had provided MWB with a practical expectation of a benefit (i.e. that Rock's payments would eventually be paid, and that the property would not be left vacant while it sought a new licensee), but this was not sufficient. To have found otherwise, would have required the revisiting of *Foakes v Beer*[27] (settled law since 1884)—where the House of Lords approved the rule in *Pinnel's Case*[28] that "payment of a lesser sum on the day in satisfaction of a greater, cannot be satisfaction for the whole". The effect of this being that "payment of part of a sum which is owed, even though the debtor might otherwise not pay it or possibly become insolvent, cannot, of itself, amount to good and valuable consideration" (as summarised by Kitchin LJ in the Court of Appeal.[29] On a different set of facts, a collateral contract might have arisen, resulting in a different outcome to the one found by the Supreme Court.

Conclusion

The decision in *Rock v MWB* protects contracting parties from the consequences of a mistaken or unintended informal variation of their IP licence agreement and so provides more legal certainty. Parties must have regard to any formalities specified in their IP licence agreement to ensure compliance if any variation is to be effective.

Where, in practice, commercial relationships between contracting parties require more flexibility with regard to the management of certain day to day matters (as with a co-development licence agreement), the parties should consider providing for alternative less formal procedures in their licence agreement so that a NOM clause does not, inadvertently, hinder their commercial endeavours.

Differences in Culture: Expanded Cells Held Patent Eligible in the US

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The Patents Trial and Appeal Board (PTAB) has decided that cells expanded in culture may be patent-eligible[1] *in the US. Cultured cells were held to be different from cells in their natural environment. This comment compares the decisions to* Myriad*, challenges the assumption that isolated cells are patent-ineligible and highlights opportunities for European invention capture, patent drafting and prosecution.*

Background

Subject-matter eligibility in the US

The types of subject-matter for which US patents may be granted has become a hot topic in recent years. Section 101 of Title 35 of the US Code (35 USC §101) sets out the types of invention which may be patented, provided they comply with other patentability requirements (such as novelty and non-obviousness). The list appears to be simple:

> "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 title." (Emphasis added.)

One may imagine that this list should not represent a significant barrier to patentability of most inventions. However, judgments handed down by the US Supreme Court have established certain judicial exceptions to patentability; US patents may not be granted for laws of nature, natural phenomena, or abstract ideas. The exception of natural phenomena is frequently applied to natural products. This means that an inventor of a new and useful composition of matter may *not* obtain a patent for their invention, if the composition of matter is a natural product.

Myriad and DNA

The commercial exploitation of natural products and their derivatives is central to the biotechnology industry. The exception from patentability for natural products in the US has attracted much attention around the world. But how is a natural product defined? If a natural product is modified in a lab, does it become patent-eligible?

The Supreme Court judgment in the *Myriad* case of 2013[2] established that isolated genomic DNA (gDNA) is not patent-eligible. The rationale of the judgment makes clear that isolated gDNA was considered patent-ineligible because it is a natural product. The gDNA did not cease to be a natural product merely because it had been isolated from its natural environment.[3]

However, another DNA molecule termed cDNA, which is prepared by laboratory procedures, was held to be patent-eligible by in the same judgment. It appears that the Supreme Court was persuaded that cDNA is not a natural product because it is structurally different from

[27] *Foakes v Beer* (1884) 9 App. Cas. 605.
[28] *Pinnel's Case* (1602) 5 Co. Rep. 117a.
[29] *MWB v Rock Advertising* [2016] EWCA Civ 553; [2017] Q.B. 604 at [38].
[1] Throughout this article the concept of "patent eligibility" refers to the types of invention which may be patented. It does not necessarily also refer to inventions for which a patent can be granted. This is because for a patent to grant, the invention must also fulfil other criteria, such as novelty and non-obviousness.
[2] *Association for Molecular Pathology v Myriad Genetics Inc* 569 US__, 133 S. Ct. 2107, 106 U.S.P.Q. 2d 1972 (2013).
[3] European law takes a different position. Isolation of a natural product from its natural environment does render a product patent-eligible in Europe.

gDNA. In particular, non-coding regions of gDNA (termed "introns") are removed during the production of cDNA. All that remains in cDNA are the coding regions of the corresponding gDNA (termed "exons").

But what about cells?

The *Myriad* case concerned DNA. However, many biotechnology applications can involve cells, rather than DNA. Such applications include advanced therapies, regenerative medicine and stem cell therapy.

