

Enhancing antibody patent protection using epitope mapping information

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ABSTRACT

As the \$100B therapeutic monoclonal antibody (mAb) market continues to grow, developers of therapeutic mAbs increasingly face the need to strengthen patent protection of their products and enforce their patents in courts. In view of changes in the patent law landscape, patent applications are strategically using information on the precise binding sites of their mAbs, i.e., the epitopes, to support patent novelty, non-obviousness, subject matter, and a tightened written description requirement for broad genus antibody claims. Epitope data can also allow freedom-to-operate for second-generation mAbs by differentiation from patented first-generation mAbs. Numerous high profile court cases, including *Amgen v. Sanofi* over rival mAbs that block PCSK9 activity, have been centered on epitope mapping claims, highlighting the importance of epitopes in determining broad mAb patent rights. Based on these cases, epitope mapping claims must describe a sufficiently large number of mAbs that share an epitope, and each epitope must be described at amino acid resolution. Here, we review current best practices for the use of epitope information to overcome the increasing challenges of patenting mAbs, and how the quality, conformation, and resolution of epitope residue data can influence the breadth and strength of mAb patents.

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Introduction

Monoclonal antibodies (mAbs) accounted for approximately \$100B of global therapeutic drug sales in 2016,¹ and the market for therapeutic mAbs is projected to grow by 12.6% annually through 2024.² Given the stakes involved, it has become exceedingly important for developers of therapeutic mAbs to obtain broad patents covering their mAbs and to enforce them in courts. However, obtaining broadly protective patents for mAbs is challenging, and changes in the patent law landscape present new hurdles to applicants and owners of mAb patents.

mAbs are often described in terms of their epitope (the part of the target protein bound by the mAb) and their paratope (the part of the mAb binding the target) (Fig. 1). Epitope and paratope information is being increasingly used by developers to strengthen mAb patents. From 2010 to 2016, the proportion of antibody patent applications having “epitope(s)” in their claims has nearly doubled from 13% to 24% (Fig. 2).³ Different companies are increasingly pursuing mAbs against the same therapeutic targets, which makes epitope information even more valuable.

Overview of mAb patents

Under U.S. patent law and in most other countries, for a composition of matter (e.g., an antibody) to be patentable, it must be novel and non-obvious (discussed below), as well as useful. Since an antibody is almost always useful for some purpose, the usefulness requirement is rarely an issue. A patent application must also contain an adequate description of the invention such that

someone “skilled in the art” is enabled to make and use the invention (the enablement requirement) and understands what the inventor has actually invented (the written description requirement). To be patent eligible, the composition also must not be a “product of nature”.

mAb compositions are usually claimed by reciting both their structure (e.g., amino acid sequence) and function (e.g. where or how they bind the target). Structural claims based on the mAb sequence are usually straight-forward to obtain and defend. However, they are more restricted in scope because they can be circumvented by functionally similar mAbs with different sequences, in many cases as little as one amino acid change. Structural claims are perhaps most valuable in protecting mAbs from generic competitors (biosimilars) that use the exact same sequence.

In contrast, functional mAb claims are broader and, as a result, more desirable because they can exclude competitors from developing new mAbs with similar mechanistic effects. The caveat is that broad functional mAb claims face more scrutiny during prosecution and in lawsuits, especially in view of court decisions that have tightened the requirement for functional claims. As discussed below, detailed epitope information can help mAb claims differentiate new mAbs, withstand legal challenges, and potentially block others.

Differentiating epitopes provides novelty

Under 35 U.S.C. §102, to be patentable an invention must be novel and not “anticipated” by the “prior art”. A claim is

