How Did the Gene Become a Chemical Compound? The Ontology of the Gene and the Patenting of DNA

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Abstract

The ability to patent is bounded by a set of conditions which define what is patentable and what is not. In the 1980s, the problem of the patentability of genes was solved by the use of an analogy between genes and chemical compounds. In this article we analyze the process of the reduction of the gene to a chemical compound, and show how this analogy made the practice of gene patenting routine long before it came to public attention. When we did eventually see public controversies surrounding gene patenting in the 1990s, the chemical analogy allowed patent offices in the US and Europe to 'close down' these debates by presenting the issues as merely technical.

Keywords

Gene, Ontology, Patent, Reductionism, Soft law

Résumé

L'octroi d'un brevet est soumis à un ensemble de conditions qui définit ce qui est brevetable et ce qui ne l'est pas. Dans les années 1980, le problème de la brevetabilité des gènes a été résolu en considérant que les gènes sont des composés chimiques. Dans cet article, nous analysons ce processus de réduction ontologique du gène et nous montrons qu'il joua un rôle clé dans la généralisation de la protection des gènes par brevets, sans que cela suscite de fortes oppositions. Cette pratique fit l'objet de vives contestations au cours des années 1990. Nous montrons que l'analogie entre gènes et produits chimiques fut à nouveau mobilisée par les Offices de brevets, aux Etats-Unis et en Europe, afin de clore les débats en présentant ce problème comme une question essentiellement technique.

Mots-clés

Brevet, Gene, Ontologie, Réductionnisme, Règles infra-juridique

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1. Introduction

It may seem strange to ask 'how did the gene become a chemical compound?' because, as we have known with certainty for the last fifty years, the gene *is* a chemical compound. This naïve question aims to introduce the issue that will be examined in this article, namely: the nature of the relationship between knowledge and ontologies, and the way in which this influences the production of intellectual property.

The Oxford English Dictionary defines 'Ontology' as 'The science or study of being; that branch of metaphysics concerned with the nature or essence of being or existence'. Biological ontology, more specifically, is concerned with the sorts of objects that there are in the biological sciences (Dupré, 2008), and this is our focus here. Most discussions of intellectual property do not foreground ontological questions but focus primarily on the analysis of case law, so our approach to these issues is somewhat unconventional. However, we hope to show that scientifically informed ideas about the nature of genes can throw new light on the extensive existing literature on gene patenting by revealing the implicit ontological assumptions that underlie the debates and influence their outcomes. We will return to this issue in a more precise way, but it is easy to see that whether one defines a gene as a chemical molecule, as a part of the human body, or as an elementary entity whose operation depends on the epistatic and epigenetic context, the concept is attached to radically different universes. As will be seen, the concept of the gene is surrounded by great uncertainty, which is growing with the increased use of high-throughput methods in biology. There are good reasons to support the argument made by the historian of science Hans-Jörg Rheinberger (2000) that the definitional uncertainty which characterizes the concept of the gene is actually necessary for the progression of knowledge. But patent law has carried out an ontological reduction by regarding the gene as a chemical compound.

This point could be made in a more general way concerning life. Within the framework of patenting, living organisms are regarded as mere 'compositions of matter'. This definitional question is at the heart of the landmark decision *Diamond v. Chakrabarty*, of the US Supreme Court (16/6/1980) (*Diamond v. Chakrabarty*, 447 US 303 (1980)). In this decision, the Court ruled that one cannot exclude microorganisms from patentability simply because they are living organisms since 'life is largely chemistry'.**[1]** Indeed, for the US Supreme Court, the relevant distinction was not between inanimate and living, but between the products of nature, whether they are alive or not, and human inventions (i.e. 'anything under the sun made by man').

This article will not rehearse the arguments surrounding the Charkrabarty decision and the patenting of 'products of nature'; instead, it is a specific discussion of gene patents and their history. Although it is now widely accepted that gene patenting is controversial, this was not always the case. As Rebecca Eisenberg notes, 'In stark contrast to the controversy surrounding the patentability of Chakrabarty's invention, the patenting of DNA sequences in the late 1970s and 1980s drew hardly any attention from the media' (Eisenberg, 2006: 318). We will go back to some of these early gene patents in the 1970s and 1980s, and explore the increasing dominance of the molecular-gene concept and the implications of the analogy between gene patents and patents on chemical compounds. Our approach is driven by an interest in how social and political factors interact with the technicalities of patent law. We show how the understanding of the gene as a chemical compound meant that objections to gene patents could be dismissed on technical grounds, keeping these issues out of the political realm.

2. The reduction of the gene to a chemical molecule

In characterizing the 'régimes d'énonciation' or the 'rules of argument' found in law, Bruno Latour (2002) shows that the law operates by 'legal reduction', which consists in attaching a fact (an entity, an event) to a legal provision in order to produce a judgement. The operation which connects a fact to a text of law is called the qualification. In this case, it is a question of defining a gene as a chemical molecule, of reducing its nature to this dimension only. After this move, the question of the patenting of the gene is then nothing but a technical business since it is a question of applying to genes the same jurisprudence that is applied to all chemical compounds.

This reduction is based on the discoveries of molecular biology of the 1950s, which changed the representation of the gene from 'Mendelian' to 'molecular' (Dupré, 2004). Mendelian genes can be thought of as hypothetical factors which are responsible for phenotypic differences between organisms (such as the 'gene' for red eyes in fruit flies). Traditional Mendelian genetics was based on the statistical association between an elementary genetic unit and a phenotypical character, but it did not have the tools to analyze the material substrate of hereditary mechanisms. At the time of the fiftieth anniversary of the rediscovery of Mendel's laws, in 1951, Hermann Muller declared:

> …the heart of the genetic theory still rests on deep and unknown factors. We do not have any true knowledge yet of the mechanisms which confer on the gene its properties --- its capacity to replicate itself, in a stable way and with the same accurate recopying of the mutations of the original gene. We do not know anything of the chemical bases of these mechanisms. (Rheinberger, 2000)

This all changed when 'molecular genes' became the focus, after the discovery of DNA in 1953. They are usually described as a stretch of DNA that codes for a particular polypeptide. What is interesting is that it is very difficult to reduce Mendelian genes (correlations with traits) to molecular genes (stretches of DNA) because it has been shown that there are usually many molecular genes which play a role in influencing one phenotypic trait, and also that one molecular gene has effects on many different phenotypic traits (Dupré, 2004; Moss, 2003).

