patents in Europe

> "*Genes are the currency of the future*": George Poste, then research director of SmithKline Beecham, 1993.[1]

The process of granting 'patents on life' began with the 1980 ruling of the US Supreme Court, in the landmark case of Diamond v. Chakrabarty, followed by decisions by the US Patent and Trademark Office (USPTO) in 1985 and 1987 that plants and animals are also patentable. It was these decisions, and the international agreements that followed, that drove corporate investment in biotechnology, because it allowed the new developments in bioscience and biotechnology to be controlled, privatised and traded.[2]

Significant US government support for genetic engineering and human genome sequencing as future drivers of competitiveness and growth began with two reports published by the US Office of Technology Assessment in 1981 (genetic engineering of micro-organisms, plants and animals[3]) and 1986 (human genetics[4]).

The idea that gene patenting and biotechnology was central to future competitiveness and growth was then rapidly adopted in the EU and by other OECD countries, leading to significant changes in research funding systems and research priorities in both health and agriculture.[5]

In 1988, a Committee of Experts on Biotechnological Inventions and Industrial Property established by the World Intellectual Property Organisation (WIPO) proposed that biotechnological products and processes should be patentable, provided the usual conditions for patenting were met. [6] The EC published the first draft of its controversial Directive on patenting in biotechnology the same year: however, it was ten years before it was adopted, due to major opposition within Europe to the idea of 'patents on life'.

In July 1997, the European Parliament finally voted in favour of a proposed European Directive on the 'Legal Protection of Biotechnological Inventions', reversing its earlier opposition to gene patenting and clearing the way for the Directive's adoption as EC Directive 98/44/EC. Lobbying for the Directive was led by Dr Nick-Scott Ram, who chaired committees on Intellectual Property and Regulatory Affairs for the BioIndustry Association (BIA), Association of British Pharmaceutical Industry (ABPI) and EuropaBio, and who was awarded the MBE for services to biotechnology in 2001.[7,8,9] The pharmaceutical company SmithKline Beecham is also credited with paying a key role in securing adoption of the Directive, especially via its lobbying and funding of patient groups such as the Genetic Interest Group (GIG), and the role of David Earnshaw, the company's Director of European Government Affairs and Public Policy in Brussels.[10,11,12] George Poste, then chair of research and development at SmithKline Beecham, was also involved in the negotiations.[13] In Britain, the Blair government was a strong supporter of the move (New Labour obtained much of its funding from biotech investors and appointed them as key advisors to the government). [14,15]

The approach taken in the Directive was supported by the Wellcome Trust (a major funder of the Human Genome Project), which opposed the patenting of 'raw' gene sequences (information on genes published without knowledge of their function).[16] Thus, although the Wellcome Trust played a key role in portraying the Human Genome Project as a battle between public and private interests, it merely supported different private interests (based on the view that Britain could win the race to identify gene functions and gene-disease associations and thus commercialise its findings at a later stage), which were threatened by Craig Venter.

In the US, a patent must be novel (not previously made public), non-obvious (to someone 'skilled in the art') and useful. In Europe, the invention must be novel, must constitute an inventive step and must demonstrate industrial applicability. These three requirements are broadly equivalent, although there are some important differences between the two different systems. In both systems, genetic sequences are argued to be novel (i.e. 'inventions' rather than discoveries) because they are patented in an isolated and purified form.

To meet the "industrial applicability" requirement (equivalent to showing 'utility' in the US), the EU Biotechnology Directive requires a gene patent 'to specify which protein or part of a protein is produced or what function it [the gene] performs'. As Calvert notes[17], patenting fits nicely into the simplified model of biology known as the 'central dogma' because this involves an assumption that if the function of the gene is discovered, then there will necessarily be a link to a protein, and that this protein will result in a trait (such as increased risk of a disease). In this sense there is a parallel between the central dogma and the patenting requirements.