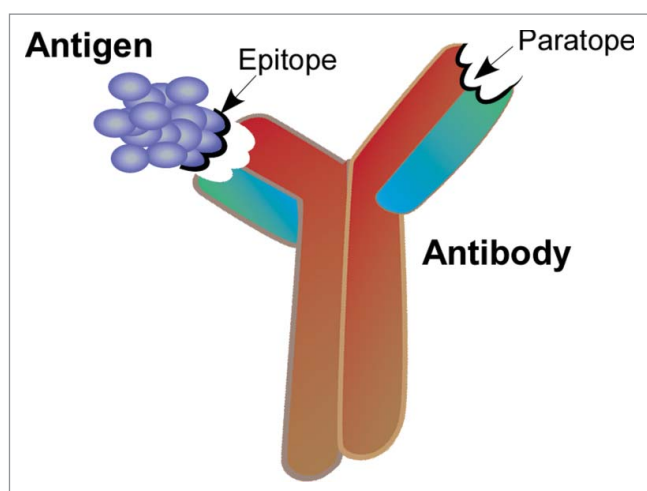


Figure 1. Epitopes vs. Paratopes. Epitopes are formed by amino acids on the target antigen, while paratopes are formed by amino acids on the binding antibody. Epitopes and paratopes interact to define the location and kinetics of binding.

anticipated if each and every element in the claim is found in a single prior art disclosure publicly available before the patent application was filed. In the case of antibodies, developers of later-generation mAbs targeting an antigen must carefully draft their patent claims to distinguish the novel features of their mAbs that are different from earlier-generation prior art to avoid “anticipation” or “infringement” problems.

Epitope information can be valuable for distinguishing later-generation mAbs from earlier-generation mAbs targeting the same antigen. This is illustrated by the *Biogen v. GSK* case⁴ in which Biogen sued GlaxoSmithKline for infringement under U.S. patent 7,682,612 (Table 1), which claims therapeutic methods using anti-CD20 antibodies (e.g., Biogen’s Rituxan®). Based on the patent application’s prosecution history, the courts construed Biogen’s patent claims to be narrowly limited to anti-CD20 antibodies “with similar affinity and specificity for the specific epitope to which Rituxan binds”. GlaxoSmithKline prevailed in this case by showing that its own anti-CD20 antibody (Arzerra®) targeted a different epitope

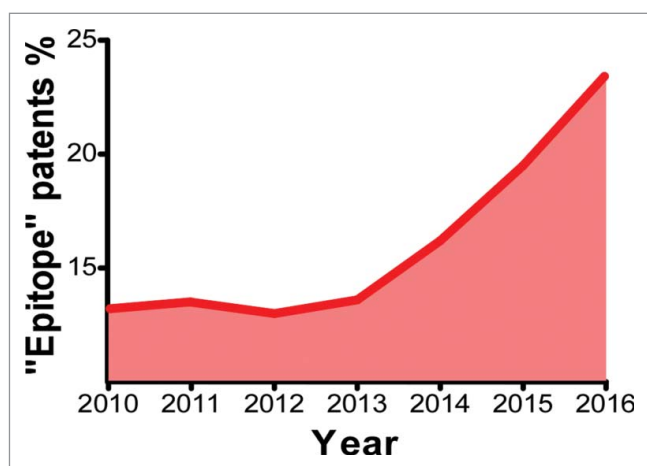


Figure 2. Antibody “epitope” patents. The percentage of patent applications with “epitope(s)” in their claims, relative to the number of patents with “antibody(ies)” in their titles, has increased from 13.2% to 23.5% between 2010 and 2016. Data obtained from the WIPO PATENTSCOPE database, which covers international Patent Cooperation Treaty (PCT) patent applications.

than that of Rituxan, thereby successfully circumventing Biogen’s patent and avoiding expensive infringement judgment. Thus, under this ruling, multiple therapeutic mAbs can be allowed against the same target as long as they can be demonstrated to have distinct epitopes (Table 2).⁵

When applying for a patent, mAb developers often use epitope information to overcome the patent office’s “anticipation” rejection. For example, claim 1 of U.S. patent 9,115,188 is directed to a mAb targeting a conformational epitope of the H5 avian influenza virus. This claim was initially rejected by the United States Patent and Trademark Office (USPTO) for lack of novelty, citing a prior art mAb that also binds to a conformational epitope of avian H5. The patent applicant overcame the rejection by pointing to data showing that the claimed mAb binds to an epitope containing at least one amino acid not involved in the prior-art mAb’s epitope, thereby successfully distinguishing the claimed mAb from the prior art mAb.

