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“Something more is necessary” –

Are genes and genetic diagnostic tests statutory subject matter for US patents?

“A discovery may be brilliant and useful, and not patentable. No matter through what long, solitary vigils, or by what importunate efforts, the secret may have been wrung from the bosom of Nature, or to what useful purpose it may be applied. Something more is necessary [1].”

“The concept of patentable subject matter ... is not “like a nose of wax, which may be turned and twisted in any direction ... [2]” [3].”

Abstract:

In a recent decision (*AMP v. USPTO*) from the US District Court, patent claims directed to DNA sequences corresponding to human genes and to diagnostic tests based on such genes have been found to be invalid, primarily on the basis that the DNA molecules claimed, which included cDNA and primers and probes, are "products of nature" and thus unpatentable. If upheld, this decision will have considerable impact on the ability of biotech companies and universities to patent the results of their research.

In this paper we will explain the basis for this decision and discuss the appropriateness of patenting discoveries and their (obvious) uses in the light of this fascinating case. While our focus will primarily be on the product claims, diagnostic method claims were also revoked in *AMP v. USPTO* on the basis that they were for mental acts or did not involve any “transformation of matter”. This will be discussed in the light of the recent US Supreme Court decision in *Bilski v. Kappos*, which focussed on the patent-eligibility of process claims.

Keywords: Patents, genes, genetic diagnostic tests, products of nature

Introduction

The human genome is naturally occurring and finite, yet numerous patents have been granted in the US and elsewhere for human genes, gene variants and gene fragments and their use in diagnostic (and other) methods. To some, this is a second enclosure of the commons – the transformation of common property into private property, the use of which is forbidden to the non-owners. Some have attempted to justify this by referring to the “tragedy of the commons” – that resources are inefficiently used, or overused, if not privately owned [4]. Others have argued that in the case of “intellectual property” the opposite applies – the “tragedy of the anti-commons” [5-6] – whereby too many overlapping private property rights can result in the underuse of scientific results.

Recently, the District Court of the Southern District of New York was asked by the Association for Molecular Pathology (AMP) and others to revoke certain claims of various patents owned or part-owned by the University of Utah Research Foundation, licensed to Myriad Genetics [7]. These claims relate to the cancer susceptibility genes BRCA1 and BRCA2 as well as to genetic diagnostic tests using those genes. In his decision of 29 March 2010, since appealed by Myriad, District Judge Robert Sweet agreed and declared these claims to be invalid.

In this paper we will explain the basis for this decision (*AMP v. USPTO* [101]), which is of great importance in finding genes, gene fragments and gene constructs to be “products of nature” and hence unpatentable. We will discuss the appropriateness of patenting discoveries and their (obvious) uses in the light of this fascinating case. While our focus will primarily be on the product claims, diagnostic method claims were also revoked in *AMP v. USPTO* on the basis that they were for mental acts or did not involve any “transformation of matter”. These method claims will be discussed briefly in view of a US Supreme Court decision from 28 June 2010 (*Bilski v. Kappos* [8]) which focussed on the patent-eligibility of process claims.

Gatekeepers to patentability - the exclusions from patentability

The gatekeepers to patentability are utility, novelty, non-obviousness, and exclusion by other means, e.g. by the statutory subject matter (SSM) test of Section 101 of the United States Patent Law or by the provisions of Articles 52(2) and 53 of the European Patent Convention.

As is clear from the opening quote of this article, novelty and utility are *necessary but not sufficient* criteria for patentability. To be patentable in the US, an invention must not only be new, non-obvious and useful but must also be *statutory subject matter* for patenting, i.e. it must fall within one of the categories of subject matter that are patentable under US law. The basic requirement for statutory subject matter is set out in 35 USC 101 (Section 101 of the US Patent Law, which is laid down in Title 35 of the United States Code [102]) as follows:

“Whoever invents or discovers any new and useful *process, machine, manufacture, or composition of matter*, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this [law]” (emphasis added).

Only if an invention passes the SSM patent-eligibility test does it need to be tested for the other patentability requirements of novelty, non-obviousness and utility, and the SSM test would seem, on the face of it, to be relatively straightforward. In patents and patent applications, inventions are always claimed either as things (e.g. products, compounds, compositions, apparatus, etc.) or as ways of doing things (e.g. as methods, processes or procedures). Whatever biologists, sociologists or philosophers may consider a “gene” to be, in patents they are claimed as chemical compounds comprising an appropriate sequence of conjoined nucleic acid residues, i.e. either DNA or RNA sequences. Thus for example, claim 1 of US Patent No. 5747282 [201] is directed to:

“An isolated DNA molecule coding for a BRCA1 polypeptide, said polypeptide having the amino acid sequence ...”

It would seem therefore that such “gene” claims should meet the SSM test since the DNA molecule is composed of atoms, i.e. of matter.