This conceptual distinction between Mendelian and molecular genes is helpful because a search for the word 'gene' in the US Patent and Trademark Office (USPTO) database reveals that the earliest gene patents are patents on Mendelian genes.**[2]** In these patents, genes were not treated as chemical compounds. For example, the US patent number 3,710,511 ('Procedures for use of genic male sterility in production of commercial hybrid maize'), granted in 1973, can be called Mendelian because it centres on a 'gene' for a particular trait, which is defined in phenotypic rather than molecular terms (Patterson, 1973). The patent is on a method of making hybrid maize, making use of 'genic' (i.e. genetically identifiable) male sterility in seeds. The patent specifies 'procedures for deriving maize seed of particular genetic compositions' by examining their phenotypes. In this way it is reminiscent of Mendel's classic pea experiments. The point is made that it is the 'chromosomal constitution' which underlies the phenotype that is being selected for, and the seed is harvested based on this chromosomal constitution. It is interesting that the link to the material substrate of the gene is made explicit, but its material form is not specified.

We may want to argue that this patent is not strictly a gene patent because the patent is on the method of producing plants with a certain genetic constitution rather than on the genetic constitution itself. However, the identification of the particular male sterility 'gene' (in a Mendelian sense) is essential to the patent, and perhaps it is only possible to have a method

patent like this on a Mendelian gene because it is not possible to specify, materially, exactly what it is that is being patented. We even see an explicit disconnection from the molecular gene in the patent text: 'An understanding of the specific chemical nature and operation of the DNA which comprises the genes of chromosomes is *not essential* to an understanding of the present invention' (emphasis added).

The rise of molecular genetics led to the demise of Mendelian gene patents such as these. As Rheinberger (2000) shows, molecular genetics caused a double rupture: it transformed a gene into a material, physicochemical entity and equipped it with informational properties. The first transformation brought about a solution to the central problem in traditional genetics: the stability of the basic units and their mechanism of replication. The second transformation brought an answer to the question of the relationship between genotype and phenotype by the description of the mechanisms of transcription (from DNA to RNA) and of translation (from RNA to amino acids). For the molecular biologist, the gene thus could be regarded as a sequence of DNA carrying information for the production of a single polypeptide, collinear with the sequence of DNA. In reality, this representation was gradually called into question, step by step (see Section 3 below).

The Cohen-Boyer recombinant DNA cloning patents were the first of a new wave of patents related to the application of molecular biology (Hughes, 2001). These patents were based on the development in the early 1970s of what became the key process of genetic engineering: recombinant DNA technology. The first of these patents (Cohen and Boyer, 1980) was not granted until December 1980 because the USPTO had suspended the review of patents related to recombinant DNA research. The application of a patent which included a claim on a microorganism constructed to degrade crude oil --- the now famous *Diamond v. Chakrabarty* case --- was then under intense scrutiny. Until the justices of the Supreme Court came to a decision, the USPTO refused to consider patent applications claiming living organisms. Indeed, the eventual positive decision in the Chakrabarty case released for review a stream of patent applications involving living organisms.

The Cohen-Boyer patent, entitled 'Process for producing biologically functional chimeras', is a patent on a novel process, which is described as 'a convenient and efficient way to introduce genetic capability into microorganisms for the production of nucleic acids and proteins'. The patent listed a wide range of areas in which this process could be applied, including the production of drugs, the fixation of nitrogen, fermentation and the utilization of specific feedstocks. The claims cover genetic constructs insofar as they are necessary for the process. However, this process patent does not claim genes as such.

One of the first patents on a molecular gene as such, patent number 4,322,499 (entitled 'Adrenocorticotropin-lipotropin precursor gene'), was filed in December 1978 and granted in March 1982 (Baxter et al., 1982). This patent is identified by Warren Kaplan (2001) as the first true 'gene' patent. It deserves to be identified as a molecular gene patent because it specifies the gene sequence precisely in molecular terms by listing the As, Ts, Cs and Gs of the sequence in the claims. The patent relates this sequence to a biological function: it codes for the production of a peptide hormone which is a precursor of a natural endorphin. The patent states that the production of this hormone will be useful for 'the therapy of stress-related diseases, for treatment of pain and for the management of psychosomatic illness'.

Another famous early molecular gene patent is number 4,431,740 ('DNA transfer vector and transformed microorganism containing human proinsulin and pre-proinsulin genes'), which was filed a year later in September 1979 and granted in February 1984 (Bell et al., 1984). This paradigmatic patent claims the process of production as well as the DNA sequence coding for

human proinsulin. The gene is protected as a product because it is seen to behave exactly like a chemical compound.

As Rebecca Eisenberg shows, early molecular gene patents such as these on genes encoding therapeutic proteins looked like a high-tech variation of the familiar practice of patenting drugs.**[3]** The courts and the USPTO treated these inventions as chemicals (Eisenberg, 2006). In a key decision of the US Court of Appeals for the Federal Circuit, *Amgen v. Chugai Pharmaceutical Co*., 927 F.2d 1200 (Federal Circuit 1991), the Court stated explicitly that 'A gene is a chemical compound, albeit a complex one…' The advantage of drawing this analogy was that 'it provided a relatively clear point of departure for analyzing patent law issues presented by the first generation of biotechnology products produced through recombinant DNA technology' (Eisenberg, 2000: 784--5). At that time, alternative means to protect invention --- based on alternative gene ontology --- were mentioned. For instance, the scientist Walter Gilbert argued that copyright was the most appropriate form of protection for DNA sequences (Roberts, 1987). But this idea did not catch on.