These examples also highlight the value of high-resolution epitope information. Some epitope mapping strategies, such as competition binning assays or peptide binding, may be inadequate for legally distinguishing epitopes (“indefiniteness”). For example, in a competition assay many mAbs will compete simply due to their large size, even though they do not bind to the exact same amino acids. In the Biogen case discussed above, site-directed mutagenesis and peptide scanning techniques were combined to identify the exact epitope residues of GlaxoSmithKline’s Arzerra, pinpointing it to a site outside the epitope of Biogen’s Rituxan.⁶ Similarly, the influenza mAb 9,115,188 patent used escape mutant selection to identify epitope residues for their virus-neutralizing mAb, so was able to identify individual amino acids in the epitope that could then be used to support the claims.

High resolution epitope mapping is especially important for epitope-directed mAb claims (e.g., “an antibody that binds to epitope X”). These claims stand under the constant threat of being anticipated by previously existing antibodies that could bind to the same epitope, but have yet to be mapped. This “inherent anticipation” issue can often be overcome with high resolution epitope information that pinpoints the exact epitope residues involved in binding, as two independently developed mAbs usually do not bind the exact same epitope residues.

Conformational epitopes are non-obvious

Under 35 U.S.C. §103, an invention may be unpatentable due to obviousness if individual elements of the invention have each been previously disclosed, and a person skilled in the art could readily combine these elements to arrive at the claimed invention. Additionally, an invention can be viewed as obvious if a skilled artisan can arrive at the invention by making trivial variations to the prior art. Antibody claims directed to linear epitopes sometimes face obviousness challenges if the sequence of the linear epitope has been disclosed by the prior art gene sequence. This happens because there is abundant literature documenting the routine practice of generating a mAb by immunization with a short linear peptide corresponding to the known protein sequence.⁷

On the other hand, a mAb claim directed to a conformational epitope is less likely to be considered obvious. A

Table 1. Patent law cases with an impact on antibody epitope patents.

Case	Patent Issue	Conclusion
Biogen v. GlaxoSmithKline (Federal Circuit, 2013)	Novelty	MABs that target different epitopes are novel
Association for Molecular Pathology v. Myriad Genetics (Supreme Court, 2013)	Patentable subject matter	Naturally occurring mABs and linear epitopes are ineligible for patents
Centocor Ortho Biotech, Inc. v. Abbott Laboratories (Federal Circuit, 2011)	Written description	Detailed mAB/epitope information must be provided to satisfy written description
AbbVie v. Janssen (Federal Circuit, 2014)	Written description	Broad mAB/epitope claims must disclose a large number of mABs/epitopes with common structural features
Amgen v. Sanofi (Court of Appeals for the Federal Circuit, 2017)	Written description	Detailed epitope information and a sufficiently large number of epitope examples provide an advantage for broad mAB claims for patent issuance and challenges

conformational epitope is defined as discontinuous residues on an antigen that come together to form an antibody-binding surface with a three-dimensional structure (Fig. 3). Conformational epitopes therefore require large regions of the target protein to be used for discovering the antibody, and thus contain large numbers of potential epitopes. Current technologies are unable to predict whether a mAb would bind to specific amino acids that come together in three-dimensional space. Therefore, creating a mAb targeting a specific conformational epitope is anything but routine, even when the prior art has disclosed the sequence or structure of the antigen.

Because of the complexity of generating a mAb against a conformational epitope, a mAb patent can be strengthened by showing that the mAb targets a conformational epitope, and so avoid an obviousness rejection by the patent office. For example, the applicant of U.S. patent 7,091,324, which is directed to a mAb targeting a conformational epitope of a hepatitis C protein, overcame the USPTO's obviousness rejection that cited a

prior art mAb with an overlapping linear epitope. The examiner's reasoning for rejection was essentially that a skilled artisan can make obvious variations to the prior art epitope sequence and use the derived variations to make the claimed mAb. However, the patent applicant successfully argued that the claimed mAb binds to a conformational epitope, and it would not have been obvious that such a mAb could be developed based on the knowledge of the prior art linear epitope sequence.

MABs binding to epitopes can be patentable subject matter

It has been held by the U.S. Supreme Court that products of nature, abstract ideas, and laws of nature are ineligible for patents. For example, in the 2013 *Myriad* case⁸ the Supreme Court held that a naturally occurring DNA segment is a product of nature and does not become patent-eligible merely because it was isolated. The implication is that a nucleotide sequence or a protein fragment is patent-ineligible if it is not distinguishable from its naturally occurring counterpart.

