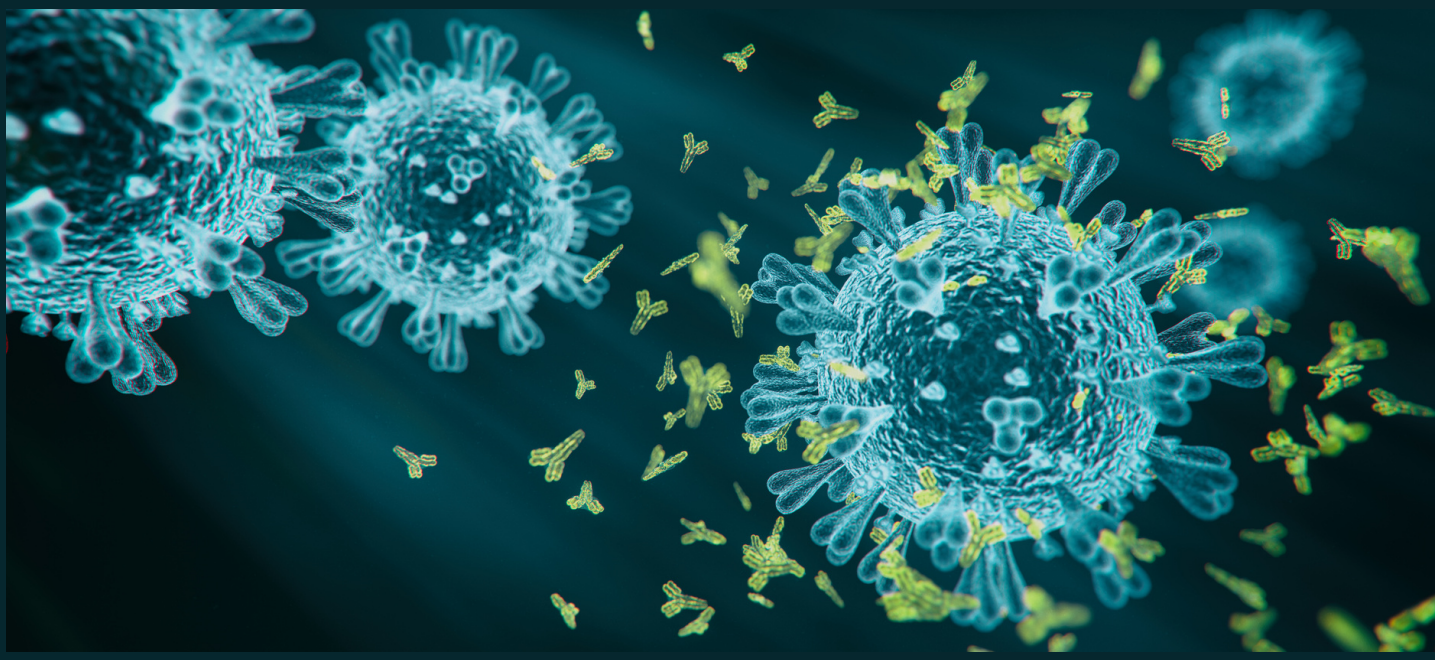
Maximising Antibody Patent Protection in Australia

Is a lack of technical expertise among Australian examiners denying applicants fair and commercially relevant protection for antibody patents and, in turn, undermining the purpose of the patent system?



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Introduction

Antibodies have become significant therapeutic treatments for a broad range of diseases including cancer, inflammatory conditions and infectious diseases. This antibody success story, which includes blockbuster drugs such as Humira (AbbVie), Keytruda (Merck), Opdivo (BMS/Ono Pharmaceutical), Infliximab (JnJ/Janssen) and Dupixent (Sanofi), is driving the development of a multitude of next-generation antibody therapeutics. However, the unique structure/function relationship of antibodies presents a challenge to obtaining commercially relevant patent protection for clinical candidates. In this regard, typically during Australian prosecution, antibody patent applications are subject to support and sufficiency objections that represent "lions in the path" of commercially relevant protection.