The analogy between genes and chemical compounds was strategically useful because patent law had reached a stage (through many twists and turns) where isolated and purified naturally occurring chemicals could be patented (Conley and Makowski, 2003; Demaine and Fellmeth, 2002). An important case in this process involved a US patent on an extracted and purified form of the naturally occurring hormone adrenalin in 1911. In a decision finding this patent valid, the court explained that 'even if it were merely an extracted product without change, there is no rule that such products are not patentable'. Since the adrenaline was made available for use by removing it from the gland-tissue in which it was found, 'it became for every practical purpose a new thing commercially and therapeutically'. The court concluded that this was therefore 'good ground for a patent' (*Parke-Davis & Co. v. H. K. Mulford Co*., quoted in USPTO, 2001: 1092).

Although the patenting of isolated and purified chemicals was not totally unproblematic from this point onwards, by the time DNA sequences started being patented, the principle had become well established, leading to the conclusion that: '[l]ike other chemical compounds, DNA molecules are eligible for patents when isolated from their natural state and purified or when synthesized in a laboratory from the chemical starting points' (Conley and Makowski, 2003: 102). Treating DNA sequences as chemicals in this way had significant implications. Notably, 'product protection' for chemical compounds, including those found in nature, is in principle 'absolute', i.e. the patent holder has the right to prohibit any commercial use of the patented product whether he or she has recognised and disclosed such use or not (Beier et al., 1985). Since genes are protected as products in this way, this means that the patent scope is large.

Because of this dominant representation of the gene, the question of the patenting of these entities did not cause any difficulty. The reduction of gene to a chemical compound induced a process of expansion, and a proliferation of patentable entities. Today, more than 2000 whole genes are patented, and there are nearly 50,000 patents on sequences of DNA. The patent claims confer rights of ownership on a large variety of entities containing nucleic acids, from gene fragments to whole genomes, including everything in between (Nuffield Council, 2002: 25). What is often overlooked is that, until the beginning of the 1990s, the patenting of genes occurred without the knowledge or involvement of the general public. The reduction of a gene to its component chemical molecule was essential here because it resolved *ipso facto* questions which would otherwise have been very delicate, such as whether a product which already exists in nature can be patentable.

In the 1980s, some argued that finding genes that were already present in nature should be an unpatentable discovery (see OTA, 1989). However, because of the precedents described here, and the reduction of the gene to a chemical compound, it could easily be argued that, like any other chemical compound, DNA molecules are eligible for patentability if they are isolated and purified, as long as they meet the other criteria for patentability. In Europe, for example, the Board of Appeal of the European Patent Office (EPO) stated that genes, although present in nature, are patentable under Article 52 (1) of the European Patent Convention if they are isolated and technically processed in such a way that they can be used for the benefit of humankind (T272/95 of 22 October 2002).

3. Opening up: ontological reduction in question

Patents on living organisms have been subject to heated dispute on various occasions. Most of the debates have been about the patenting of higher life forms, particularly the shift from patents on microorganisms to patents on plants, and the shift from patents on plants to patents on animals (Edelman and Hermitte, 1988; Kevles, 2002; OTA, 1989). The first animal patent was issued in April 1988 to Harvard University for mammals genetically engineered to contain a cancer-causing gene (US patent 4,736,866). This patent provoked intense public debates on ethical concerns related to biotechnology applications.

Interestingly, however, in the context of this turmoil the ontology of the gene as a chemical compound was not discussed until the beginning of the 1990s. For about ten years, this ontological assumption was not challenged, and the patenting of genes and DNA sequences was routine practice. In the early 1990s, however, the debate crystallized in the face of two important conflicts, which we will single out here because they show how apparently merely technical issues became politicised: (1) patents on expressed sequence tags and (2) the preparation of the European Directive on the legal protection of biotechnological inventions.

Both these conflicts have to be understood in the context of growing opposition to gene patenting, an opposition which built on increasing scientific understanding of the complexity of genes, and which led to concerns about the 'tragedy of the anticommons'.

Patents on Expressed Sequence Tags

In 1991 and 1992, a team from the National Institutes of Health (NIH) led by Craig Venter applied for two patents which claimed thousands of partial cDNA sequences (2750 and 4448 respectively). The function of these partial sequences, called 'Expressed Sequence Tags' (or ESTs), was not known at the time, but since they were expressed, it was assumed that they had a functional role to play in the organism that would be discovered with further research.

This attempt to patent ESTs started to reveal the cracks in the ontological assumption that a gene should be regarded as a chemical compound. Patents were filed on these gene fragments *not* because of the chemical properties of the molecules *per se*; instead they were filed on the expectation that ESTs would be part of genes coding for proteins, and that these proteins would turn out to be biologically (and, it was hoped, therapeutically) useful. In other words, the gene fragments were not patented because they were chemical compounds but because they were carriers of information (Rai, 1999).

The filing of these patents led to controversy in both the political arena (in the White House, in Congress, in the French and Italian Ministry for Research, etc.) and the scientific arena (involving scientists such as James Watson, and bodies such as the Human Genome Organisation). The objection made was that these patents did not adequately fulfil the 'utility requirement' because the only utility that was claimed in the applications was that the partial

sequences could be used as probes for the discovery of genes. For example, in a 1997 report the US National Research Council argued against the patenting of ESTs on the grounds that patenting should move towards 'functional aspects of the genes, rather than being primarily descriptive' (1997: 54). Similarly, the Human Genome Organisation (HUGO)**[4]** 1995 statement argued that 'the patenting of partial and uncharacterized cDNA sequences will reward those who make routine discoveries but penalize those who determine biological function or application' (Human Genome Organization, 1995). Because ESTs were being treated as chemical compounds, a patent on an EST would cover all applications which involved that EST sequence. For this reason, in a 1997 Statement, the HUGO Intellectual Property Committee urged patent offices such as the USPTO 'to strictly limit the claims on ESTs to specified uses since it would be untenable to make all subsequent innovation in which EST sequences would be involved in one way or other dependent on such patents' (Human Genome Organisation, 1997).