This case law has limited the ability to patent isolated epitope residues (i.e., in the *absence* of an antibody). Previously, it was possible for a company to patent the isolated epitope residues of an antigen without reference to an antibody (see, e.g., U.S. patent 8,029,801, claiming an isolated polypeptide comprising an epitope of a virus). However, under *Myriad*, an isolated epitope claim will most likely be found as ineligible patent subject matter if the claimed sequence is identical to that found in nature. A less risky route in terms of patent eligibility is to claim antibodies that bind these epitopes (e.g., claiming "An isolated antibody that binds epitope X"). Inclusion of the antibody changes the object of the claim to patentable subject matter (i.e., the antibody) while still broadly claiming any antibody that binds those residues.

Another strategy for meeting the patentable subject matter requirement is to claim epitopes containing man-made mutations or other modifications to the natural sequence, as often occurs with vaccine scaffolds and engineered immunogens. This can enable a claim to show a marked difference in subject matter from its natural counterpart while preserving the key antigenic features of the natural conformation.

Claims directed solely to antibodies isolated directly from patients without further modification are likewise considered "naturally occurring" and are likely patent-ineligible under the Interim Patent Eligibility Guidance issued by the USPTO.⁹ However, most therapeutic antibodies are patent-eligible as they are usually generated by artificially eliciting immune responses in animals or isolating them from man-made phage or yeast libraries. In practice, even "naturally occurring" therapeutic antibodies are nearly always further engineered during development, and so are patent-eligible because their sequences have been altered (e.g., by point mutation, chimerization, or humanization).

Written description requires multiple high-resolution epitopes

Perhaps the toughest challenge faced by broad mAb claims is the written description requirement under 35 U.S.C. §112(a). A patent applicant must adequately describe the claimed invention to

Table 2. Patent examples claiming epitope information.

Example Patent No.	Patent Issue	Conclusion
US7682612 (Biogen's Rituxan), US9115188 (Influenza epitope)	Novelty	Novel epitopes distinguish claimed mABs from prior-art mABs
US7091324 (Hepatitis C epitope)	Obviousness	Conformational epitopes render mABs non-obvious over prior-art linear epitopes that bind to the same region
US8829165 and US8859741 (Amgen's PCSK9 mABs)	Written description	Broad claims to a mAB genus should be supported by detailed epitope information and a large number of examples, and can give the patent owner an advantage in infringement suits against its competitors

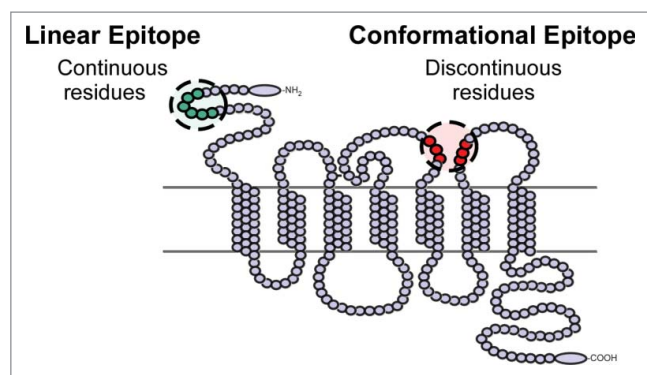


Figure 3. Linear vs. conformational epitopes. Linear epitopes consist of continuous residues on a protein sequence. Conformational epitopes consist of residues that are discontinuous in the protein sequence yet come within close proximity to form an antigenic surface on the protein's three-dimensional structure. Conformational epitopes are less obvious and more patentable than linear epitopes.

show that the inventor is in possession of the invention at the time the application is filed. The policy rationale is the quid pro quo nature of patents: a patent owner discloses the invention to society in exchange for the ability to exclude others from practicing the patented invention. Therefore, a mAb claim risks being invalidated under the written description requirement if the claim is broader than the disclosed invention.