If only life were so straightforward. Where the commonsense interpretation of the wording of a law leads to results which are bizarre, or perhaps unintended by the legislators who framed the law, the courts have shown a tendency to impose less than straightforward interpretations.

The US courts are no strangers to this habit of judiciary-made law and certain categories of invention are deemed to fail the SSM test. Obviously, under a common law system such as the US, laws such as the Patent Act are drafted against a background understanding that they will be interpreted by courts and hence that the legislators need not cover every possibility in

the statute. Thus, when we refer to “judiciary-made law”, we are concerned with interpretations of statute law that are not evidently derivable from either the wording of the law or the deliberations of the legislator. Clearly courts must interpret, and clearly the legislator cannot foresee all possible future developments that may occur (particularly when the law concerns inventions). However, judiciary-made law must always be subject to scrutiny. This was made eminently clear when the US Supreme Court advised the Federal Circuit in *Bilski v. Kappos* [8] that its “machine or transformation of matter” (MOTM) test was not infallible. The judiciary-made law in relation to the SSM test for products is illustrated by the 1980 decision of the US Supreme Court in *Diamond v. Chakrabarty* [9]:

“[C]omposition of matter” has been construed ... to include “all compositions of two or more substances and ... all composite articles, whether they be the result of chemical union, or of mechanical mixture ... [10]” ... This is not to suggest that [35 USC 101] has no limits or that it embraces every discovery. The laws of nature, physical phenomena, and abstract ideas have been held not patentable. Thus, a new mineral discovered in the earth or a new plant found in the wild is not patentable subject matter. Likewise, Einstein could not patent his celebrated law that $E = mc^2$; nor could Newton have patented the law of gravity. Such discoveries are “manifestations of ... nature, free to all men and reserved exclusively to none [11]” [9].”

The claims under consideration in *Diamond v. Chakrabarty* related to a genetically engineered microorganism that was not naturally occurring. Finding those claims acceptable, as not being directed to a product of nature, the Supreme Court distinguished over the earlier case *Funk Bros. Seed Co v. Kalo Inoculant Co* [11] as follows:

“Concluding that the patentee had discovered “only some of the handiwork of nature,” the [Funk] Court ruled the product [a combination of known bacterial species] nonpatentable: “Each of the species ... infects the same group of ... plants which it always infected. No species acquires a different use.

...The bacteria perform in their natural way. Their use in combination does not improve in any way their natural functioning. They serve the same ends nature originally provided and act quite independently of any effort by the patentee.” ...

Here, by contrast, the patentee has produced a new bacterium *with markedly different characteristics from any found in nature* and one having the potential for significant utility. His discovery is not nature’s handiwork, but his own; accordingly it is patentable subject matter under [35 USC 101] [9].”
(emphasis added)

Likewise, in a case from 1931, *American Fruit Growers, Inc v. Brodges Co* [12], the Supreme Court had acknowledged that the claimed product, treated fruit, was not to be found in nature but held that the fruit did not become an article of manufacture (as opposed to a product of nature) unless it “possesses a new or distinctive form, quality, or property” as compared with the naturally occurring article.

However, a particular problem arises where the crux of an invention lies in something which is not patent-eligible but where the patent claims have been written so that the invention as claimed at first sight seems to comply with Section 101. Should the invention then pass or fail the SSM test, and if it passes can the claims be rejected on another basis? The US Supreme Court made it clear in *Parker v. Flook* [3] that making the determination of patent-eligibility under Section 101 “depend simply on the draftsman’s art ... would ill serve the principles underlying the [Section 101 prohibitions]”.

Association for Molecular Pathology et al. v. United States Patent and Trademark Office et al.

This brings us to the case that is the focus of this article. As mentioned earlier, the District Court of the Southern District of New York was asked by the Association for Molecular Pathology and others to declare certain claims of seven patents [201-207], owned or part-owned by the University of Utah Research Foundation and licensed to Myriad Genetics, to be invalid for failing the SSM test. The claims at issue related to the cancer susceptibility genes BRCA1 and BRCA2, as well as to genetic diagnostic tests using those genes. District Judge Robert Sweet decided that those claims were indeed invalid.

One of these claims has already been quoted above in full. However, for present purposes they may be very roughly paraphrased as having the following typical forms:

- A. An isolated DNA molecule comprising the nuclear DNA coding for a natural polypeptide.
- B. An isolated DNA molecule comprising cDNA coding for a natural polypeptide.
- C. An isolated DNA molecule comprising an oligonucleotide capable of hybridising to native DNA coding for a natural polypeptide.
- D. A method for detecting a DNA defect comprising analysing the relevant sequence in the patient's DNA [or comparing the relevant sequence in the patient's DNA with a reference sequence].
- E. A method for screening a drug comprising growing in the presence or absence of the drug, detecting the rates of growth, and comparing the rates of growth.

In the human cell, DNA is of course associated with other cell components and thus "isolated DNA" is intended to confer novelty on the claimed subject matter. Here it may be noted that,

under *European* patent law, while Art. 52(2) and (3) EPC exclude “discoveries” “as such” from patentability, Rule 29(2) EPC explicitly permits claims to isolated DNA by stating 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 [13].”