Two key points arise from this example. First, the conflict was brought about by technological developments. In the context of the genome projects and functional genomics, gene hunting was no longer a matter of reverse engineering (from the protein to the gene), whereby the cloning of one gene required years of PhD work. Thanks to public and private databases (such as GeneBank and Incyte), and bioinformatics algorithms, gene functions could be predicted with so-called *in silico* research. This meant it became much easier to identify putative genes, and explains why there was a sharp increase in patenting during this period.

Second, this case shows the importance of scientific institutions like the NIH and international bodies like HUGO in making voluntary agreements to adapt patenting practices to the rapid evolution of knowledge. In 1994 the NIH decided to withdraw both EST applications; however, this was not because of a regulatory decision, but because of peer pressure from the broader scientific community. The new standard was adopted by the HUGO Intellectual Property Committee, a hybrid forum gathering patent lawyers and scientists from academic research and the private sector. This voluntary agreement was not followed by some start-ups, who attempted to capture as many as potential genes as possible and applied for patents which claimed high numbers of sequences: e.g. Incyte (1.2 million sequences), Human Genome Sciences (2.5 million), Hyseq (0.9 million), Genset (0.1 million) (Marshall, 1997).

The key role of HUGO in the setting of this new standard was not related to the ethical issue that the DNA sequences were human --- which was not discussed in this context --- but to the fact that scientific resources were highly concentrated on human genomics. It is also necessary to note that the objections to ESTs were not related to the ontology of the gene as a chemical compound, although, as we have seen, ontological tensions were behind the dispute. The concerns raised were mainly about sub-optimal incentives related to possible 'hold-ups' by owners of patents on ESTs. This is a classic problem of allocation of intellectual property rights when invention is cumulative (Scotchmer, 1991). The importance of this problem for biotechnology research was identified in the beginning of the 1990s (Joly and Hermitte, 1991), and became widely known as the 'tragedy of the anticommons' a few years later (Heller and Eisenberg, 1998). Statements made by HUGO were not only important in the ESTs debate, but were also influential in the production of the USPTO utility guidelines in 2001, which are discussed below.

European Directive 98/44/EC on the legal protection of biotechnological inventions (1995--1998)

The gestation of the European Biotechnology Directive 98/44/EC was exceptionally long and difficult,**[5]** primarily because of ethical concerns regarding the patentability of parts of the human body. The original proposal was adopted by the European Commission in 1988. After 6 years of intensive preparation, the European Parliament eventually rejected the amended Directive in March 1995. After two years of fervent negotiations, the European Parliament agreed to the outline of a redrafted Directive proposed by the Commission. Because of lasting opposition within the Parliament under pressure from environmental NGOs and other stakeholders, it still took almost one year to get to the final version which was adopted by the European Parliament in July 1998.

In contrast to the US Supreme Court decision which stated that 'anything under the sun made by man' may be patented, the European directive states that the human body or its parts cannot be patented. The very notion of 'human genes' raises an ontological question since such genes are both chemical molecules *and* parts of the human body. How is it possible to acknowledge that DNA sequences are patentable inventions while maintaining that parts of the human body cannot be patented? The compromise established in the directive rests on Article 5, which, again, is based on the precedent set by patents on chemical compounds, where naturally occurring compounds can be patented if they are isolated and purified and if they meet the criteria for patentability. While Article 5.1 states that parts of the human body, including the sequence or partial sequence of a gene, cannot constitute patentable inventions, the following paragraph goes on to say that 'an element isolated from the human body or otherwise produced by means of a technical process, including the sequence or partial sequence of a gene, may constitute a patentable invention, even if the structure of that element is identical to that of a natural element'.

Thus, according to the directive, a gene is not a part of the human body when it is isolated; it is a chemical compound --- and therefore, a patentable invention. This technical compromise became politicized when it was challenged by the Greens and by MPs of other political groups, who argued that this was cynical and hypocritical and that human genome had to be preserved as a Common Heritage (Schoen, 2002). In response, there was intensive lobbying for the adoption of the Directive by the European Parliament, which stressed the key importance of the economic and medical arguments. According to SmithKline Beecham lobbyist Simon Gentry, the company allocated 30 million Euros from the start for a pro-Directive campaign (Corporate-Europe-Observer, 1988). Part of this campaign was direct support of patient charities and organizations, and using this to actively manipulate and instrumentalize patient interest groups, which were by far the most influential lobby groups in respect to the Directive. Many Members of the European Parliament voted in favour of the Directive under strong pressure from these interest groups in what was described as 'the largest lobby campaign in the history of the EU'. On the day of the July 1997 vote, a number of people in wheelchairs from some patient interest groups demonstrated outside the main hall in Strasbourg, chanting the pharmaceutical industry's slogan, 'No Patents, No Cure', in an emotional appeal to Parliamentarians to vote for the Directive.

Even though the Directive was adopted in 1998, after ten years of negotiation and two re-drafts, the debate was later re-opened in some European Member States. For example, the French debate became high profile at the beginning of 2000, when MP and former Minister of Health François Mattéi launched a petition calling for the directive to be altered before being implemented. By July 15, there were about 7,000 signatories, including former Science Minister

Hubert Curien, some Nobel Laureates, the President of the influential Cystic Fibrosis Patients' organization AFM, etc. (Louët, 2000). On June 7 at the National Assembly, Justice Minister Elisabeth Guigou added that the Directive, which would override national law, was 'not compatible' with existing French legislation, specifically 'the 1994 bioethics law, the industrial property code, and the civil code, which forbid commercialization of the human body'. How is it possible to explain this late French debate? Interestingly, F. Mattéi explains this by the lack of public debate surrounding the preparation of the directive: 'Opposition is emerging only now because at the time there was no public discussion about the directive in France' (quoted by Louët, 2000).

The debates over ESTs and the Directive both problematized and politicized what had previously been seen as an unexceptional technical activity, but behind both these debates was growing scientific and economic concern about gene patents.