Recent court cases have tightened the written description requirement for antibodies. Previously, an “antibody exception” would allow a mAb claim to satisfy the written description requirement merely by describing the antigen target without describing an actual mAb.^{10,11} However, in *Centocor v. Abbott*¹² the court held that the antibody exception only applies in the situation of a “newly characterized antigen” where it is routine to create an antibody targeting the antigen. In view of this and subsequent cases (see below), applicants must be in possession of the antibodies claimed.

Clarifying written description requirements further, in *AbbVie v. Janssen*,¹³ the court held that for a broad claim covering a “genus” of mAbs to satisfy written description, the specification must describe a representative number of mAb species within the genus or common structural features shared by the genus. This reasoning also applies to epitopes: a broad claim requires describing a sufficiently large number of mAbs that share the epitope, and each epitope must be described in detail.

When drafting a mAb patent claim, an applicant can claim the mAb by its function (e.g., “An isolated mAb that binds the antigen at epitope amino acids 1, 2 and 3”) or by its structure (e.g., “An isolated mAb consisting of CDRs with the sequences of X, Y, and Z”). Claims directed at mAb function rather than mAb structure offer broader protection against competitors’ mAbs. However, broad functional claims face tough challenges in view of *AbbVie*’s written description requirement.

The value and risk of such broad functional claims are illustrated by the high-profile case *Amgen v. Sanofi*¹⁴ over two antibodies (Amgen’s Repatha[®] and Sanofi’s Praluent[®]) targeting proprotein convertase subtilisin/kexin type 9 (PCSK9). Amgen’s patents (U.S. 8,829,165 and 8,859,741) claim a broad genus of mAbs based on their epitopes. In this case, Amgen sued Sanofi/Regeneron for infringing its patents by producing a mAb targeting the same epitope claimed by Amgen’s patents.

The breadth of Amgen’s issued patents left Sanofi/Regeneron no option other than admitting infringement and hoping to challenge the patents’ validity. A representative claim of the 8,829,165 patent states: “An isolated monoclonal antibody, wherein, when bound to PCSK9, the monoclonal antibody binds to at least one of the following residues: S153, I154, P155, R194, D238, A239, I369, S372, D374, C375, T377, C378, F379, V380, or S381 of SEQ ID NO:3, and wherein the monoclonal antibody blocks binding of PCSK9 to LDLR”. The broad language “at least one of the following residues” (which could be one, two, three, or any combination of these residues) was the key in allowing Amgen to prevail. At the same time, the broad scope of such claims makes them vulnerable to written description challenges if Amgen cannot provide a large and diverse number of mAb and epitope examples.

For Amgen’s 8,829,165 patent to meet the written description requirement, Amgen supported the claims with several mAb examples, as well as a co-crystal structure showing the epitope residues on PCSK9 and how these residues are critical for PCSK9 to interact with the LDL receptor and perform its biological functions. Amgen also described additional mAbs that bound to the same region containing the critical epitope residues. As Amgen argued in response to the USPTO’s initial written description rejection,¹⁵ the detailed information provided not only numerous representative species within the scope of the genus claim, but also the structural features that correlate with the function of the claimed mAb. Armed with this epitope information, when Sanofi/Regeneron challenged the validity of Amgen’s patents in court, Amgen was able to convince a jury that the patents described the broad mAb claims in sufficient detail to satisfy the written description requirement.

After the jury verdict, Sanofi/Regeneron filed a post-trial motion to challenge the result. The motion was denied by the District Court (January 3, 2017), a major loss for Sanofi/Regeneron, which, at least in the short term, resulted in the loss of billions of dollars of company market value (after announcing the penalty, Regeneron shares fell 5.8% and Sanofi shares fell 2.8%, while Amgen shares rose 2.5%). The Court also granted Amgen’s request for a permanent injunction against Sanofi/Regeneron (although the injunction was stayed pending appeal), which is atypical for health-related products where public interest in access to drugs usually outweighs the patentee’s interests. Other pharmaceutical companies, led by Eli Lilly and AbbVie, filed amicus curiae briefs supporting each side of the case.^{16,17} This case has now been remanded back to the lower court (October 5, 2017, Court of Appeals for the Federal Circuit ruling) so that the jury can consider whether Amgen’s patents are supported by a “representative number of species” of antibodies binding the particular epitope.