Judge Sweet’s determination that the claims failed the SSM test was based on different grounds for the “isolated DNA” product claims and for the diagnostic method claims. Since our main focus in this article is on the claims to isolated DNA, we shall consider these first.

The product claims

Clearly, the product claims meet the SSM test for “compositions of matter” as set out in the *first part* of the first quote from *Diamond v. Chakrabarty* [9] above – the molecules covered by the claims are “compositions of two or more substances”, i.e. nucleic acid molecules, which are the result of “chemical union”. The point at issue is whether they fail the judiciary-made law as being naturally occurring substances, that is to say discoveries which are “products of nature” [14-15].

DNA does not exist in nature in isolated form; however, isolation or purification of native DNA does not change the fact that the DNA *itself* is a product of nature. Is the position different if the DNA claimed is an artificially synthesised (partial) copy of DNA that occurs in nature having the relevant characteristics of the natural DNA, and what are those characteristics? In other words, can the *wording* of a claim (e.g. as an isolated, purified,

truncated, or synthetic version of a natural product) enable that claim to meet the SSM test? Judge Sweet thought not.

The question of the inherent patentability of DNA has not previously been considered by the US courts and the clearest guidance in case law comes from that relating to products which occur in nature. The practice before the US Patent and Trademark Office has been to follow the decision, from 1911, of the highly respected Judge Learned Hand (like Judge Sweet, of the District Court of the Southern District of New York), which upheld a patent claim to a purified form of a naturally occurring substance (adrenalin) in the case *Parke-Davis & Co v. H K Mulford & Co* [16]. In this case Judge Hand stated:

“[E]ven it were merely an extracted product without change, there is no rule that such products are not patentable. [The inventor] was the first to make it available for any use by removing it from the [material] in which it was found, and, while it is of course possible logically to call this a purification of the principle, it became for every practical purpose a new thing commercially, and therapeutically. That was a good ground for a patent.”

Earlier case law from the US Supreme Court had held that purification of a product of nature did *not* allow it to pass the SSM test. In particular, in 1874, in *American Wood Paper Co v. Fibre Disintegrating Co* [17], the Supreme Court had commented:

“There may be many things well known and valuable in medicine or in the arts which may be extracted from divers substances. But the extract is the same, no matter from what it has been taken. A process to obtain it from a subject from which it has never been taken may be the creature of an invention, but the thing itself when obtained cannot be called a new manufacture.”

Here, we should note that the statutory basis being applied for acceptance or rejection of the claims is different: in *Parke-Davis* [16] Judge Hand is affirming the *novelty* of the purified adrenalin; in *American Wood Paper* [17] the Supreme Court is denying that an extract is a “new manufacture”, i.e. pointing out that it does not pass the SSM test; and the point at issue in *AMP* [101] is whether the isolated DNA is a “composition of matter”, i.e. statutory subject matter as required by Section 101 of the US Patent Law. Nonetheless, as noted by patent law scholars Merges and Duffy: “the law since *Parke-Davis* has been nearly uniform in agreeing with Judge Hand’s analysis [14]”.

In other words, *AMP* turns the courts squarely back to the question as to whether a product of nature in a form in which it does not occur in nature is statutory subject matter, irrespective of whether it is novel and useful. In his decision, Judge Sweet relied upon *American Wood Paper* [17], and commented that Myriad (one of the defendants) relied heavily on *Parke-Davis*[16]. Judge Sweet distinguished over *Parke-Davis* by arguing that the point at issue before Judge Learned Hand had been one of novelty (the modern-day [35 USC 102] question), and not of patentable subject matter (the [35 USC 101] question before him in *AMP*).

This brings us to an unusual aspect of Judge Sweet’s decision – his overwhelming reliance in relation to the product claims on Supreme Court cases, even ones somewhat long in the tooth, rather than on case law from the Court of Appeal (the court level above his own, whose precedent he would normally be expected to follow, for example the 2nd Circuit’s affirmation of Judge Hand’s decision in *Parke-Davis* or the 4th Circuit’s decision in *Merck & Co v. Olin Mathieson Chemical Corp* [18] which appeared to downgrade the importance of the product of nature argument.). This is unusual since it was entirely predictable that the *AMP v. USPTO*

decision would be appealed to the Court of Appeal for the Federal Circuit (herein the "Federal Circuit"), and indeed such an appeal has meanwhile been filed. It is almost as if Judge Sweet's decision were written in the expectation that the appeals process will go right up to the Supreme Court.