Cells are the biological units that make up living organisms. Most cells have DNA inside them. The DNA encodes genetic information, acting like a set of instructions for the cells to build their own component parts. Cells can even regulate how their own genetic information is expressed in response to their environment. This regulation is known as "epigenetics" and involves chemical changes to a DNA molecule, such as DNA methylation, or modifications to other molecules that package the DNA within the cell, known as histones. These chemical changes do not change the sequence of the DNA but may affect how other cellular components interact with a DNA molecule. The function of a gene in a cell requires other cellular components to interact with the DNA molecule that encodes the gene, enabling the gene to be "expressed". Therefore, epigenetic changes to DNA can alter gene expression and therefore change the characteristics of the cell (or the cell "phenotype").

Guidance issued by the US Patent Office (USPTO)[4] since the *Myriad* decision suggests that merely isolated cells are not patent-eligible. The rationale for this position is similar to the reasons why gDNA was held patent-ineligible in Myriad. Specifically, mere isolation of a product from a natural environment is not enough to prevent the product from being considered a product of nature.

The USPTO guidance also suggests that cells are patent-eligible when transformed in a lab by, for example, the introduction of DNA not naturally found in the cells. This type of transformation, termed "recombinant DNA technology", has long been of interest in biotechnology. For example, since the 1970s, most insulin for administration to manage diabetes is produced by E-coli bacteria that have been transformed in a lab by the introduction of DNA encoding human insulin. Some cutting-edge biotechnology such as CAR-T cell therapy also applies recombinant DNA technology to engineer a patient's own immune cells to target a cancer.The rationale for this position parallels the reasons why cDNA was held patent-eligible in *Myriad*.

But what about cells that have undergone epigenetic changes? Such changes are made by the cell itself, rather than by direct intervention by investigators in a lab. However, epigenetic changes can result from a change in the environment of the cell resulting from laboratory procedures. Epigenetic changes can be functionally important and long-lasting, even heritable. So could a cell that has not been genetically modified, but has been placed in a new environment long enough for epigenetic changes to take place, be patentable in the US?

The PTAB decisions

Four decisions of December 2017 addressed this question. In each case, the Board found that cells that had been expanded in culture were not a product of nature. Hence, the Board decided that the cells were patent-eligible under 35 USC §101.

The applications

The four applications to which the PTAB decisions relate each included claims defining (among other features):

- "A cell culture comprising isolated expanded human cells …";
- "The cells having undergone at least 10 to 40 cell doublings in cell culture[5]…".

The cells of each invention had therefore been removed from their natural environment and grown in a non-natural environment in a laboratory. The cells were able to grow and divide in this non-natural context, producing more cells (hence the references to the cells being "expanded" and undergoing "doublings"). As the cells were expanded in culture, the cells changed over time beyond merely increasing in number.

The arguments

The US Examiner had rejected the claims of all four applications during prosecution as failing to comply with 35 USC §101. The Examiner considered that the cells "do not differ significantly from those found in nature". Thus, he decided that the claims defined a natural product, which was not patent-eligible.

In reaching their decision, the Board considered what would be needed for the cells to be "different" from the cells that occur naturally in a human. The Board recognised that cells may express different genes and proteins at different times during cell culture. However, the Board considered that in order for the cells to be different from those occurring in nature, the difference must be relatively permanent (e.g. a modification to the DNA of the cell), rather than a transient and reversible change to the cell.[6] In other words, the Board were looking for a structural difference between the cultured cells and the cells originally isolated from the human donor.

[4] See "Nature-Based Examples", No.9, Cells (16 December 2014), *https://www.uspto.gov/sites/default/files/documents/mdc_examples_nature-based_products.pdf* [Accessed 5 December 2018].
[5] In one case, the number of cell doublings specified is 40, rather than 10–40.
[6] It is debatable whether the change should need to be relatively permanent. The claimed cells have been expanded in culture and have adapted to this unnatural environment. The expanded cells are useful in ways that the cells *in vivo* are not. If the cells as claimed are different from the cells in nature, and these differences result in new uses of the cells, is it really important that the differences cannot be undone?

The US attorneys representing the applicant provided arguments based on scientific publications and an expert declaration. They contended that the documents filed amounted to

> "extensive evidence showing that epigenetic changes and changes in cellular phenotype occur when cells, such as those claimed, are isolated and expanded and have undergone 10-40 cell doublings in culture, and that these changes are sufficient to demonstrate that the claimed cells have markedly different characteristics from their closest naturally-occurring counterpart".

The expert declaration opined on the relevance of the scientific publications. The expert described how the publications showed why one would expect a cell to change in culture. This was essentially because the cell has to adapt, for example via attachment proteins, to a completely unnatural environment.

The outcomes

On the basis of these arguments, the Board reversed the Examiner, citing the appellant's evidence that cells in culture (which would include the claimed cells) are structurally different from those cells found occurring naturally in the human body. The cells expanded in culture were therefore held to be patent eligible. The Board remitted the applications for further examination accordingly.