Scientific arguments against gene patents

For years, scientists have lived with the co-existence of different definitions (ontologies) of the gene. As Rheinberger (2000) argues, the definition of the gene changes over time and varies according to discipline. For a biophysicist, the gene is characterized by the atomic coordinates of a macromolecule, while for a biochemist the gene is defined by the stereochemical properties of a sequence of DNA. In molecular genetics, genes are informational elements positioned on chromosomes, which can control functions or products. In molecular evolutionary biology, genes are the complex products of processes (such as changes, duplications, rearrangements), which affect sections of DNA in a complex chromosomal environment. In developmental biology, genes are hierarchical sets of instructions which induce the differentiation and whose activation depends on their state of differentiation.

At the end of the 1990s prestigious scientific institutions started to criticise the ontological reduction of the gene to a chemical compound in the context of gene patenting. For instance in Germany, Professor Ernst Ludwig Winnacker, President of the Deutsche Forschungsgemeinschaft (the German Research Foundation), objected to the treatment of genes as chemical substances because of the implication that a researcher who patents the gene can commercially exploit all future possible uses of this gene. He argued that

> Since the human genome was deciphered, we know of several genes which produce, not only one, but thousands of proteins. According to the European Directive on biotechnology, the patentee who identifies only one of these functions also has rights on all the 999 other proteins. The other researchers are left empty-handed. (*Die Woche* 8 June 2001, quoted in Straus, 2003: 172)

Importantly for our purposes, this is an ontological point about the nature of the gene and how it differs from a chemical compound. Unlike a chemical compound, where there is a specific relationship between a chemical and its function, the diversity of mechanisms of gene expression means that there is no specific relationship between a gene and what it does in an organism. A gene could potentially produce thousands of different proteins, all with different functions. Since one gene can have multiple functions, we need a more sophisticated understanding of the relation between structures and functions than we have with chemical compounds.**[6]**

The inadequacy of gene patenting is further reinforced by new developments. Scientists such as Jean Weissenbach of the French Genethon criticise the very notion of the 'function of a gene', which emerges as the consensual condition for gene patenting. Weissenbach points out

that genes operate at three different levels of function: the molecular level (the biochemical function of the gene), the biological level (the biological process within which the protein plays a role) and a third level related to the role of the protein in the whole organism. Weissenbach explains:

> The same product of a gene --- or sometimes several products of the same gene --- may have several molecular functions, which take part in several biological processes and may correspond to various cellular entities. Hence the difficulty of describing accurately the functions of the product of a gene, which are all called --- but this is linguistic abuse --- 'gene function'. (Biofutur, 2000)

Even the esteemed pages of the journal *Nature* have started discussing the difficulty of defining the gene. For example, the title of a paper published in *Nature* in May 2006 is 'What is a gene?' (Pearson, 2006). This paper describes the increasingly problematic nature of the concept, quoting geneticists who explain how teaching undergraduates about genes used to take approximately two hours, but now takes close to three months. It also describes the outcome of two days of intense debate among twenty-five leading bioinformatic researchers, which led to the (rather unsatisfactory) definition of the gene as: 'a locatable region of genomic sequence, corresponding to a unit of inheritance, which is associated with regulatory regions, transcribed regions and/or other functional sequence regions' (Sequence Ontology Consortium, 2006, quoted in Pearson, 2006: 401).

The difficulty of defining the gene is based on the recognition of the complexities which characterise gene expression, such as alternative splicing (where the DNA sequence can be cut and re-connected in various different ways), overlapping genes, genes within genes and genes which spill over the boundaries of the chromosomes. Furthermore, it has been found that much of the genome actually codes for RNA rather than proteins. The discovery of short 'microRNAs' and other RNA molecules now known to be vital in controlling many cellular processes, along with the newly revealed ferment of RNA transcription activity, contributes to the conclusion that RNA actively processes and carries out the instructions in the genome (Gibbs, 2003). Research has also pointed to the importance of epigenetic inheritance, which involves the activation or repression of various genes.

These diverse understandings of the gene show that the legal reduction of the gene to a chemical compound can no longer be supported in the context of the current practices of the scientific community. Although there have been many *ad hoc* contractual arrangements which make it possible to maintain the circulation of knowledge in spite of patents on genes (e.g. non-exclusive licenses and narrower patents), many think that these are merely adaptive solutions and that the problem of gene patenting should be re-addressed in a more fundamental way.

The trigger for change is so forceful that even Professor J. Straus, one of those who pushed in favour of the ontological reduction in the 1980s cannot stand aside:

> Any simple equation of a gene sequence (identical to the natural one) with (absolutely) new synthetic molecules, or 'ordinary' chemical substances found in nature, disregards the, by now, known and substantial differences between these categories of products. … Under such circumstances limiting the scope of protection to the function(s) disclosed seems necessary. (Straus, 2003: 186)

Economic arguments against gene patents

As Straus intimates, the scientific finding that most genes have multiple functions has important economic consequences for gene patents because it is often the case that new functions of patented genes are discovered which were not known at the time the patent was granted. For example, a patent on the CCR5 receptor was filed by the company Human Genome Sciences (HGS) in 1995, and granted in 2000. It was initially patented because it belonged to a family of cell receptors which play a role in inflammatory disease, but further research by the Université Libre de Bruxelles established that CCR5 is the key co-receptor for HIV, making CCR5 a very important potential drug target. After this discovery, HGS gained rights over this function as well, although they were not aware of the receptor's potential importance in AIDS treatment at the time they filed the patent. This allowed them to acquire a 'hold up' position on downstream research on the receptor (Nuffield Council, 2002).

Examples like this show how gene patenting can lead to negative consequences for future research on therapeutically important compounds, and how companies can potentially acquire monopolies on genetic testing for serious diseases. This has led some economists to oppose the patenting of genes. A key statement here is Heller and Eisenberg's (1998) paper on the 'tragedy of the anticommons', which argues that the existence of patents leads to the neglect of large areas of research which would otherwise be ripe for innovation and exploitation. Although their thesis has been contested, and arguments have been made that DNA patents do not always have negative effects on research access (see Caulfield et al., 2006), Heller and Eisenberg's argument has been very influential.