Before ruling on the isolated native DNA claims, Judge Sweet summarised:

“In sum, the clear line of Supreme Court precedent and accompanying lower court authorities, stretching from American Wood-Paper [17] through to Chakrabarty [9], establishes that purification of a product of nature, without more, cannot transform it into patentable subject matter. Rather, the purified product must possess “markedly different characteristics [9]” in order to satisfy the requirements of [35 USC 101].” (references added)

Turning to the question as to whether the isolated DNA did in fact possess “markedly different characteristics” from native DNA, Judge Sweet noted that DNA is “relatively inert chemically”, that it is a physical carrier of information, and that this “informational quality is unique among the chemical compounds found in our bodies”. He proceeded to comment that:

“In light of DNA's unique qualities as a physical embodiment of information, none of the structural and functional differences cited by Myriad between native BRCA1/2 DNA and the isolated BRCA1/2 DNA claimed ... render the claimed DNA “markedly different [9]”.” (reference added)

Judge Sweet thus found the claims to isolated native DNA to be directed to unpatentable products of nature. Recent developments suggest that there may well be some support for Judge Sweet's position in the Federal Circuit, as Judge Dyk made clear in an August 2010 opinion in *Intervet Inc. v. Merial Limited and Merial SAS* [103]. While the point at issue in

Internet v. Merial related to claim construction, at least one claim was to “isolated DNA” and Judge Dyk commented that such claims raise serious questions of patentable subject matter:

“The mere fact that ... a DNA molecule does not occur in isolated form in nature does not, by itself, answer the question. It would be difficult to argue, for instance, that one could patent the leaves of a plant merely because the leaves do not occur in nature in their isolated form [103].”

To determine whether or not something is “markedly different” from a product or phenomenon of nature is in itself a form of “obviousness” test, although not in the same manner as applied under Section 103 – it is a test to determine whether the claim seeks to monopolize that which, as an abstract idea or phenomenon of nature, should be open and free for all to use.

Thus far, while diverging from the position established in a District Court judgment by Judge Hand in *Parke-Davis & Co v. H K Mulford & Co* [16], Judge Sweet seems to have indeed been following Supreme Court precedent. Isolated native DNA is after all native DNA in a purified form – the DNA itself, in its relevant structure as an information carrier is wholly unchanged. In cDNA however the DNA structure is cut and spliced, and in DNA primers the DNA structure is truncated. Nonetheless, Judge Sweet also found that the claims to isolated cDNA and DNA primers were unpatentable since the subject matter was not “markedly different” from the native, genomic DNA. Here, Judge Sweet found that the appropriate SSM test was “whether, considering the claimed invention as a whole, it is sufficiently distinct in its fundamental characteristics from natural phenomena to possess the required “distinctive name, character, [and] use [19]” [101].”

More particularly, in the case of cDNA and DNA primers and probes, Judge Sweet found that the fundamental property of the DNA molecules was their informational content. Since this was the same as in the native DNA, the DNA constructs and fragments were not markedly different from the native DNA, the product of nature, and thus failed the SSM text:

“This conclusion is driven by the overriding importance of DNA's nucleotide sequence to both its natural biological function as well as the utility associated with DNA in its isolated form. The preservation of this defining characteristic of DNA in its native and isolated forms mandates the conclusion that the challenged composition claims are directed to unpatentable products of nature [101].”

It is quite clear that, in normal patent terms, the claimed isolated native DNA, cDNA and primers were *novel*, i.e. nothing existed in the prior art which fell within the scope of the definitions set out in the claims. Moreover, since the sequences of the BRCA1 and BRCA2 genes were not known, it is difficult to argue that the DNA as claimed was *obvious* having regard to the prior art as defined in the statute. Additionally, at least the primers had *utility*, e.g. for DNA amplification in a first stage in a diagnostic test for genetic abnormalities. Thus the only basis for rejecting the DNA claims would indeed seem to be by giving teeth to the Supreme Court's earlier judgements that products or manifestations of nature should not be patentable.

The method claims

This article is primarily concerned with the patentability of DNA. However, the subject of the patent-eligibility of the diagnostic method claims in *AMP v. USPTO* is of obvious interest to

the molecular diagnostics industry and the inclusion of a brief discussion is warranted due to the developments that have occurred since Judge Sweet's decision was handed down.

Although *AMP v. USPTO* is wholly concerned with patent-eligibility under 35 USC 101, the words in Section 101 that were at issue for the DNA claims were different from those primarily at issue for the method claims; in the former "manufacture" and "composition of matter", and in the latter "process". Subsequent to Judge Sweet's decision, the US Supreme Court has handed down a decision in *Bilski v. Kappos* [8] which addresses the meaning of this term "process", whether any series of steps is a "process" or whether something more is required. The subject matter of concern in Bilski's application was a business method but the Supreme Court's decision is of importance for any process which produces *information* as its product. Thus it is of particular concern for molecular diagnostic methods.

In *In re Bilski* [20], the Federal Circuit had applied the so-called machine or transformation of matter (MOTM) test - a process "is surely patent-eligible under [35 USC 101] if: (1) it is tied to a particular machine or apparatus, or (2) it transforms a particular article into a different state or thing".