Antibody structure and function

Antibodies are protein molecules of the immune system that bind to, and are involved in neutralising, foreign substances/pathogens (commonly referred to as "antigens"). Structurally, antibodies are typically Y-shaped protein molecules that consist of two identical polypeptide "heavy chains" and two identical polypeptide "light chains". Each heavy and light chain consists of:

(a) a variable domain, having three hypervariable regions called complementarity determining regions (CDRs)) ie, three CDRs of the heavy chain variable domain (VH) and three CDRs of the light chain variable domain (VL); as well as

(b) one or more constant domains, each of which is made up of conserved amino acid sequences.

Antibody structure and function is a mature field of technology in which it is well known that the 6 CDRs are involved with the generation of antibody binding diversity. Importantly, however, it is also well established that the CDR3 of the VH alone is sufficient for generating most antibody binding specificities.[1] In other words, the CDR3 region of the VH has been shown to be the major structural correlate that confers antibody binding specificity. As such, the 6 CDRs of an antibody are not necessarily required to produce a functional binding antibody. This, however, appears to be at odds with current Australian Patent Office prosecution practice.

Patent Office practice

A frequent challenge for antibody patent applicants involves addressing support and sufficiency patent requirements. These "disclosure requirements" are set out in sections 40(2)(a) and 40(3) of the Australian Patents Act 1990 as below.

40(2) A complete specification must:

(a) disclose the invention in a manner which is clear enough and complete enough for the invention to be performed by a person skilled in the relevant art....

40(3) The claim or claims must be clear and succinct and supported by matter disclosed in the specification.

A frequent challenge for antibody patent applicants involves addressing support and sufficiency patent requirements. These "disclosure requirements" are set out in sections 40(2)(a) and 40(3) of the Australian Patents Act 1990 as below.

[1] Xu and Davis Immunity 2000 Jul;13(1):37-45.

Essentially, the Australian sufficiency provisions (section 40(2)(a)) require that the invention be "enabled" across the full scope of the claims by what is described in the specification (discussed in more detail below). The support provisions (s 40(3)) require a consideration of the technical contribution detailed in the specification and whether the scope of the claims includes subject matter that goes beyond that technical contribution. Support and sufficiency have been described in the Australian Courts as "two-sides of the same coin."[2]

The question of enablement is approached by the Patent Office as being a two-step test involving "plausibility" and "undue burden". Plausibility relates to whether the invention would work across the entire scope of the claims. However, significantly, plausibility has been confirmed as a low threshold test, which a "reasonably credible" claimed use or "educated guess" can suffice. It has also been confirmed that an undue burden only exists if practicing the invention across the entire scope of the claim constitutes a "research program".[3]

Antibody claims

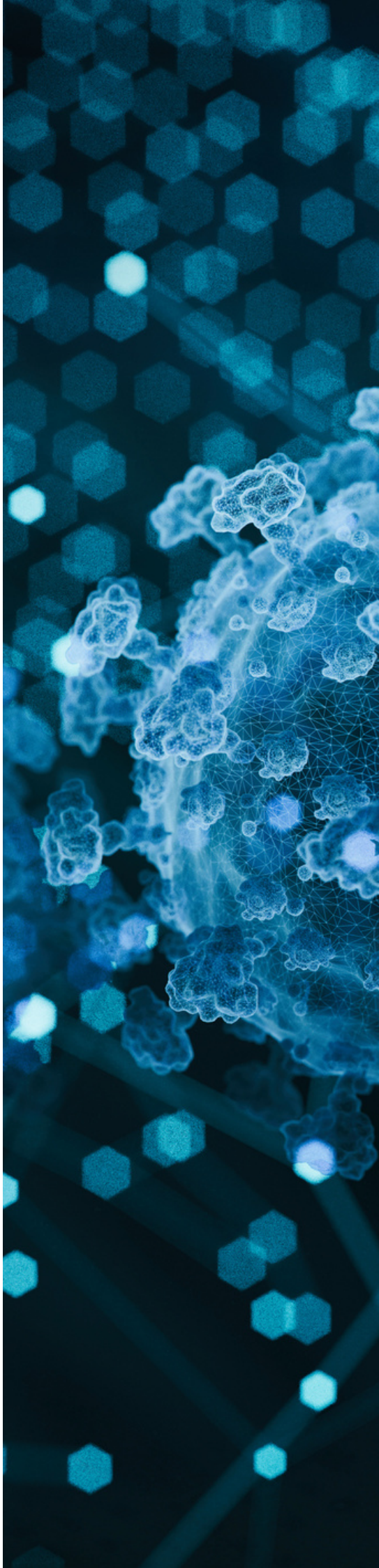
The tension between broad antibody claims, which do not include sequence limitations, and the Australian disclosure requirements, relates to the position taken by the Patent Office that generally requires claims to define 6 specific CDR sequences.