Despite the fact that changing understandings of the nature of the gene are implicit in these discussions, the question of gene ontology has rarely been addressed in the vast literature on the economic implications of gene patenting. An exception is a 2003 report for the French Prime Minister, which argues that the assumption that the gene is a chemical compound is the very reason why there are many problems related to gene patenting (Henry et al., 2003). They say:

> Of course, genes or proteins are molecules; but these are natural molecules, and moreover they are centres of information, codes and essential instruments to control metabolism. Their respective functions may not be bypassed; an economist will say that they do not have any substitutes. They are 'essential facilities' in the sense of economics and antitrust law. In these conditions … we have to prevent the granting of patents on genes or proteins as products.

Whilst the idea of a gene as an 'essential facility' may be challenged, the wish to design property rights according to the nature of the object of protection needs to be highlighted (cf. Bonaccorsi et al., forthcoming).

4. Closing down: the re-entrenchment work of the patent offices

We have seen how key controversies, combined with economic and biological arguments, 'opened up' gene patenting and made it into an issue for public debate. In this section we will examine how the patent offices in the US and Europe countries worked to 'close down' those debates, in ways which did not challenge the ontological assumptions on which gene patenting is based.

The re-entrenchment work of the USPTO

The anxiety provoked by the patenting of DNA, particularly the furore caused by the EST patent applications, did result in changes in the practices of patent offices. In the USPTO, the most notable development has been the publication of its Utility Examination Guidelines in January 2001 (USPTO, 2001).**[7]** Although these guidelines do not have the force of law --- they define the procedures to be followed by USPTO personnel in their review of applications --- the importance of soft law in this area should not be underestimated. In the decision *In re Fisher*,**[8]** in September 2005, the US Court of Appeals for the Federal Circuit drew upon the Utility Examination Guidelines to confirm the USPTO rejection of Monsanto's patent applications on ESTs. This case law is considered to be a stamp of approval for the guidelines. There is also some evidence that these new standards are diffusing into examination procedures in Europe. For example, the UK Patent Office's Guidelines say that they would expect to see UK applications fulfilling these requirements (see UK Patent Office, 2006).

The effect of the Guidelines was the addition of three new words to qualify utility: 'specific', 'substantial' and 'credible'. The examiner has to determine 'if the applicant has asserted for the claimed invention any specific and substantial utility that is credible' (USPTO, 2001: 1098). In the case of gene patents, for a utility to be specific, it must be particular to the nucleotide sequence being claimed rather than just stating a general utility. For example, it is not sufficient to state that a gene is a 'diagnostic', it is necessary to specify for which condition. For a utility to be substantial, there must be a real-world use, meaning that speculative utilities are not accepted. Substantial utility is not met if the invention is just used to learn about the properties of DNA itself (Kamstra et al., 2002). For the utility to be credible, the usefulness of the invention must be theoretically possible. These extra requirements are meant to overcome the more dubious claims to utility made for nucleotide sequences such as ESTs.

These revised utility guidelines do not unpack the previously under-characterised idea of utility, but instead qualify the notion of 'use' by bringing in other concepts. The question now revolves around asking what the words 'specific', 'substantial' and 'credible' actually mean. Adding new words does not automatically make the requirement more stringent. The most important point, however, is that the assumption that a gene has only one function is still very much alive within these guidelines. This is because only 'one credible assertion of specific and substantial utility' (USPTO, 2001: 1098) is necessary to satisfy the utility requirement. Thus there is no change in the assumptions that are made about the ontology of the gene, and no recognition of the potential difficulties caused by multiple functions.

As is usual in the US, public comments were requested before the introduction of these guidelines. The responses to these comments by the USPTO makes us think of the 'dialogues of the deaf' of Professor Calculus in Tintin, where the characters manage to talk past one another completely. (For example: 'It will rain today, it is necessary to bring in the linen because it will be wet'. Response: 'No, no, I say to you that the rain is a phenomenon of condensation of the steam which intervenes under precise conditions of temperature and pressure.')

Several of the comments objected that anyone who discovers a gene will be granted a broad patent covering a number of possible applications, but the USPTO's response was simply that with 'a patent claiming a new chemical compound…The patentee is required to disclose only one utility' (USPTO, 2001: 1094). Here the familiar point is made that patents on genes should be treated the same as patents on other chemicals. Other comments stated that the scope of patent claims directed to DNA should be limited to applications or methods of using DNA, and should not encompass the DNA itself. This was also rejected on the grounds that 'Patent law provides no

basis for treating DNA differently from other chemical compounds that are compositions of matter' (USPTO, 2001: 1095).

Several comments argued that the scope of DNA patent claims should be limited to uses that are disclosed in the patent application, and that allowing claims that encompass DNA itself would enable the inventor to assert claims to 'speculative' uses of the DNA that were not foreseen at the time the patent application was filed. But in response it was emphasised that 'A patent on a composition gives exclusive rights to the composition for a limited time, even if the inventor disclosed only a single use for the composition' (USPTO, 2001: 1095). We can see that because the USPTO persisted in the idea that the gene should be treated as a chemical compound, meaning that it was only necessary for one function of the gene to be disclosed to satisfy the utility requirement, all the submitted comments were easily dismissed on apparently merely 'technical' grounds.

The re-entrenchment work of the EPO

Like the USPTO, the EPO revised its guidelines (in line with the EU Biotechnology Directive) in the face of the EST controversy. The EU Directive introduced the requirement that for gene patents it is necessary 'to specify which protein or part of a protein is produced or what function it performs' (EU Directive, 1998, Recital 24).**[9]** But as we have seen above, the idea of a gene's function is not straightforward. This is an issue which patent examiners are aware of, and until recently different examiners adopted divergent practices (for example, some examiners assumed that merely identifying that a gene produces a particular enzyme was sufficient to identify a gene's function, while others imposed much more stringent requirements [interview with EPO examiner]). In the face of this uncertainty, there has been some recent case law which has directly addressed the issue of gene function.