In reaching their decision, the Board summarised how the Examiner failed to persuasively identify a defect in the appellant's evidence:

> "In our opinion, as with utility rejections under Section 101, the PTO has the initial burden of establishing that the claimed subject matter is a judicial exception to patentability. See *In re Swartz*, 232 F.3d 862, 864 (Fed. Cir. 2000) (utility under 35 U.S.C. 101). Once this burden was met, as it was here, 'the burden shifts to the applicant to submit evidence sufficient to convince' the ordinary skilled worker (id.) that the claimed subject matter is not directed to a judicial exception, specifically in this case, to a product of nature. Appellants provided rebuttal evidence, as discussed above, that the claimed cells are structurally different from those cells found occurring naturally in a human body. The Examiner did not persuasively identify a defect in Appellant's evidence, particularly in [the Appellant's expert's] scientific logic about the pertinence of data from other pluripotent stem cell lines to the claimed cells because of their adaptation to cell culture, as well as the consistency between [the Appellant's expert's] statements about the properties of the claimed cells with those of other stem cells as summarized in the Findings of Fact."

It therefore appears that the publications and the logical case made in a Declaration by the Appellant's expert was especially persuasive. Although the Declaration summarised evidence that the cell type referred to in the application undergo epigenetic changes in culture, the underlying data was not submitted. This is interesting because it suggests a reasoned extrapolation from one cell type to another can be persuasive when made by a credible expert in the field.

These decisions do not determine exactly what changes would be considered significant enough for isolated expanded cells to be patent eligible in other cases. The Board appears to have been convinced by the indirect evidence that cells would be expected to change in culture and the corroboration by an expert that this was indeed the case for this particular cell type. However, the precise changes that take place are controlled by the cells themselves, once placed in the unnatural cell culture environment. For this Board, these changes were sufficient for patent eligibility. It will be interesting to see whether future decisions concerning other cell types adopt analogous reasoning.

Future directions and significance

The PTAB is not a high-profile jurisdiction in the US. These decisions do not represent a major shift in US law. However, the decisions do illustrate how the existing US law can be applied in the field of cell biology, and how to overcome rejections before the USPTO.

All too often for practitioners, ground-breaking inventions can fall foul of US approaches to subject-matter eligibility. These decisions are therefore welcome as they show that technically sensible arguments can prevail in the context of 35 USC §101.

Isolated cells

Many practitioners may have adopted a view that the post-*Myriad* US approach is diametrically opposed to the European approach to isolation of biological material and patent eligibility. Some consider that in the US isolation is never enough for patent eligibility. In contrast, in Europe isolation is always enough for patent eligibility. This distinction in practice across the Atlantic does seem clear in the case of gDNA. But is the distinction really so clear in the context of cell biology? Is the view that merely isolated cells are not patent eligible in the US challenged by the facts of these cases?

In many cases the isolation of cells from their natural environment could cause long-lasting structural differences to the cells. Of course, this may not always be the case. Accordingly, the examples given in the USPTO guidance documents explicitly assume that isolation does not change the cells. However, if for example, relatively permanent epigenetic changes can be shown to occur on isolation of some cell types from their natural environment, could the isolated cells be patentable, even without expansion? There could be merit to the

argument that some cells may be sufficiently changed by mere isolation from their natural environment to be rendered patent-eligible in the US.

This line of reasoning does not necessarily contradict *Myriad*. A structural change does occur to gDNA on isolation, namely the severing of covalent bonds within the DNA molecule. However, any structural change occurring on isolation of gDNA is presumed not to affect the information content (and therefore function) of the DNA. However, if a structural change occurs to DNA within a cell following isolation as a result of epigenetic processes, then this change could result in a long-lasting functional change in the cell. It seems open to debate on the particular facts of a case whether isolated cells should be patent eligible in the US.

This speaks to European practitioners involved in invention capture or the drafting and prosecution of patent applications. Perhaps we should not immediately assume that a newly isolated cell type with identifiable commercial usefulness will be patent-ineligible in the US. It is a purely factual question. The question may need to be contested before the USPTO. But in some cases, the argument may be worth having.

How does this affect innovators in Europe?

The US approach to patent eligibility contrasts with the position in Europe. In Europe, *isolated* biological material such as DNA and cells is patent-eligible (other requirements of patentability such as novelty and inventive step are required for a patent to be granted, however). No further transformation of biological material is necessary to surpass the basic patent eligibility hurdle in Europe. The decisions of the PTAB described above do not have any bearing on European law.

Nevertheless, the US represents a key market for many European innovators. Legal developments in the US may therefore be watched closely in Europe to inform global IP strategy. It is helpful for all practitioners involved in IP commercialisation to understand the challenges and opportunities presented by different markets. US legal developments are therefore of interest to European patent attorneys, technology transfer officers and investors, for example.