In *Bilski v. Kappos* [8], the Supreme Court found that while the MOTM test was an important *example* of how a court could determine patent-eligibility of a process under 35 USC 101, the Federal Circuit had erred in treating it as the *only* test. The Supreme Court also vacated two of the Federal Circuit's other decisions in which the MOTM test had been applied. Thus the patent-eligibility of processes under 35 USC 101 will be considered by the Federal Circuit in the near future in three cases: *AMP v. USPTO* [101]; *Classen v. Biogen* [104]; and *Prometheus v. Mayo* [21].

In the method claims of *AMP v. USPTO*, as can be seen from the paraphrasing of those claims above (as "methods of detecting a DNA defect comprising analysing [or comparing] the relevant sequence"), the only required process step is of "comparing" or "analysing". This was held by Judge Sweet to involve only an abstract mental process, which is unpatentable under 35 USC 101. While in practice such methods may involve extracting or amplifying material for detection, or, as in the "method of screening" claim type paraphrased above, growing and measuring growth rates, these steps were compared by Judge Sweet to data-gathering steps, i.e. steps which could not enable a process claim to meet the MOTM test.

In *Classen v. Biogen*, the decision of the Federal Circuit that was handed down in December 2008 was that Classen's claims were not tied to a particular machine or apparatus and did not involve transformation of a particular article into a different state or thing. Thus they were found to *fail* the MOTM test. Representative of Classen's claims is claim 1 of US Patent No. 5723283 [208]:

“A method of determining whether an immunization schedule affects the incidence or severity of a chronic immune-mediated disorder in a treatment group of mammals, relative to a control group of mammals, which comprises immunizing mammals in the treatment group of mammals with one or more doses of one or more immunogens, according to said immunization schedule, and comparing the incidence, prevalence, frequency or severity of said chronic immune-mediated disorder or the level of a marker of such a disorder, in the treatment group, with that in the control group.”

This claim requires three steps: immunogen administration; detection of a disorder parameter; and comparison.

In *Prometheus v. Mayo*, by contrast, the Federal Circuit decided in September 2009 that Prometheus's claims *passed* the MOTM test. Representative of Prometheus' claims is claim 1 of US Patent No. 6355623 [209]:

“A method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder, comprising:

(a) administering a drug providing 6-thioguanine to a subject having said immune-mediated gastrointestinal disorder; and

(b) determining the level of 6-thioguanine in said subject having said immune-mediated gastrointestinal disorder,

wherein the level of 6-thioguanine less than about 230 pmol per 8×10^8 red blood cells indicates a need to increase the amount of said drug subsequently administered to said subject and

wherein the level of 6-thioguanine greater than about 400 pmol per 8×10^8 red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.”

This claim requires two steps: drug administration; and drug concentration determination.

Molecular diagnostics tests, such as the ones covered by the *AMP v. USPTO* decision, do not necessarily involve administration of a drug to the test subject but they do involve an analyte determination step. Accordingly, the Federal Circuit's decision in *Prometheus v. Mayo* that the *determination* step involved a transformation of matter holds out the possibility that the Federal Circuit may again apply the MOTM test to overturn Judge Sweet. If the *method* claims of Myriad, Classen and Prometheus are all found by the Federal Circuit to pass the MOTM test, then the MOTM test will survive – albeit not as a test for excluding processes from patentability, as the Supreme Court has indicated that this would be incorrect, but as a test which, if passed, would confirm patent-eligibility under 35 USC 101.

The possibility that the method claims of Myriad, Classen and Prometheus may all be found to pass the MOTM test is suggested by the reasoning adopted by the Federal Circuit in *Prometheus v. Mayo*. The Federal Circuit framed its acceptance that the determination step was transformative of matter as follows:

“Determining the levels of 6-[thioguanine] ... in a subject necessarily involves a transformation, for those levels cannot be determined by mere inspection. Some form of manipulation, such as the high pressure liquid chromatography method specified in several of the asserted dependent claims or other modification of the substances to be measured, is necessary to extract the metabolites from a bodily sample and determine their concentration. As stated by Prometheus's expert, "at the end of the process, the human blood sample is no longer human blood; human tissue is no longer human tissue." ... That is clearly a transformation [21].”

While Mayo had argued that the sample transformation was merely a necessary data-gathering step, the Federal Circuit considered that the transformation was "central to the purpose of the claims" [21].

Although the determination step of the Classen claims could perhaps have involved "mere inspection", Classen also required the administration of an immunogen. Hence the Federal Circuit may decide to follow the logic of its *Prometheus v. Mayo* decision where it found that drug *administration* was also necessarily transformative:

“[M]ethods of treatment are always transformative when a defined group of drugs is administered to the body ... When administering a drug ... the human body necessarily undergoes a transformation. The drugs do not pass through the body untouched without affecting it [21].”

Similarly, the drug screening method claims of *AMP v. USPTO* involve use of a drug, which, being transformative by the logic of the *Prometheus v. Mayo* decision, should mean that these claims too could pass the MOTM test, thereby making it unnecessary for the time being to formulate an alternative to this test for method claims.