The Directive is clear that isolated DNA is patentable in Europe: for this reason, some commentators have suggested that the US Myriad patent case will have little impact in Europe. However, other aspects of the Directive are less clear, especially what exactly is needed to demonstrate "industrial applicability", which has led to different decisions being made by different courts at different times.[18]

Extent of gene patenting

The system of granting patents in Europe is complicated because companies can apply for patents in individual countries as well as at a European level, via the European Patent Office (EPO) in Munich, Germany. The EPO covers not just EU member states but also other European countries such as Switzerland and Norway.

A 2008 report from the UK Intellectual Property Office shows that the numbers of patents for inventions in the general field of biotechnology, which includes genomics and genomic medicine, represent a significant portion of the overall numbers of patents applied for in the last 20 years.[19] From 1985 to 2000, the numbers of biotechnological patents increased significantly, however there has been a decline since 2000. The downturn is most noticeable in relation to patents for new human genes. There has instead been an increased emphasis on the diagnostic uses of genetic information. The courts' interpretation of a valid use has also become more restricted: one recent UK court case confirmed that patents based on speculative uses (many of which were granted in the past) will not be considered valid in the future.[20]

The discovery of a new link between a human gene and a disease forms the basis of many patent applications. The main claimed uses of DNA patents filed between 1996 and 1999 were as research tools (27% of DNA patents) and as genetic tests or diagnostics (18%): although many such patents had no immediate therapeutic value.[21]

However, the UK Intellectual Property Office reports that the numbers of patents for mere detection of common genetic variations (the simplest of which are known as SNPs, or single nucleotide polymorphisms) has been in decline since 1998. The focus of activity has switched towards diagnostic methods based on the discoveries of correlations of SNPs and haplotypes (haploid genotypes: a combination of genetic variants at different places on the same chromosome, that may be inherited together) with diseases, particularly cancer. UK companies which are particularly active in this area are AstraZeneca, GlaxoSmithKline, ICI, and the University of Oxford's technology transfer company, Isis Innovation, as well as Imperial College Innovations Limited and University of Cambridge Technology. The Medical Research Council (MRC), UK Government and the charity Cancer Research UK have also applied for patents in these areas (although Cancer Research UK regards some of its patents as defensive, given its past involvement in the dispute with Myriad). Two UK hospital trusts, Tayside Universities Hospitals and St James & Seacroft University Hospitals, have recently begun to file patents in the area of gene expression profiles and SNP/haplotypes respectively.

The decline in human gene patents partly reflects the large number of genes that have already been patented, but it also reflects the failure of the idea that identifying and patenting genes 'for' common diseases would underpin a global revolution in health and form the foundation of a new medical biotech industry. These so-called third-generation biotech firms focused on the applications of genomics and bioinformatics (the fruits of the Human Genome Project) rather than on producing genetically-engineered drugs (such as human insulin) or second-generation products such as EPO. They suffered from (i) the increasing recognition of biological complexity; and (ii) the bursting of the "biotech bubble" that developed in the late 1990s.[22] Since then, venture capital investors have invested in early stage biotech products rather than business models that rest solely on buying and selling human genetic data.

The most striking feature of patent activity in relation to agriculture has been in the area of genetic engineering of plants. Between 1990 and 2000, Oldham and Cutter identified approximately 15,064 publications in this area in the global patent data, increasing to 29,684 by 2004 and 32,667 by 2005.[23] The reason is that patenting gives commercial companies increased control over the global market for seeds. Under European patent law there is an exemption for "essentially biological processes for the production of plants or animals", which means that most non-GM plants cannot be patented, although this exemption is currently being tested as companies seek to expand patenting beyond GM to include conventional breeding.[24] Many of the relevant patents are concentrated in the hands of the six global seed companies, Monsanto, Dow, DuPont, BASF, Bayer and Syngenta. However, UK spin-out companies such as the John Innes Centre Innovations Ltd (the technology transfer company of the UK Biotechnology and Biological Sciences Research Council's John Innes Centre) are also active in this area.

Nevertheless, commercial-scale products remain restricted to two traits (herbicide tolerance and insect resistance), mainly in maize and soya.

