

Biotechnology patentability – the latest from the EPO

The European Patent Office's approach to biotechnology patentability is evolving along with the industry. The latest developments are reviewed in three key areas

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Since the European Patent Office (EPO) was founded 35 years ago, biotechnology has become an established industry – albeit one that changes constantly. In order to keep pace with that sector, the EPO needs to revisit frequently its own rules on what is patentable and what it means in practice.

This chapter reviews the developments in patentability in three key areas of biotechnology:

- therapeutic monoclonal antibodies;
- stem cells; and
- plant biotechnology/breeding.

Therapeutic monoclonal antibodies

The success of existing therapeutic monoclonal antibodies has resulted in an upsurge of activity in this field in recent years. Antibodies have acquired significant commercial importance as highly specific drugs for the treatment of diseases including cancers and autoimmune diseases. A wave of patent filings has accompanied these developments.

No specific directives govern the patentability of antibodies in Europe. The EPO's requirements have instead evolved with the technology. Some of these requirements arise from decisions of the EPO's Board of Appeal, but examiners are also guided to an extent by the EPO's internal policies.

Patents covering antibodies to novel and

inventive targets are routinely granted by the EPO. The EPO considers it straightforward to obtain antibodies to a new protein and so does not require such antibodies to be exemplified. This approach was developed in the era when many new genes and proteins were being cloned and patented, and it was therefore common for targets to be novel and inventive (non-obvious).

However, most new antibodies are now to known targets. The antibodies must be clearly defined in order for the EPO to determine that they are novel. This can be an issue where the antibodies are defined functionally in terms of their binding properties or activities, rather than structurally. In such cases data showing that the antibodies in the prior art do not possess the same properties may be required. However, the biggest hurdle is that of non-obviousness. This hurdle cannot be overcome at the EPO purely because the structure of the antibody is not obvious.

It has long been accepted that non-obviousness can be established by demonstrating that an antibody to a known target produced by a known method has an unexpected technical effect. This is generally the best approach if there is data demonstrating a difference between the new antibody and the antibodies in the prior art.

Sometimes it may be possible to establish that there was no reasonable expectation of obtaining a particular antibody using known methods. In 2011, for example, the EPO's Board of Appeal found human monoclonal antibodies to be inventive over a mouse antibody that neutralised the same protein. This was because the likelihood of obtaining neutralising human antibodies using the known techniques would not have been reliably predicted. Because

the known human antibodies were non-neutralising antibodies, the newly invented ones exhibited an unexpected technical effect.

In 2012 the Board of Appeal held an antibody to be inventive even though it did not offer an improvement over a known antibody specific for the same protein. The new antibody was held to be inventive because it bound to a particular part of the protein that could be considered to be a novel target. Binding to that part of the protein could therefore be viewed as an unexpected effect of the antibody. Treating a specific part of a known protein as a novel antibody target is consistent with the EPO's original approach based on treating wholly new proteins as novel targets.

A patent must also describe the claimed antibodies in a manner that enables them to be obtained without excessive difficulty. What constitutes sufficient disclosure depends on the manner in which the antibodies are defined and what is known in the prior art. The EPO has granted – even recently – patents to antibodies defined only by functional properties. In such cases, either the specification or the prior art must describe tests to determine whether an antibody satisfies the functional definition. It has, however, become more common for antibodies to be defined by reference to:

- a structural feature (eg, amino acid sequence); or
- both structural and functional features.

Structurally, an antibody is composed of heavy and light polypeptide chains, each having constant and variable regions. Within each variable region, three sub-regions known as complementarity determining regions (CDRs) are key to the antigen binding properties that make antibodies useful. EPO examiners generally insist that any structural definition include the sequences of all six CDRs. However, where data shows that fewer CDRs are required to achieve a technical effect, or that the CDRs may be modified while maintaining a technical effect, the antibody may be defined accordingly.

Non-obviousness is increasingly an issue in obtaining patents for antibodies and there is a trend towards more precise structural and functional definitions. The EPO may

therefore appear to be getting stricter in this area. However, as each case is judged on its facts and by reference to the ever-increasing amount of prior art, the changes reflect natural developments in a fast-advancing field, rather than a tightening of the EPO's underlying standards.

Stem cells

The European Patent Convention (EPC) does not allow an invention to be patented if exploiting it commercially would be contrary to morality.

Since biotechnology sometimes has an ethical component, the European Union provided in 1998 some legislative guidance in the form of a directive concerning which biotechnological inventions are contrary to morality. The EPO subsequently updated the EPC to include these rules. In addition to human cloning, the directive renders uses of human embryos for industrial or commercial purposes unpatentable.