Irrespective of its outcome, this case suggests that epitope claims must be supported by both detailed epitope mapping data and a sufficient number of examples. Specifically, applications will need a sufficiently large number of antibodies that bind to the specific epitope residues of interest to demonstrate true intellectual possession of the claimed epitope that can justify the breadth of the claim. It is also worth noting that determining whether a patent provides an adequate written description is a factual issue tasked to a jury. At least in this case, the epitope data in Amgen’s specification was successfully used to convince the jury in the initial District Court trial that the written description requirement was satisfied.¹⁸

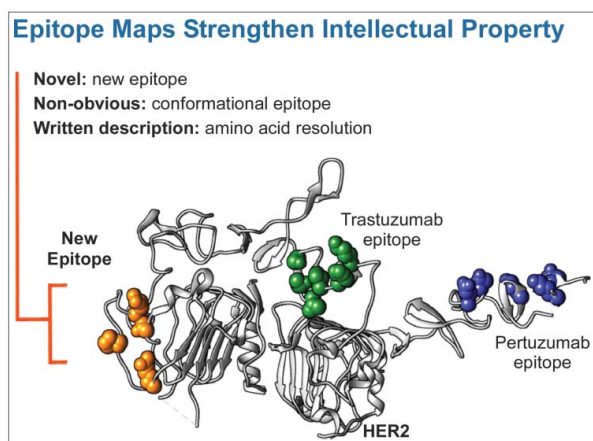


Figure 4. Epitope maps strengthen intellectual property. The amino acid binding site for a novel epitope (Fynomer C12, orange residues) strengthens intellectual property by providing novelty (compared to other epitopes, such as those for trastuzumab and pertuzumab on HER2), non-obviousness (because the epitope forms a conformational epitope of discontinuous residues), and support for written description (by identifying the specific amino acids energetically required for its binding).

Based on these cases, patent applicants should consider defining the binding epitopes for their mAbs at the highest resolution possible. Different kinds of epitope mapping strategies produce various levels of epitope detail. Some strategies, such as peptide mapping, hydrogen-deuterium exchange, and competition binning assays, may not provide sufficient detail (at the amino acid level) to satisfy the written description requirement for claiming individual amino acids in an epitope. In contrast, other strategies, such as co-crystallography and comprehensive site-directed mutagenesis, provide this level of detail.¹⁹ In the case above, the Amgen 8,829,165 patent chose co-crystallography as its primary means of epitope mapping. Mapping a large panel of mAbs would strengthen their patent claims around the genus even further.

The situation in Europe

European patent law does not have a written description requirement. However, it appears that examiners at the European Patent Office (EPO) treat epitope-based claims with increasing scrutiny, with the rationale that their scope is indefinite. Examiners sometimes consider a definition by epitope or binding competition as an “unusual parameter,” where no meaningful comparison with the prior art can be made. In such situations, the EPO stipulates that the onus of proof lies with the applicant to demonstrate that an unusual parameter is a genuine distinctive feature distinguished from the prior art.²⁰

Hence, at the EPO, epitope-based claims must overcome the novelty and non-obviousness hurdles more than written description. Amino acid-level epitope information can help to overcome this bar by demonstrating that the claimed epitope has not previously been covered by existing antibodies.

Conclusion

Epitope-based antibody patent claims are an attractive claim species to provide patent protection with broader scope than structure-based patent claims, but are subject to substantial

scrutiny. By strategically leveraging epitope information, developers of mAbs can strengthen their patents by distinguishing their mAbs from others’ (novelty) and by demonstrating that their mAbs’ binding epitopes are not linear (non-obviousness) (Fig. 4). Furthermore, providing amino acid-level epitope details for a large number of mAbs can help to meet the tightened written description requirement for broad genus antibody claims.

Disclosure statement

X.D. and B.J.D. are employees of Integral Molecular. B.J.D. is a shareholder of Integral Molecular. Integral Molecular uses high-throughput site-directed mutagenesis (Shotgun Mutagenesis) to define mAb epitopes, internally and commercially. U.S. is a European Patent Attorney involved in the prosecution of epitope based antibody patents, but is not involved in procedures related to any of the patents discussed herein. The information provided herein reflects the personal views and considerations of the authors, and not of their organizations or clients.

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