No Patents on Seeds (a campaign group based in Munich), has recently highlighted how the current practice of the European Patent Office (EPO) is eroding the existing legal prohibition on patents on conventional plant breeding.[25] According to recent research that was conducted by Ruth Tippe from No Patents On Life![26], at least 250 patent applications on genetically engineered plants were filed at the EPO in 2010.[27] A further 100 patent applications that cover conventional plant breeding were identified. Patents on conventional breeding are filed in increasing numbers, especially by Monsanto, Syngenta and Dupont. In addition about 25 patents concerned with animal breeding were applied for at the EPO. In 2010 about 200 patents on seed with and without genetic engineering were granted at the EPO.

Concerns about gene patenting

Concerns about patents in medicine have generally focused on how the granting of monopoly rights increases prices and can restrict access to vital drugs (for example, for treating HIV). However, restrictions on access to useful technologies may not be the greatest concern in the area of gene patenting, where many (although not all) applications of these genetic technologies themselves may be harmful or undesirable.

The Food Ethics Council describes additional concerns that[28]:

- Intellectual Property (IP) protection is based on an individualistic model of invention and creativity, rewarding a small number of individual 'inventors' in what is usually a collective process.
- A proliferation of biologically-based patents, including patents on DNA sequences, is threatening to grid-lock research in some areas.
- IP creates a market for knowledge that may not meet many of society's needs.
- IP selectively rewards certain types of knowledge (knowledge that can be patented).

Restricting access

Whilst there is concern is that access to genuinely useful genetic tests may be restricted or blocked if genes are patented, this has not happened extensively in Europe.[29] This appears to be due to a combination of a higher bar for patenting, a greater role for charities and the not-for-profit sector in funding research, and cultural opposition to paying patent fees in social healthcare systems (including involvement of healthcare professionals in opposing patents in some cases).

Blocking research

There is more concern in Europe about 'patent thickets' and the potential to block useful research or restrict academic openness. Some of these concerns apply to patenting in general (particularly its increased use in universities) not just gene patents. For example, the 2007 report of workshop on EU patent policy reported that:[30] "*An increasing number of claims per patent, an increasing patent-to-R&D ratio, increasing delays in patent applications, and an increasing use of divisionals, all point to a strategic use of patents which is directed more toward preventing others from innovating, rather than to reap the rewards for innovation*".

Assessment of the effects of university patents in Europe are difficult because patents are just one of a set of new technology transfer activities developed over the last 10 to

20 years.[31] However, possible negative impacts of university patenting include negative impacts upon the culture of open science and threats to future scientific investigation from the existence of patents on previous research.

There is a recognised tension between the academic need to publish and the commercial requirement for secrecy, in order to be 'first to file' patents on inventions. The core principle of Europe's Paris Convention (1883) for the Protection of Industrial Property is the first-to-file system: that is, the person that receives the patent is the first to file an application, regardless of whether he/she is the original inventor. Public disclosure, in a scientific publication or discussion with colleagues prevents a subsequent patent application because the invention is no longer regarded as new (it does not meet the requirement of 'novelty'). Unlike the US system, the European patent system does not allow a 'grace period' in which the inventor is allowed some months after publication to file the application.[32] This impacts on the open system of publication that has traditionally underpinned the dissemination of scientific knowledge, because researchers cannot disclose findings without their funders losing the patent, and thus they may be required to delay publication.[33] However, this does not appear to be a major issue in the area of gene patenting.

The patent thickets that result from different companies and institutions patenting multiple pieces of information (which they claim to be 'inventions') may also act as a block to more useful research and development, although it is difficult to demonstrate concrete evidence for this. For example, the not-for-profit Malaria Vaccine Initiative attempted to map the intellectual property it might need to license to develop a malaria vaccine for poor people. The map was extremely complex and involved multiple, overlapping patents held by many different inventors, some with conflicting claims.[34] Negotiating through these patent thickets can be difficult and expensive and may delay and discourage research and innovation, as well as adding to costs.[35]

Influencing research priorities

A more fundamental concern about gene patents is their influence on research priorities.