Nonetheless, in considering Myriad's appeal from Judge Sweet's decision in *AMP v. USPTO*, the Federal Circuit will also have to consider the interpretation of 35 USC 101 at least in relation to the DNA *product* claims. In *Bilski v. Kappos* [8], the US Supreme Court made it abundantly clear that the Federal Circuit should look for guidance to the Supreme Court's own earlier decisions, and more specifically those of *Gottschalk v. Benson* [22], *Parker v. Flook* [3], and *Diamond v. Diehr* [23]. As we explain further below, for the DNA claims, as opposed to the method claims, *Parker v. Flook* seems to be the most pertinent case.

However, we would suggest that the method claims in *AMP v. USPTO* might also be found to be “obvious” applications of products of nature since the material used performs in its natural way. This would have to be under the SSM test of Section 101 rather than the normal obviousness test of Section 103, as only the question of Section 101 is before the courts. Nonetheless, it seems perhaps more likely that the method claims will simply be found by the Federal Circuit to pass the MOTM test and hence also the SSM test. Thus a final determination of the patent-eligibility of claims directed to methods employing products of nature may therefore require further appeal to the US Supreme Court.

The meanings of “discovery”

In the case of human genes, we must distinguish between a variety of possibly patentable “inventions”, the justification for their patentability, and the consequences of their being patented. There is little doubt that novel and inventive *processes* for identifying or extracting genes and gene defects, or for the use of genetic information or nucleic acid constructs, can represent legitimate subject matter for patenting, as long as “inventive” is not defined merely by reference to the *published* state of the art. But how about the *genes themselves, their variants and their uses*? More particularly, what about variants and uses of a gene – for example, the gene as an isolated molecule, the corresponding cDNA, or appropriate primers, and genetic tests for the presence or absence of the gene or its variants – which would be obvious if the gene was already known?

To the extent that native genes, their variants, and their correlation with disease states are *pre-existing*, identification of the gene and its variants represents a *discovery*, in one sense of the word “discovery”.

This identity as a discovery is important both in terms of US and European patent law, in the former case since the US Constitution [105] (from 1787) guarantees patents for discoveries in Article 1, Section 8 in the following terms:

“The Congress shall have Power ... To promote the Progress of Science and useful Arts, by securing for limited Times to ... Inventors the exclusive Right to their ... Discoveries.”

As far as Europe is concerned, since Article 52 of the European Patent Convention (from 1973) [13] denies patentability to discoveries in the following terms:

“(1) European patents shall be granted for any inventions ... (2) The following in particular shall not be regarded as inventions ... (a) discoveries ...”

How can two such major trading regions differ by 180 degrees in the patentability of “discoveries”? The answer, we suggest, lies in the change in the meaning of “discovery” in the intervening two centuries as well as in the shift from a Newtonian to a quantum world view.

In current usage, “discovery” of something is normally *to find something that was pre-existing and whose properties were already taking effect at the time of discovery* – one discovers a previously unknown plant or mineral, or discovers that energy is proportional to mass squared or that the attractive force between two bodies decreases with the square of the distance separating them, or that the square on the hypotenuse equals the sum of the squares of the lengths of the other two sides of a right angle triangle, or indeed that CCTGGG...CCC codes for BRCA1 protein or that CTC rather than CCC at position X of that coding correlates to increased susceptibility to breast cancer. (This is a purely spurious sequence/location just used for illustration).

At the time the US Constitution was drafted, however, discover/discovery had a *second meaning* which would have been well known to the drafters, not least since it is set out in the then dominant and new English dictionary, that of Samuel Johnson [24]. That was *the revealing of something that had been (kept) secret*.

In this context, it is interesting to mention the findings of historian Christine MacLeod, who has studied the history of the English patent system between 1660 and 1800 [25]. She draws

interesting parallels between the evolution of conceptions of “invention” and the development of the patent system. According to MacLeod, until the Enlightenment English intellectuals held a fatalistic view on technological progress: the pace of progress was predetermined by ‘Providence’.

“Providence kept a stock of useful inventions, to be released and materialized at appropriate times, provided humankind made an effort to discover them ... Symptomatic, perhaps, of this is the frequent use — noticeable in patent applications — of the words ‘discover’ or ‘find out’, where we would now write ‘invention’ [25].”

This illustrates a *third meaning* of discovery that is highly relevant to patent law – where *something is identified which had not previously been in existence or operation* (i.e. had not been in effect). For example, where a product of a marine microorganism, if injected into the human brain, can slow the progress of Alzheimer's, then to use the product to treat Alzheimer's would involve the application of a "discovery" which had not been previously in effect.