Stem cells can differentiate into many specialised adult cell types, such as liver cells or heart cells. They can thus self-renew to produce more of themselves. Of particular interest are 'pluripotent' stem cells capable of differentiating into any adult cell type.

A key aim of stem cell technology is to repair damaged tissues or replace damaged organs using these cells. The idea is that pluripotent stem cells can be stored and used when needed. If so-called 'autologous pluripotent stem cells' – derived from the patient's own tissues – are used, then the new tissue or organ will avoid the problems of rejection that arise with donated tissues or organs. Such proposals have been championed in recent times by celebrities with serious injuries or degenerative disorders, such as Christopher Reeve and Michael J Fox.

There are two key types of pluripotent stem cell: embryonic stem cells (ESCs) and induced-pluripotent stem cells (iPSCs). As their name suggests, ESCs are derived from early stage embryos. iPSCs are adult cells (usually skin cells) that are devolved to an embryonic stage using genetic modification.

In October 2011 the European Court of Justice (ECJ) ruled in *Brüstle v Greenpeace* that any invention involving the use of human ESCs

is unpatentable. The ECJ's reasoning was that such cells are inherently derived from human embryos and as such constitute use of human embryos for industrial or commercial purposes. Interestingly, the ECJ held that it does not matter when the use of human embryos takes place in the context of the invention. Thus, it does not matter that a person could implement the invention without actually using an embryo – for instance, by purchasing a human ESC from a stem cell bank.

The decision remains controversial. The ECJ seemed to focus on the exact wording of the directive and to ignore its overriding purpose. The ECJ did not consider in detail whether EU countries see human ESCs as contrary to morality. Commentators have noted that it is odd to conclude that human ESCs are immoral when their derivation, sale and use are sanctioned throughout the European Union (albeit with strict controls to avoid misuse). It is perhaps especially surprising to draw this conclusion when ESCs are typically derived from spare embryos created during *in vitro* fertilisation, with parents giving their consent in the hope of helping others or advancing scientific knowledge.

The fact that the ECJ focused on the exact wording of the exclusion is also surprising because there was no public knowledge of human ESCs when the directive was drafted. The discovery of human ESCs was made public a few months after the directive came into force in 1998.

The scientific community reacted negatively to the ECJ decision. For instance, Professor Sir Ian Wilmut, one of the creators of the cloned sheep Dolly, was quoted as saying: "It is very much to be regretted that the [ECJ] has taken this view. It will unfortunately make it less likely that companies in Europe will invest in the research to develop treatments to use embryonic stem cells for treatment of human diseases."

However, the ECJ decision may not be the final word on this issue. There may be commercial and political pressure to reverse the ruling once patients are being treated using human ESCs. Incidentally, UK Prime Minister David Cameron was asked whether he will do what he can to clear this blockage during Prime Minister's Questions in the House of

Commons in January 2013.

For the time being, the EPO has at least partially implemented the ECJ decision and grants no patents that concern the use of human ESCs if, when the patent application was filed, the ESCs could be made only by destroying human embryos. However, the EPO will grant patents that concern products such as culture apparatus or culture media that are suitable for use with human ESCs because "their production normally does not require the use of human embryos".

In any case, many other types of stem cell and their uses can be patented in Europe. The exclusion concerns uses of human embryos and so has no bearing on the patentability of non-human ESCs. Nor does it affect the patentability of stem cells derived from adults, such as adult stem cells or iPSCs.

Lastly, most countries outside the European Union (including the United States and Japan) consider human ESC-related inventions to be patentable. Practice in Europe may liberalise in the future, although there are no signs of when that may happen.

Plant biotechnology/breeding

Also excluded from patentability are plant (and animal) varieties and essentially biological processes for the production of plants (and animals). Plant varieties have historically been excluded to avoid overlap with plant variety rights – a separate form of intellectual property applicable to new varieties of plant. Such rights still have a valuable role, but some plant innovations are increasingly of a type to which patents are better suited.

Genetically modified (GM) crops brought these issues to the fore in the 1990s. Although EU regulators have been reluctant to permit their commercialisation, they are in principle now clearly patentable if the patent claims are written correctly. In 2000, the *Novartis* decision of the EPO's Enlarged Board of Appeal confirmed that plants are patentable, notwithstanding the variety exclusion, provided that the patent claims do not specify individual varieties. An individual GM variety would be excluded, but the invention that a GM plant represents is usually amenable to a broader, allowable definition. Other related aspects, such as transformation processes and

transformed plant cells, can also be claimed.

Although the position is reasonably clear for GM technology, it is less so for plant breeding. One might imagine that classically bred plants would be excluded from patentability and protectable only by variety rights. One might also imagine that non-biotech breeding processes that produce plants by crossing would be excluded as essentially biological. However, recent technologies – such as marker-aided selection, which speeds up breeding processes – have caused the EPO's Enlarged Board of Appeal to examine the issues in its *Broccoli* and *Tomatoes* cases.