An EPO board of appeal decision (case T0898/05 of July 7 2006) is particularly relevant here. In this case we see the EPO using phrases that are similar to the 'specific, substantial and credible' of the USPTO. For example, it is pointed out that if the function of a molecule is known, but this function cannot be linked to any 'immediate concrete benefit', then industrial applicability cannot be acknowledged, and that function is adequate to fulfil industrial applicability only if 'a practical application (a profitable use in a wider sense) is derivable in a straightforward manner'. However, as with 'specific, substantial and credible', these terms do not help specify the idea of function, but instead just leave us wondering how words such as 'concrete' should be interpreted, what a 'practical' application is, and what it means for something to be derivable in a 'straightforward' manner.

In a very interesting parallel to the Weissenbach quotation above, the decision T0898/05 also attempts to separate out different levels of function. It identifies structural function, molecular function (biochemical activity), cellular function (function in a cellular process) and biological function (influence of a cellular process in a multicellular organism). But it is still assumed that the 'concrete' benefit of the DNA sequence would be 'provided by the potential elucidation of at least one function' of the polynucleotide (Pallard and Majer, 2006). Although we do see patent practitioners trying to grapple with the subtleties of function, the point remains that only one function needs to be identified to satisfy the utility requirement. From the perspective of both the USPTO and the EPO, the ontology of the gene is stabilized, the frame remains the same, and it is merely a question of refining the law within this context.

Recent developments

In a recent and surprising decision in April 2010 (*Association for Molecular Pathology v. USPTO*, or 'the Myriad decision'), the United States District Court for the Southern District of New York has finally challenged this ontological reduction. Judge Sweet concluded that DNA is distinct in its essential characteristics from any other chemical found in nature on the grounds that:

> Genes are of double nature: on the one hand, they are chemical substances or molecules. On the other hand, they are physical carriers of information, i.e., where the actual function of this information is coding for proteins. Thus, inherently genes are multifunctional. (Declaration of J. Straus in the Court Decision, p. 122)

The decision goes on to argue that:

> This informational quality is unique among the chemical compounds found in our bodies, and it would be erroneous to view DNA as 'no different' than other chemicals previously the subject of patents. (Declaration of J. Straus in the Court Decision, p. 123)

The Court held that DNA retains its informational character in isolated and purified form, concluding that the claimed isolated DNA 'is not markedly different from native DNA as it exists in nature' and constitutes unpatentable subject matter. This decision has been appealed and may still be reversed. It is therefore too early to analyze its implications for gene patenting. But if the decision is not reversed, it will have taken nearly twenty years since the protests related to patents on ESTs for the ontological reduction to be challenged in a landmark Court decision. In any case, the reasoning of the US District Court contrasts with the patent offices', since these later institutions were unable to reassess the ontological reduction in the light of new scientific knowledge.

The relationship between law and science

This analysis allows us to make a few comments on the relationship between law and science. Both domains have to deal with fuzzy and uncertain objects, but they do so in very different ways.

Our first claim is that there is a greater tolerance for 'fuzzy' objects in science because various definitions of a gene can coexist in different disciplinary contexts, as discussed above, and it is normal that definitions of scientific objects evolve and change over time. In contrast, in law the aim is to fix categories and produce firm definitions in order to reduce legal uncertainty. In our case, the ontological reduction of the gene to a chemical compound was instrumental since it resolved many of the key issues related to gene patents: how to draw boundaries between natural and purified DNA, and between invention and discovery, etc. Seeing the gene as a chemical compound allowed the mobilisation of longstanding experience of courts and patent examiners in this emerging field. In the US, because Justices of the Supreme Court finally decided that patents on life were unproblematic, the process of reduction occurred mainly at the USPTO (the European trajectory is different and we come back to this below). But the interpretation of statutory law is not neutral. Such interpretations are often overlooked since they are generally considered to be merely technical.

This leads us to our second claim, which is that there is a difference between the two fields in terms of their reversibility. In science reversibility is common. It is often the case that

scientific knowledge comes to be thought of as wrong, and what is accepted as correct changes over historical time. In law, by contrast, we see lower levels of reversibility, because law progresses (in theory) in a single direction (Latour, 2002).**[10]** This question of reversibility relates to the issue of the relative speeds of the two domains. One of the dominant narratives used in framing law--science interactions is that the law is always behind and cannot keep up with the speed of scientific and technical change (Jasanoff, 2007). However, perhaps a better way to understand this situation is to recognise that we ask the law to rule in urgent situations, when scientific objects are not stabilized. The corollary of this point is that law is increasingly developed in the form of infra-legal standards (such as voluntary agreements and guidelines), instruments which have the appearance of technical documents but which often encapsulate political choices. The use of 'soft law' in this way allows the law to deal with fuzzy and changeable scientific objects.**[11]** However, as shown by our analysis, there is also a strong irreversibility within soft law. The way the problem is framed at the outset, and in our case the way the ontology of the gene was reduced, has lasting consequences. Despite the recasting of the ontology of the gene in scientific contexts --- because of the reversibility of scientific knowledge --- the work of the USPTO is deeply entrenched in the original frame. Solutions are explored to deal with problems that arise in gene patenting but they never challenge the basic elements of this frame, namely that a gene is not only a chemical compound but that it is also a multi-functional carrier of information. In this case, a Court decision is necessary to challenge the original frame. However, even if it is upheld, the Myriad decision comes very late, when the issue of gene patenting is no longer of great strategic and economic interest. Furthermore, it may be expected that, if confirmed, this decision will concern only isolated human genes, without further modification. And finally, a challenge to the ontological reduction of patent offices in the mid 1990s would have had a much greater impact.

The *Chakrabarty* decision accepted the ontological distinction between natural and artificial as clear-cut. The European case offers an interesting contrast. In Europe, the Commission requested a new Directive in order to harmonise the European market. Ironically, the preparation of the Directive resulted in turmoil and triggered many questions about the ontology of 'human genes'. The acknowledgement of the variable ontology of 'human genes' was overcome by a distinction being made between the gene *per se* (naturally occurring in human bodies) and the gene as an invention: isolated, purified, and ready to circulate in industrial and market spheres. However, concerns which were triggered in the course of the preparation of the Directive, lasting disagreements, as well as the wording of the text, leave room for greater flexibility than in the US, where the initial decision was unambiguous. It remains to be seen whether these different trajectories will make a difference to the way the patenting of DNA sequences will be dealt with in the future on either side of the Atlantic.