The statutory subject matter test

Now we must turn back to the statement from *Funk Bros Seed Co v. Kalo Inoculant Co* [11], approved in *Diamond v. Chakrabarty* [9] above, that some "discoveries are manifestations of nature, free to all men and reserved exclusively to none". We would suggest that what is meant in US patent law by an unpatentable discovery is a discovery in the sense of something already in existence and effect (e.g. the law of gravity, that energy and matter are interrelated,

a newly found mineral, a newly found plant, an algorithm, and other products or phenomena of nature).

If such pre-existing discoveries are “free to all men”, then so too must be their use in manners which would have been obvious had their existence been known. Otherwise, their exclusion from patentability would be substantially ineffective as their discoverer could patent and so monopolise all those obvious uses.

Such exclusion could be on two possible bases: failure to pass the SSM test; and obviousness relative to prior art extended to include “the library of nature.”

It has been suggested by the US Supreme Court that the key to the patentability of a discovery lies in transforming a "useless" discovery into a useful product or process:

“The mere discovery of a new element or law or principle of nature, without any valuable application of it to the arts, is not the subject of a patent. But he who takes this new element or power, as yet useless, from the laboratory of the philosopher and makes it the servant of man ... is the benefactor to whom the patent law tenders its protection [26].”

This is indeed essentially the current approach in Europe by the European Patent Office.

However, where a use of a discovery is immediately apparent, then simply proposing that use and seeking to patent it would prevent the discovery from being "free to all men". The question therefore arises as to whether the SSM test can be completely divorced from any

consideration of novelty, obviousness and utility – if it is to maintain the freedom to mankind of pre-existing discoveries, phenomena of nature and so forth?

In *Funk Bros Seed Co v. Kalo Inoculant Co*[11], the US Supreme Court went part-way to answering that question:

“Discovery of the fact that certain strains of each species of these bacteria can be mixed without harmful effect to the properties of either is a discovery of their qualities of noninhibition. *It is no more than the discovery of some of the handiwork of nature, and hence is not patentable.* The aggregation of select strains of the several species into one product is an application of that newly discovered natural principle. But however ingenious the discovery of that natural principle may have been, the application of it is hardly more than an advance in the packaging of the inoculants. ... The bacteria perform in their natural way. ... *They serve the ends nature originally provided, and act quite independently of any effort of the patentee.* There is, of course, an advantage in the combination. ... But a product must be more than new and useful to be patented; *it must also satisfy the requirements of invention or discovery* [11].” (emphasis added)

In other words, an aggregation of the natural or known, without some new and unforeseeable effect, does not turn a discovery which is unpatentable under 35 USC 101 into a patentable invention. The next step came with *Parker v. Flook* [3], a case regarding a method utilising an algorithm:

“Whether the algorithm was in fact known or unknown at the time of the claimed invention, as one of the “basic tools of scientific and technological work [22]” ... *it is treated as though it were a familiar part of the prior art.* ...

[The assumption that] if a process application implements a principle in some specific fashion, it automatically falls within the patentable subject matter of § 101 and the substantive patentability of the particular process can then be determined by the conditions of [novelty and nonobviousness] is ...

untenable ... *It would make the determination of patentable subject matter depend simply on the draftsman's art, and would ill serve the principles underlying the prohibition against patents for "ideas" or phenomena of nature.* The rule that the discovery of a law of nature cannot be patented rests not on the notion that natural phenomena are not processes, but rather on the more fundamental understanding that they are not the kind of "discoveries" that the statute was enacted to protect. The obligation to determine *what type of discovery is sought to be patented* must *precede* the determination of whether that discovery is, in fact, new or obvious [3]." (reference and emphasis added)

Thus the determination as to whether something passes the SSM test should involve a determination of whether what is claimed is a discovery akin to products or phenomena of nature. On the face of it, the Supreme Court also seemed to be saying that if the claimed subject matter passes the SSM test of 35 USC 101, then to be patentable it must also pass the tests for utility and novelty and obviousness under 35 USC 102 and 103, with the prior art to be considered expanded to include the "library of nature." That would have had far-reaching consequences, as was noted by the US Court of Customs and Patent Appeals in *In re Bergy* [27], shortly after it had been asked by the Supreme Court to consider the implications of the *Parker v. Flook* decision:

"Another principle stated in *Flook* is that a "mathematical algorithm" or formula is like a law of nature in that it is one of the "basic tools of scientific and technological work" and as such must be *deemed* to be "a familiar part of the prior art," even when it was not familiar, was not prior, was discovered by the applicant for patent, was novel at the time he discovered it, and was useful. *This gives to the term "prior art," which is a very important term of art in patent law, particularly in the application of [35 USC 103], an entirely new dimension with consequences of unforeseeable magnitude* [27]." (emphasis added)

Thus, the Court of Appeals here seemed indeed to understand the Supreme Court to have intended that the prior art applicable under the normal test for obviousness (under 35 USC 103) should be extended to include “the library of nature.” However, a closer look at the words used by the Supreme Court and quoted above would suggest instead that the Supreme Court intended that the SSM test under Section 101 should involve going beyond the wording adopted by the patent draftsman to see whether the claims are intended to monopolize a discovery that should be open and free for all, i.e. that the product of nature exclusion extends beyond the products themselves to their obvious modifications and uses.