The Enlarged Board of Appeal concluded that inclusion of such technical steps in what is otherwise a claim to a breeding process does not avoid the essentially biological process exclusion. This rules out, for example, claims to marker-aided selection processes and methods that begin with transformation to produce a first-generation transformant, but are then continued to produce downstream generations by breeding. This is unfortunate for patent holders, but claims to transgenic plants as products *per se* cover any generation and the EU Biotechnology Directive also confers some additional protection on downstream generations.

Taking account of practice following the *Broccoli* and *Tomatoes* cases and the legislative exclusions themselves, there are some positive aspects to the EPO's established position on plant-related inventions. However, that position is considerably more restrictive than the position in the United States, where there are no policy-based restrictions and even individual plant varieties can be patented if novel and inventive. Elsewhere, the position varies widely: some countries are more liberal than the EPO, whereas others forbid claims to plants entirely.

The response to the *Broccoli* and *Tomatoes* cases has been to claim non-GM plant inventions in product format. Although an essentially biological process for the production of plants cannot be patented, the EPC does not preclude explicitly the patenting of the product of such a process – for example, a plant obtainable by a breeding process. This is vital for so-called 'native trait' applications that are becoming more common in light

of improvements in technologies such as molecular markers. Here, the invention is the identification of the part of a plant's genome responsible for a beneficial trait, which may not be a single gene as in a GM situation, but can nonetheless be transferred from one genetic background to another by breeding. Such inventions are therefore not confined to a single variety and can be claimed generically in line with the EPO's Enlarged Board of Appeal's *Novartis* decision. These inventions also cannot adequately be protected by plant variety rights, because such rights relate to single varieties, whereas a native trait is a more broadly based contribution requiring more extensive protection. Such product claims are in practice often hard to secure for other reasons, but current case law supports them in principle.

This position is controversial, however. The seed industry considers that it needs and deserves such claims to protect its investment in the development of new plants. By contrast, breeders' groups argue that, compared to the narrower and weaker protection of a plant variety right, patent claims on non-GM plants unduly restrict their members' freedom to develop new varieties. There is also criticism from lobby groups opposed to patenting in agriculture.

The EPO's Enlarged Board of Appeal is therefore considering the question of whether products of processes excluded from patentability should also be unpatentable. For procedural reasons, it is uncertain whether it will be able to provide an answer or on what timescale. However, the issue has also been raised by an anti-patent group in another case and so will have to be resolved at some point. It is possible that another door for patentees in Europe will be closed as a result, but in the meantime applicants can work only to the current practice and await developments. **iam**

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Pamela Tuxworth is a partner of J A Kemp with over 10 years' professional experience. Much of her day-to-day practice involves prosecuting patent applications at the European Patent Office (EPO) and elsewhere, and handling oppositions and appeals before the EPO.

She handles European patent applications across a range of biotechnology and life sciences subject matter. Her substantial experience of oppositions and appeals at the EPO includes, in particular, multi-party oppositions on antibody cases.

Dr Tuxworth's client base includes US and European antibody companies, academic institutions and government bodies. She also handles both European and foreign applications for small biotech companies developing new technologies. Notably, she acted for BioVex Limited, handling its patent portfolio and several EPO oppositions prior to its high-value acquisition by Amgen.



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Lee Chapman is a partner of J A Kemp, experienced in drafting and prosecuting patent applications, particularly in the United Kingdom, the United States and Japan, and before the EPO. Dr Chapman is also experienced in preparing and handling oppositions and appeals before the EPO and conducting due diligence and freedom to operate exercises.

He handles cases across a broad range of biotechnology subject matter, but has particular drafting and prosecution experience in the fields of stem cells, nanopore sequencing and sensing, antibodies, genes and proteins, new administration regimes and medical uses. In the stem cell field, Dr Chapman acted on behalf of Wisconsin Alumni Research Foundation in the landmark case that led to the EPO's Enlarged Board of Appeal Decision G2/06 on the patentability of human embryonic stem cells.



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Andrew Bentham is a partner of J A Kemp whose patent practice concentrates on EPO prosecution and opposition/appeal work and representation of universities in the life sciences fields. With an academic background in plant sciences, he has a particular interest in plant biotech and breeding and can advise on plant variety right issues, as well as patents in the agricultural sector.

He has been involved in some 50 EPO opposition proceedings, many involving multiple opponents and including cases relating to second medical uses, antibodies and genes, as well as plant science aspects such as transformation and gene silencing.

Among his clients are UK and foreign academic institutions, small and medium-sized biotechs, multinational pharmaceutical companies and agriculture-sector businesses, including one of the world's largest seed companies.