Conclusion

This article started by asking how the gene came to be treated as a chemical compound in intellectual property debates. A patent search revealed that some of the earliest gene patents should be understood as 'Mendelian' (because the chemical form of the gene was not specified in the patent), but the move to molecular biology led to the rise of molecular gene patents, where the genetic sequence was listed in the patent claims. Molecular biology, which made it possible to identify the chemical sequence of the gene, also made it possible to see genes as chemical compounds. This analogy solved the problem of the patenting of naturally occurring entities by applying to genes the isolation and purification requirements that were applied to patents on chemicals. Another advantage of the chemical analogy was that the ontology of genes became a

non-question in the patent context, and there were no challenges to gene patents until approximately twenty years after the granting of the earliest patents on genes.

The debate on the patenting of genes did open up in the early 1990s, and public controversies politicized the issue. We discussed this 'opening up' by focusing on two important incidents: the patenting of biotechnological tools (ESTs) and the controversy surrounding the implementation of the EU Directive. The former incident had its roots in scientific developments, while the latter was more clearly political. Both of these controversies have to be understood in the context of scientific and economic challenges to the gene-patenting paradigm. Some of the negative economic consequences of gene patenting became apparent in the 1990s with the rise of monopolies and potential technological hold-ups, along with discussion of the problem of the anticommons. Simultaneously, genomics and high-throughput biology revealed the growing complexity and increasing ambiguity of the notion of the gene. It became clear that genes can be defined in various ways and that they often have many different functions at different biological levels. Genes are now understood as components of complex and dynamic networks of regulation and interaction which constitute living systems (Auffray et al., 2003).

When gene patenting did at last become an issue for public debate in the early 1990s, the patent offices 'closed down' these debates, without questioning their own ontological assumptions. Both the USPTO and EPO did change their guidelines, but for both patent offices it remained the case that just one function needed to be disclosed for a gene patent to be granted. The gene was still treated as a chemical compound. Its ontology remained stable, although the soft-law guidelines allowed the system to adjust to new technological developments. This ontological stability meant that objections to gene patents could be deflected and dismissed on apparently technical grounds, keeping intellectual property issues firmly out of the political realm. Although commentators such as James Boyle argue that "A broader debate about genetic patents within intellectual property scholarship would be of particular benefit" (Boyle, 2003: 19), such a broader debate would require the entry of non-technical arguments into patent disputes.

We have seen how the patent system is incredibly good at adapting to scientific, economic and political challenges without changing its fundamental assumptions. This adaptation is the result of a complex mix of legislative reforms, court decisions, and the production of soft law by patent offices. We have argued that patent offices were instrumental in the ontological reduction of the gene to a chemical compound and in the re-entrenchment processes, which protected this dominant conception against external criticism. Soft law played a key role in adapting the patent system to new knowledge and new economic challenges. The ontological reduction of the gene was instrumental to this end. However, our study also shows the inability of patent offices to reconsider their conceptual frames on the basis of changes in scientific knowledge. Patent offices persisted with the ontological reduction and for this reason performed poorly as an arena in which the implications of new scientific knowledge could be debated. The recent Myriad decision shows that Courts may have a greater ability to reverse such ontological considerations, but the time and resources required for correcting initial errors will probably be exceedingly high.

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Notes

1. Application of Malcolm E. Bergy, John H. Coats and Vedpal S. Malik. Application of Ananda M. Chakrabarty. US Court of Customs and Patent Appeals, March 29, 1979, 596 Federal Reporter, 2d Series, 952, at 952-53, 955, Docket number: 76-712, 77-535. Permanent Link: http://vlex.com/vid/bergy-coats-vedpal-ananda-chakrabarty-38402631.

2. Because searchable patent databases only start in the 1970s, the fact that the earliest gene patents are usually thought to have been issued at this time is probably merely a feature of the availability of patent data. For this reason, we do not claim to have identified the 'first' patent, but instead to provide a snapshot of a typical patent at the time. See Yoon Kang (2007).

3. Note that, in Europe, patenting drugs was a highly contentious issue in the early 20th century. Most of the European countries rejected patents on new drugs before WW2. Thus the long tradition of patenting drugs is quite specific to the situation in the US. See Gaudillière (2008).

4. HUGO was a key arena in the 1990s. The IPR Committee was then chaired by J. Straus (http://www.hugo-international.org/committee_ip.htm).

5. For a detailed account of the history of the European Directive 98/44/EC, see Schoen (2002).

6. For further discussion of the relation between structures and functions in gene patenting, see Bonaccorsi et al. (forthcoming).

7. The USPTO issued the first Utility Examination Guidelines in 1995 (Federal Register / Vol. 60, No. 135 / Friday, July 14, 1995). The 1995 Utility Guidelines introduced the need for specific and credible utility. In the 2001 Guidelines the revised comments provide a more detailed definition of both requirements and add a new one: the utility has to be substantial.

8. *In re Fisher*, 421 F.3d 1365, 1371, 76 USPQ 1225, 1230 (Fed. Cir. 2005).

9. This applies to those gene patents 'where a sequence or partial sequence of a gene is used to produce a protein or part of a protein' (EU Directive 1998, Recital 24).

10. As stated by a referee, irreversibility is not absolute and indeed we can find many examples where law has been challenged and legal decisions have been reversed. However, there are both functional arguments (the necessity to reduce legal uncertainty v. productivity of scientific controversies) and symbolic ones (legal decisions are not considered as falsifiable, or refutable), which explain differences in the degree of reversibility of science and law.

11. Although the argument that soft law helps to reduce the law-lag should be discussed on a case-by-case basis since the production of standards may also be very protracted. See Borraz (2007).

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