Numbers of patent applications and income from intellectual property have become measures of both university and industry success which underpin policy-makers' attempts to shift towards a 'knowledge-based economy'. It can therefore be argued that scientific knowledge that can be made the subject of a patent application is being favoured above the acquisition of other knowledge. For example, a link between a gene and a disease can be patented as part of a genetic test, but a link between an environmental exposure and a disease cannot: such studies are therefore no longer central to a research funding system which regards 'translation' of ideas to patents to marketable products as its central aim. Similarly, a GM animal, micro-organism or crop can be patented and form the basis of a university spin-out company and be used to raise venture capital investment, but improved farmland management or new agro-ecological techniques do not fit into this narrow view of innovation.

Because patents are claimed before publication, and hence prior to peer review and to replication of the discovery by other scientists, the shift from patenting inventions to patenting discoveries also has important implications for what counts as scientific knowledge. Most statistical associations between genes and diseases later turn out to be wrong (they are refuted by later research) – as do most discoveries in science.[36,37]

Therefore 'knowledge' that is patented – the key measure of the knowledge-based economy – does not represent a scientific consensus about what has been established, or meet traditional definitions of knowledge as established by the 'scientific method'.

It is thus not only *access* to biological discoveries that is controlled and shaped by the patent system, but what constitutes scientific knowledge itself.[38] Although it is clearly not the only factor driving research agendas, the commodification and prioritisation of 'genetic information' (and misinformation) via patent claims therefore plays a key role in the 'geneticisation' of both health and agriculture: including the focus on genes as the explanation for ill-health and the promotion of GM crops and animals as new production systems.

Patenting in the biosciences is now ubiquitous and patent applications are often not declared in scientific papers, raising additional issues about conflicts-of-interest and transparency.[39,40] Scientists who are named as inventors on patents will in some cases have a direct financial interest in the promoting the claims of 'industrial applicability' made in the patent. In other cases, the patent may not confer a direct financial reward, but defending the claims made in it may still be important for the scientist's career and future funding.

Issues for discussion

Timing and implications for different sectors

Where access to useful human genetic tests has been limited in Europe, this has largely been due to limited healthcare resources and limited expertise in rare diseases, rather than due to patenting. In contrast with the USA and Canada, the impacts of Myriad's patents on the BRCA1/2 mutations associated with familial breast cancer on access to such tests in the EU has been relatively limited, and the scope of Myriad's patents in Europe has been restricted by legal action and objections from the medical and scientific communities.

Although DeCode (the US company based in Iceland) has patented numerous discoveries of links between genes and common diseases, GeneWatch understands that this has not prevented US companies such as 23andMe including DeCode's genes in their tests and refusing to pay licensing fees. The medical profession has not sought access to DeCode's tests in Europe because they are not regarded as clinically useful. DeCode filed for bankruptcy in 2009, although it continues to trade as a private company.[41]

Whilst the aims of genetic engineering companies have always been relatively clear cut (to create and control markets in seeds and other products), human gene sequencing has been pursued by a variety of commercial and state interests, with different business models.

Initial investments and the promotion of the idea of a genetic cause for cancers and diet-related diseases, were made by the tobacco, nuclear and chemical industries in a (very successful) attempt to focus research on supposed genetic causes of these diseases *inside* the human body, and to promote the idea of genetic screening and targeted medical interventions as an alternative to measures that would restrict their products or pollution. [42,43,44] Later, the pharmaceutical industry became interested in genetic

screening as a means to expand the drug market to healthy people categorised as 'at risk' of common diseases, and more recently Web 2.0 companies have been interested in genetic risk assessments as a way to develop personalised marketing of "wellness" products to wealthy consumers.[45] This means that, while gene patenting is central to genetic engineering, different vested interests have, at different times, promoted and opposed human gene patenting, or wished to expand or restrict its applicability. Currently, US market leaders such as Google's gene testing company 23andMe and the gene chip company Affymetrix oppose gene patenting on the grounds that people have a "right to know" their genetic make-up.[46,47,48] However, this is a claim that suits their own business interests by conflating knowledge of the sequence with controversial interpretations of its meaning for an individual's genetic risk. It also reflects an expectation that gene testing itself is not the main expected source of future revenue: personalised marketing of products such as functional foods is where future income is expected.