For example, a typical objection made against an antibody claim that does not include 6 CDR sequences of the exemplified antibody may recite,

> *"...the specification has not provided any explicit disclosure or general principle that could be applied across the full scope of the claims, such that the skilled person can plausibly discern which residues in the CDRs can be modified and activity retained. It is well known in the art that the six CDRs of an antibody are critical to activity, and that even a single amino acid change in the CDRs can perturb this activity".*

In other words, Examiners believe, in certain cases, for antibody claims to be enabled they must define an exemplified antibody's 6 CDR sequences. However it is clear, as detailed above, that satisfying the Australian disclosure requirements relates to enablement, which does not mean exemplification, ie specifically making and testing the antibody.

The exception to the "6 CDR sequence rule" according to the Australian Patent Manual of Practice and Procedure is that broader antibody claims are permitted when the applicant has characterised an antibody's epitope (that being the specific part of the antigen that is recognised by the antibody) and shown that other antibodies can be raised against the epitope. In these circumstances, the Patent Office takes a position that broad claims covering all antibodies against the epitope represents a "principle of general application" that can be applied across the scope of the claims without the need for CDR sequence limitations. However, generally, this experimental approach is not taken by applicants in antibody specifications.



[2] Merck Sharp & Dohme Corporation v Wyeth LLC (No 3) [2020] FCA 1477

[3] Evolva SA [2017] APO 57

Undermining commercially relevant protection

The issue that applicants face is that claims defining 6 CDR sequences can readily be avoided by third parties. This may involve changing one amino acid in, for example, the CDR1 of the VL of a competitor antibody. Such a competitor antibody would, according to what is well known about antibody structure and function, exhibit identical or substantially identical binding specificity as the claimed antibody, but fall outside the scope of the antibody claim. This scenario is clearly inconsistent with the purpose of the Patents Act 1990, which functions to provide incentives for innovation and knowledge sharing by granting commercially relevant monopoly rights.

Being granted a patent with claims that require, as a minimum, exemplified embodiments, and that based on the common general knowledge can readily be worked around by a potential infringer is not in line with the purpose or object of the Patents Act 1990.

Maximising antibody patent protection in Australia

Australian Patent Examiners have taken an unnervingly narrow stance that antibody CDRs contribute to antibody binding specificity in a uniform manner. This position is, arguably, scientifically unsound because it does not take into account the well-known dominance of the VH CDR3 in conferring antibody binding specificity.

Ideally, addressing or preventing sufficiency and support objections that insist on 6 CDR sequences, could be accomplished by showing, in the specification, examples of variations to the CDR sequences, such as outside the VH CDR3, that do not impact functional antibody binding. However, this is generally not a practical approach for applicants seeking the earliest possible priority date. For this reason, arguments rebutting a disclosure objection should be heavily weighted on:

- the well-known structure/function relation of antibodies and CDRs;
- the low threshold of plausibility; and
- the routine nature of varying CDR sequences, which could not be considered a research project.

Based on the above approach, it is conceivably predictable that certain variations in CDR sequences would not impact antibody binding specificity. It follows that if such CDR sequences variations were covered by a claim, that claim should be considered enabled in the absence of exemplification.

Conclusions

Changing well-established Patent Office practice, such as that currently implemented for antibody applications represents a great challenge for applicants and their patent attorneys. However, such changes can be achieved, generally through requesting a hearing during prosecution. This, for example, occurred in *Arrowhead Research Corporation [2016] APO 70*, which set an important precedent for gene-based patentable subject matter in Australia, and relied on significant evidence from a technical expert supporting the Applicant's position. Given the issues facing antibody patent applicants in Australia, clarification of disclosure requirements is urgently required that ensures the available protection for antibodies is in line with the purpose of the Australian Patents Act 1990.

This article was written by Grant Shoebridge. Please do not hesitate to get in touch if you have questions regarding this topic.

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