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IP FRONTIERS

Patenting antibodies: You get what you ask for, or do you?

Production of complex macromolecules called antibodies are an important way in which the body responds to invasion by foreign organisms such as viruses and bacteria. The development of vaccines to artificially spur the production of antibodies as a way of preventing infectious disease represents one of the earliest attempts in medicine to harness the disease-preventative power of antibodies.

By the mid 1970s, technologies were being developed that would enable the production of large quantities of purified antibodies from animal cells and tissues, and eventually humans. Today, antibodies are genetically engineered to recognize a variety of disease targets and are used to prevent and treat many conditions, from blindness (e.g., wet age-related macular degeneration) to cancer. As a result, antibodies are rapidly becoming one of the largest classes of new therapeutic agents.

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Daily Record Columnist

As the cost of bringing a therapeutic antibody to market approaches or exceeds $1 billion, much of which is earmarked for activities related to regulatory approval, incentivizing the development of these potentially valuable drugs by obtaining patent coverage is critical. Unlike conventional small molecule therapeutics, however, obtaining broad patent coverage of antibodies presents some challenges.

In order to be effective, antibodies need to have a couple of important properties: they need to be highly specific for the target and bind to the target with high affinity. In other words, they need to be able to find the right target and then hold onto it.

Antibody specificity and affinity derive from antibody structure and are exquisitely sensitive to minor changes in the antibody's chemical structure. To ensure therapeutic efficacy, tinkering with the antibody structure may be necessary not only to enhance antibody affinity but also to improve its longevity in the blood. An antibody that is initially identified as having the requisite specificity will likely undergo further tweaking before a clinically effective form is realized.

Because the precise antibody structure must be determined empirically, the challenge for the inventor is the uncertainty of obtaining patent protection for an antibody that is ultimately efficacious but not identical to the antibody currently being studied. In the absence of any predictable method for deducing the optimal antibody structure, the temptation to claim broadly initially should be avoided in favor of a strategy of sequential patent filings covering improvements as the antibody is developed.

Based on my experience, it is fairly common for scientists to expect to receive broad patent coverage for their antibody. In their view, in addition to covering their current antibody, the claims should encompass many other antibodies, which could be readily obtained using standard methodologies, even if they have not actually made them. Such "other antibodies" can include similar antibodies and antibodies to similar targets that also may be clinically relevant.

Sometimes these views are formed based on their perception of the scope of protection achieved by others in the field over the last two decades.

Alas, in the same two decades, a number of court decisions have articulated a standard for patentability, particularly for biological molecules, such as antibodies, that has attempted to bring the scope of patent claims back in line with what is disclosed. Based on the philosophy that a patent is granted as a *quid pro quo* for the disclosure of a useful invention, the courts have fashioned a written description requirement that seeks to ensure that a potential patentee gets what he deserves — and little more.

In a line of cases beginning with *Regents of the University of California v. Eli Lilly & Co.* in 1997, which first proposed that there is a written description requirement for patentability separate from the enablement requirement, the subject matter to which a patentee is entitled has been increasingly circumscribed so that the metes and bounds of the claim are not unlike shrink wrap that snuggly conforms to that which the patentee actually

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invented and disclosed.

In *Lilly*, the identification of a DNA sequence for rat insulin did not entitle the patentee to rights to DNA sequences of other vertebrate or even mammalian species, since the patentee failed to describe DNA sequences for any insulin other than rat, even though the technology was available at the time to isolate DNA from other species based on the knowledge of the rat insulin.

At the time, the purported rationale for imposing a written description requirement was to protect the public, the industry and the true inventor from overreaching claims, perceived at the time as a persistent problem in the field of recombinant DNA.

The test for written description, as articulated in the decisive written description case, *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336 (Fed. Cir. 2010) (*en banc*), is whether the disclosure "conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Id*. at 1351. Though the courts have repeatedly held that actual reduction to practice is not required to satisfy the written description requirement, most "possession" scenarios are those in which reduction to practice has been actual rather than constructive.

In a recent case specifically addressing the written description of antibodies, *Centocor v. Abbott* (Fed. Cir. 2010), Centocor attempted to assert its patent, which claimed fully human anti-tumor necrosis factor- (TNF-) antibodies, against its competitor's fully human anti-TNF antibody. The court construed *Centocor's* claims to encompass human antibodies, which would have been infringed by *Abbott's* antibody, but for one fatal flaw. *Centocor's* description of a humanized antibody, that is, an antibody that was a combination of human and mouse regions, was insufficient to provide a written description of a fully human antibody as claimed.

In developing their antibody, *Centocor* pursued the conventional approach of starting with an antibody derived from mice, and "humanizing" it by replacing all but the antigen binding regions with human sequences. On the other hand, *Abbott* employed a newer strategy of isolating the antibody's antigen-binding region from a human library. The court found that *Centocor* had never actually produced an antibody that was completely human and therefore, was unable to disclose it. *Centocor's* claims were invalidated.

Prior to the decision in *Ariad*, there was much debate regarding the wisdom of a separate written description requirement, particularly since there was no remedy for salvaging a failed description after the filing date of the application. At the end of the day, the written description requirement has the practical effect, at least with respect to biological inventions or discoveries, of preventing overreaching by an early stage player and precluding later ones.

As long as newly described antibodies are able to avoid being labeled obvious over earlier ones given the general availability of ever changing antibody-generating technology, written description may not cause too much mischief. At any rate, thanks to *Ariad*, the requirement for written description is a fact of patent life.

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