Whilst it is clear that preventing gene patenting in Europe would have removed one of the motivations for pouring substantial R&D funding into human genetic research, the impact that invalidating human gene patents now would have on research priorities is therefore less than clear, and may indeed be marginal. Further, ending human gene patenting would be more likely to facilitate than hinder an expansion in human genetic testing and whole genome screening. Whilst some genetic tests are undoubtedly useful (i.e. patients would benefit from access to them), most tests have no known clinical utility and are part of a marketing strategy rather than of benefit to health.[49,50,51] A world in which everyone's DNA is online or in databases would also be a world in which governments could track every individual and their relatives: with serious negative implications for privacy and human rights. Other policies (gene test regulation and requirements for consent to store and access samples) may therefore be more significant for future developments in this area.

However, in some other areas (such as GM mosquitoes and GM farm animals and micro-organisms) it seems likely that the small-scale biotech companies that have invested in these areas would collapse in the absence of gene patents, thus opening up an opportunity to debate research priorities and reform the research funding system more broadly.

The implications of ending gene patents for GM crops would also end the main reason for investment in this area and possibly bring companies such as Monsanto to their knees. On the other hand, the seed industry will strongly resist any policy initiatives in this area for this reason. It is also unclear to what extent existing GM crops might continue to be planted, or even be cultivated more widely, if the licensing fees associated with these patents no longer needed to be paid.

Context

Key features of the policies developed to underpin the biotech economy are:

- Protectionism in 'knowledge' – rather than manufactured goods - via patents and intellectual property rights (IPRs), which confer monopoly rights on 'inventors' and patent applicants;
- Pre-competitive government subsidy of particular 'science-based' business strategies, via public investment in R&D, plus tax incentives for venture capital investors;

- The use of public-private partnerships to share the risk of investments, and public procurement to stimulate demand;
- Restructuring of education and universities to provide employees and researchers with the required technical and business skills, and to create the "*informed consumer*";
- A commitment to 'light touch' regulation of new technologies, on the grounds that government intervention will stifle innovation.

Joly notes that the privatisation of agricultural research and development is related to economic policies and to "*the promises associated with the biotechnology revolution, and specifically the 'molecularisation' of life sciences, which prompted major changes in research and development (from the experimental field to the research laboratory, increasingly disciplinary and reductionist research and development, concentration of research in a small number of institutions), and the patentability of life forms*…".[52] Beyond the fundamental reorganisation of research and development, implications include: further standardisation of farming practices and products; increased dependency of farming systems on patented technology, commodity markets and privatisation of information; and further erosion of genetic diversity.

Thus, gene patenting is only one aspect of a group of fundamental changes that have led to consolidation of many different aspects of the food and health industries and to increased control over research priorities as well as markets. Whether a campaign to end gene patenting is the right priority to expose and change this system may vary from country-to-country and at different times. It is also clear that alternatives need to consider some of these broader questions, such as who makes decisions on R&D investments and how such decisions can be made more accountable and democratic.

Scope

Whatever can or cannot be achieved by an attempt to end gene patenting in Europe, it is clear that attempts to prevent the scope of patents being broadened to include whole plants, animals and seeds (and to prevent biopiracy) must continue.

Potential for a gene patenting campaign in Europe?

Because the legal basis of gene patenting, history of legal challenges and practice of human genetic testing differ in Europe, there is no equivalent of the Myriad legal case and no constituency of patients that are being denied access to potentially useful tests as a result of gene patents. However, many other adverse impacts of gene patents exist, particularly their role in driving investments in particular types of R&D and in supporting a narrow view of innovation. Any campaign would therefore need to consider:

- a strategy for changing the research investment system as a whole (including, but not limited to, changing the patents system);
- the key points for intervention to restrict or revise the patents system (which may be very different from the US case).

An important starting point may be to convince policy makers of the failure of the current system to deliver the promised "genetic revolution" in health or agriculture, and the associated economic growth and social benefits. For this to be successful, alternative systems to support sustainable innovation will need to be devised and highlighted.

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