That said, in the field of BRCA genes, what was the discovery? Quite simply that a protein known to be linked to a genetic problem, was coded for in a known manner by DNA and that abnormalities in the protein, linked to the problem, correlated with particular abnormalities in the coding DNA. Hence that CTC at position X rather than CCC was bad rather than good. This was a discovery of something already in existence – a phenomenon of nature.

Following the US Supreme Court’s reasoning that manifestations of nature ought to be “free to all men and reserved exclusively to none” [11], if one is to be free to use phenomena of nature in any meaningful manner, one must be free to put this information into use in the manners known and obvious at the time (e.g. by preparing primers, amplifying the patient’s DNA and seeing if the coding is CTC or CCC). The design of the native DNA was a pre-existing fact, the design of cDNA was likewise, and the design of a primer could clearly be an evident use of the knowledge of the CTC/CCC discrepancy at position X.

How does this compare with other forms of “bioprospecting”? Let us take two examples, both relating to newly found marine microorganisms which produce new compounds. First,

an antibiotic which enhances the microorganism's survival by killing competitors. Second, a compound which acts as an enzyme in breaking down absorbed nutrients, but which, when administered into the cerebrospinal fluid of a human, slows down the progression of (microorganism-unrelated) Alzheimer's disease. In the first case, the use of the compound as an antibiotic would be an obvious use had the microorganism been known to produce it as an antibiotic. In the second case, while the compound itself would be an unpatentable discovery (a product of nature), its use in treating Alzheimer's would be non-obvious and hence patentable.

Accordingly, the Supreme Court's guidance might well impact on other areas of biology-based "inventions" rather than simply being limited to DNA and molecular diagnostics. The potential effects on investment and development are, we believe, immense, and should be of great concern to the pharmaceutical industry in general as well as to universities that seek to patent discoveries made by their researchers. For already granted patents, clarification of the meaning of the Statutory Subject Matter test could of course imply that some of those patents will be found invalid in future *inter partes* litigation (just as Judge Sweet has found some of Myriad's claims in granted patents to be invalid). For the market, one effect might be to discourage investment/activity in relation to products of nature known or thought likely to exist in certain locations. However, the other side of the coin would be that, with fewer broad upstream patents, proliferation of R&D might very well be encouraged, perhaps leading to improved consumer choice and greater competition. Just because one cannot patent "all tests for BRCA1" would not prevent many novel and inventive tests being patented – one may think in this context of the assays for homocysteine, which have been patented despite the fact that, since homocysteine levels were of known diagnostic relevance, no patent could cover *all* homocysteine assays.

Conclusion

If *AMP v. USPTO* is upheld on appeal, it will have a major impact on those seeking to patent genes and other materials found in nature as well as their obvious variants and uses. This is particularly important to the molecular diagnostics industry, as diagnostic tests routinely involve determining the presence, absence or concentration of a natural material in a body sample and comparing the results with a predetermined "healthy" or "unhealthy" limit. Likewise it is of particular importance to the pharmaceutical industry in seeking to patent drugs which occur in nature or which are simple modifications of such drugs. Thus the outcome of *AMP v. USPTO* may impact not only upon the patenting of DNA having diagnostic utility but also on the patenting of therapeutically useful DNA, methods of DNA therapy, and the use of recombinant DNA for drug production.

As we have attempted to show in this article, Judge Sweet seems to have indeed been following Supreme Court precedent. Isolated native DNA is native DNA in a purified form – the DNA itself, in its relevant structure as an information carrier is wholly unchanged. In cDNA the DNA structure is cut and spliced, and in DNA primers the DNA structure is truncated. Nonetheless, Judge Sweet rightly found that the claims to isolated cDNA and DNA primers were also unpatentable since the subject matter was not “markedly different” from the native, genomic DNA. As to the method claims, in our view these too were rightly rejected, but what we regard as an important ground for rejection of these claims is not mentioned in Judge Sweet’s analysis: the fact that the methods in question are *obvious applications of (unpatentable) products of nature* since the material used performs in its

natural way, and that besides products of nature themselves, such obvious applications must also be excluded by the SSM test.

Thus we feel that the US Constitution's blessing to the patenting of discoveries should *include* the serendipitous (the third meaning of “discovery” discussed above), “inventions” which might have been considered to be pre-ordained but not pre-existing. The other forms of discovery should in our view be excluded from patentability – as our common heritage, waiting to be discovered and available to all, the property of none, i.e. the products of nature, phenomena of nature, manifestations of nature, etc. Otherwise, patent monopolies would simply go to those with the greatest resources to search and not those who “invent”. As is clear from the opening quote of this paper, the expenditure of effort (time and money), however great, does not in itself justify the grant of a state-sanctioned monopoly – something more is necessary.

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